Genetics inMedicine | CORRESPONDENCE

Response to Esplin et al.

I thank Dr. Esplin and colleagues for their thoughtful letter[1] as they have raised important nuances regarding my recent commentary on virtual panels.[2] Their first point centers on the question of whether primary and secondary findings are a dichotomy, suggesting instead that there is a continuum. I agree with this point as it fits well with my overall thinking about biology and medicine, which is that the topics of these disciplines are essentially never categorical and are instead spectra or continua. There is an irresistible tendency to put things into apparently handy and useful bins, until some clear-thinking person comes along and points out the fallacies of doing so. This is a critical and complex topic for the epistemology of our field, but one must at the same time be practical. The practical approach would be to admit that some genes are clearly secondary, some are clearly primary, but there are plenty that are in between. Having accepted that, one must then decide what to do about it. This matters—because this false dichotomization is generally implemented by returning only pathogenic and likely pathogenic variants for secondary findings, but returning the full spectrum of pathogenicities for primary variants. What one should do if this is instead a spectrum or continuum is unclear. A simple, interim proposal would be to make a determination that, based on the indication for the test, whether each gene that is on the (actual, not just virtual) panel is primary or not. If it is primary, treat it as such; if it is not primary, and it is on the American College of Medical Genetics and Genomics (ACMG) secondary findings list, treat it as secondary. This approach ignores some of the complexities and nuances raised by Esplin et al., but is practical.

The challenge that Esplin et al. raise is much bigger than this and should provoke us to think beyond our current exigencies. Genomics has challenged our thinking in biology because the scale of the data upends our prior notions about what an experiment should be and how it should be designed. Analogously, genomics is straining our prior notions about what a genetic test is and how it should be implemented. Perhaps big panels, exomes, and genomes aren't really medical tests at all, and that is why it is so challenging to fit them into medical testing models and practice. Perhaps, instead of being a medical test, these technologies are instead gigantic, parallel conditional probability generators that simultaneously modify the patient's prior probabilities for hundreds or even thousands of heritable disorders. This would fit into a model of diagnosis and susceptibility risk being framed in Bayesian terms, which is how great diagnosticians actually think. Were we to begin to think in this way, the categories of primary and secondary become absurd and irrelevant. Instead, the patient represents an enormous and ever-changing spectrum of prior probabilities of disease, and the genomic data are used to continuously calculate posterior probabilities of disease likelihoods that can be presented to the clinician for consideration and further evaluation. While this approach is far into the future, it offers a framework to fundamentally resolve the problem highlighted by Esplin et al. Through efforts like the EMERGE program, we can move toward advances in the electronic health record and clinical decision support that can actually use genomic data to advance health care, rather than to simply support reimbursement.

Esplin et al. also raise important questions about health services delivery organization and costs were secondary findings to be implemented for virtual panels. Of course, the first and most obvious response is that this does not have to happen at all if testing laboratories were to change their processes to constrain the molecular interrogation to the genes that are clinically indicated. This would entail costs, but it is a solution that should be considered. It is worth emphasizing that if the gene is not molecularly interrogated, there is no secondary finding to return. If virtual panels (in addition to exomes and genomes) do continue to be widely used and secondary findings policies implemented, there will be strain on the health-care personnel and increased costs. It also bears emphasizing that a new test does not have to decrease costs—it has to add quality-adjusted life years (QALYs) to the health-care system at an acceptable cost (currently about $100,000 per QALY). Preliminary data suggest that secondary findings do exactly that.[3] Were this to be borne out then we have a good problem on our hands—a cost-effective approach to opportunistic genomic screening. Our professions (clinical genetics, genetic counseling, and the relevant subspecialties) should seize that opportunity and with all haste, ramp up our systems to achieve this important objective. It would be difficult to imagine a better opportunity for medical genetics to thrive and take its rightful place at the forefront of genomics as a model of modern, patient-centric, preventive health care.

ACKNOWLEDGEMENTS

The author is supported by the Intramural Research Program of the National Human Genome Research Institute. The opinions expressed here do not necessarily represent the views of the National Institutes of Health.

DISCLOSURE

The author is a member of the medical ethics committee of the Illumina Corp and receives royalties from Genentech, Inc. The author receives salary and grant support from the National Institutes of Health.

Submitted 30 August 2018; accepted: 31 August 2018
Published online: 4 October 2018

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Advance online publication 4 October 2018. doi:10.1038/s41436-018-0303-2