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.

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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.

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