associated with diverse genetic and epigenetic alterations. In addition to the mutation of the *COQ6* gene, 11 shared heterozygous variants, including *MYPN*, *COQ6*, *CKMT1A*, *CYP11A1*, *DUOX1*, and *TRIOBP*, were identified in members of the family affected by disease. Potential pathogenetic roles of these mutations should also be carefully studied and excluded. We accept these as limitations of our study. In addition, we hope this brief report serves the useful purpose of stimulating such additional genetic studies in the future. We believe that future studies will bring further insight into the oncogenic roles of alterations of CoQ10 biosynthesis genes and novel mechanisms of schwannomatosis without known causative gene alterations.

DISCLOSURE

The authors declare no conflict of interest.

Keqiang Zhang, PhD[1], Jia-Wei Lin, MD[2], Wen-Ta Chiu, PhD, MD[3] and Yun Yen, PhD, MD[1,4]

[1]Department of Molecular Pharmacology, Beckman Research Institute of the City of Hope National Medical Center, Duarte, California, USA; [2]Department of Neurosurgery, Taipei Medical University–Shuang Ho Hospital, Taipei, Taiwan; [3]Institute of Injury Prevention and Control, Taipei, Taiwan; [4]PhD Program for Cancer Biology and Drug Discovery, College of Medical Science and Technology, Taipei Medical University, Taipei, Taiwan. Correspondence: Yun Yen (yyen@coh.org)

REFERENCES

1. Trevisson E, Clementi M, Salviati L. Is there a link between *COQ6* and schwannomatosis? *Genet Med* 2015;17:312–313.
2. Zhang K, Lin JW, Wang J, et al. A germline missense mutation in *COQ6* is associated with susceptibility to familial schwannomatosis. *Genet Med* 2014;16:787–792.
3. Deutschbauer AM, Jaramillo DF, Proctor M, et al. Mechanisms of haploinsufficiency revealed by genome-wide profiling in yeast. *Genetics* 2005; 169:1915–1925.
4. Portakal O, Ozkaya O, Erden Inal M, Bozan B, Kosan M, Sayek I. Coenzyme Q10 concentrations and antioxidant status in tissues of breast cancer patients. *Clin Biochem* 2000;33:279–284.

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doi:10.1038/gim.2014.212

Key emerging themes for assessing the cost-effectiveness of reporting incidental findings

To the Editor: We congratulate Bennette et al. for an innovative first step to addressing a challenging issue—how to assess the cost-effectiveness of reporting incidental findings (IFs) discovered with sequencing technologies—as described in their article, "The Cost-Effectiveness of Returning Incidental Findings From Next-Generation Genomic Sequencing."[1] At the University of California at San Francisco Center for Translational and Policy Research on Personalized Medicine, we are conducting related analyses that further inform these issues.[2] We would like to highlight key emerging themes and suggestions for future work and to discuss the importance of some assumptions made by Bennette et al. that could greatly impact the findings of cost-effectiveness analyses.

Of particular importance for future work is the need to examine the likely cost-effectiveness in real-world settings. Bennette et al.[1] assumed that individuals would remain at risk but *not* be detected through any other means during their lifetime (other than for familial hypercholesterolemia). However, particularly for the two most prevalent conditions they examined (hereditary breast and ovarian cancer; Lynch syndrome), many individuals with the conditions will be identified even if there is no sequencing. By assigning all benefits to the detection of IFs, the cost-effectiveness of reporting IFs in real-world settings will seem better. We thus suggest that future analyses consider including a background rate of detection rather than using "nothing" as a comparator, which would enable the findings to be more comparable with those of other analyses that follow the standard approach of comparing an intervention to current practice.[3]

Other simplifying assumptions that Bennette et al.[1] acknowledge could affect their results. First, aggregating results of different models is a reasonable first step, but it is unclear how sensitive the results are to the assumptions of individual models and whether it is reasonable to aggregate possibly heterogeneous findings—with different populations and modeling approaches—into an overall cost-effectiveness ratio. Many previous studies (e.g., Vegter et al.[4]) have noted the heterogeneity found across cost-effectiveness analyses of genetic testing. In future research, it would be helpful to develop a transparent means of aggregating results so that they can be readily replicated. Second, future analyses could take into account interactive effects, namely, the differences in life-expectancy from finding one result when evaluating the potential effects of another result. The likelihood of finding more than one IF in a given person is very small in the current analysis but will increase as more returnable IFs are identified in the future. Third, in real clinical practice, it is possible that unproven and potentially costly management strategies could be used in a fraction of individuals receiving a given IF result. Not accounting for this may miss an important determinant of downstream clinical effectiveness and cost.

In sum, the approach of Bennette et al.[1] provides an important initial approach for analyses that can continue to refine approaches to defining and measuring the value of new genomic testing technologies that return multiple results. It should be noted that the results to date suggest that reporting IFs may be cost-effective in certain scenarios but are not generally

cost-saving as some have claimed or hoped, and that many simplifying assumptions may overestimate the cost-effectiveness of reporting IFs. Future research can continue to refine the modeling approaches and estimates used.

DISCLOSURE

The authors declare no conflict of interest.

Kathryn A. Phillips, PhD[1], Uri Ladabaum, MD, MS[2,3], Mark J. Pletcher, MD, MPH[3,4], Deborah A. Marshall, PhD[3,5] and Michael P. Douglas, MS[3]

[1]Department of Clinical Pharmacy, Center for Translational and Policy Research on Personalized Medicine (TRANSPERS), Philip R. Lee Institute for Health Policy; and Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, California, USA; [2]School of Medicine, Stanford University, Sanford, California, USA; [3]Department of Clinical Pharmacy, Center for Translational and Policy Research on Personalized Medicine (TRANSPERS), University of California San Francisco, San Francisco, California, USA; [4]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California, USA; [5]Department of Community Health Sciences, Cumming School of Medicine; O`Brien Institute for Public Health, University of Calgary, Calgary, Alberta, Canada. Correspondence: Kathryn A. Phillips (Kathryn.Phillips@ucsf.edu)

REFERENCES

1. Bennette CS, Gallego CJ, Burke W, Jarvik GP, Veenstra DL. The cost-effectiveness of returning incidental findings from next-generation genomic sequencing. *Genet Med*; e-pub ahead of print 13 November 2014.
2. Phillips KA, Trosman JR, Kelley RK, Pletcher MJ, Douglas MP, Weldon CB. Genomic sequencing: assessing the health care system, policy, and big-data implications. *Health Aff (Millwood)* 2014;33:1246–1253.
3. Gold MR. *Cost-Effectiveness in Health and Medicine*. Oxford University Press: New York, 1996.
4. Vegter S, Boersma C, Rozenbaum M, Wilffert B, Navis G, Postma MJ. Pharmacoeconomic evaluations of pharmacogenetic and genomic screening programmes: a systematic review on content and adherence to guidelines. *Pharmacoeconomics* 2008;26:569–587.

doi:10.1038/gim.2015.13

Response to Phillips *et al*.

To the Editor: We thank Dr Phillips and colleagues for their interest in our work and for raising several important points in assessing the cost-effectiveness of reporting incidental findings from clinical sequencing.[1]

We agree with the importance of comparing a novel intervention to current practice—indeed a key concept in cost-effectiveness analysis—and would like to clarify that we included a "baseline rate of detection" within our original modeling framework.[2] In other words, individuals who carry a mutation that is not returned as an incidental finding receive ongoing surveillance according to practice guidelines. It is because of this baseline rate of detection that the individual-level incremental health benefits associated with incidental findings for the more prevalent conditions (hereditary breast and ovarian cancer and Lynch syndrome) are relatively small, despite the availability of effective prophylactic interventions that could dramatically reduce an individual's risk.

Regarding heterogeneous findings from different models, we evaluated all relevant studies for each clinical condition and specifically noted heterogeneity in results, as well as how different assumptions or inputs in each study likely contributed to these differences. We also independently verified with several clinical genetics experts the key assumptions and modeling inputs of each study included in our policy model. Because of space limitations, this work is summarized in the article's Supplementary Methods and Materials online for interested readers.

The potential for interactive effects between incidental findings within our modeling framework is low based on the frequency of the diseases considered as incidental findings; we estimated ~0.01% chance for an otherwise healthy 45-year-old. We therefore decided that the considerable increase in model complexity to account for potential interactive effects was not worth the negligible expected difference in our results. We agree that if the number of potential incidental findings to be returned increases dramatically, this will be an important point to revisit.

Finally, it is possible that unproven and potentially costly management strategies could be used in a fraction of individuals who receive an incidental finding. It is also possible that individuals with an incidental finding will receive *less* treatment than expected based on recommended management strategies developed primarily for selected high-risk populations. We addressed this uncertainty in our model by assigning probabilistic distributions to these costs. However, there is a paucity of evidence about how individuals will respond to receiving incidental findings in terms of health-care utilization or other behaviors, which highlights the importance of ongoing research efforts such as the National Human Genome Research Institute–funded Clinical Sequencing Exploratory Research program.[3] We look forward to refining and updating our model in response to the evidence that emerges from this and other research.

DISCLOSURE

The authors declare no conflict of interest.

Caroline S. Bennette, PhD, MPH[1], Wylie Burke, MD, PhD[2], Gail P. Jarvik, MD, PhD[3] and David L. Veenstra, PharmD, PhD[4]

[1]Department of Pharmacy, Pharmaceutical Outcomes Research and Policy Program, University of Washington, Seattle, Washington, USA; [2]Department of Bioethics and Humanities, University of Washington, Seattle, Washington, USA; [3]Department of Medicine and Genome Sciences and Division of Medical Genetics, University of Washington, Seattle, Washington, USA; [4]Department of Pharmacy, Pharmaceutical Outcomes Research and Policy Program, University of Washington, Seattle, Washington, USA. Correspondence: David L. Veenstra (veenstra@u.washington.edu)

REFERENCES

1. Phillips KA, Ladabaum U, Pletcher MJ, Marshall DA, Douglas MP. Key emerging themes for assessing the cost-effectiveness of reporting incidental findings. *Genet Med* 2015;17:314–315.
2. Bennette CS, Gallego CJ, Burke W, Jarvik GP, Veenstra DL. The cost-effectiveness of returning incidental findings from next-generation genomic sequencing. *Genet Med*; e-pub ahead of print 13 November 2014.
3. Berg JS, Amendola LM, Eng C, et al.; Members of the CSER Actionability and Return of Results Working Group. Processes and preliminary outputs for identification of actionable genes as incidental findings in genomic sequence data in the Clinical Sequencing Exploratory Research Consortium. *Genet Med* 2013;15:860–867.

doi:10.1038/gim.2015.11