Overall, these data only demonstrate that the p.Asp208His substitution is a "typical" loss-of-function *COQ6* mutation; they do not provide any explanation of why it is associated with schwannomatosis, and it is not possible to exclude that this variant is just an incidental finding unrelated to the disease is not possible.

Schwannomatosis requires adequate follow-up to promptly detect novel schwannomas and possible complications. The identification of a novel gene associated with schwannomatosis has important implications in genetic counseling because it allows both the prenatal and the presymptomatic diagnosis of this adult-onset condition in at-risk family members.

Unless further experimental evidence explaining the link between the *COQ6* heterozygous missense mutation and the susceptibility to schwannomatosis is provided, we are skeptical about the opportunity of screening for the *COQ6* gene in patients affected by schwannomatosis (and screening for schwannomas in individuals with heterozygous mutations in *COQ6*).

DISCLOSURE

The authors declare no conflict of interest.

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Response to Trevisson *et al*.

To the Editor: First, we thank Trevisson et al.[1] for their valuable contribution to this subject and their comments on our brief report. In our study, we reported a familiar schwannomatosis without mutations of *SMARCB1/INI1/hSNF5* and *LZTR*, the two known causative genes for schwannomatosis. Using genome and exome sequencing, we found a heterozygous loss-of-function mutation of the coenzyme Q10 (CoQ10) biosynthesis monooxygenase 6 (*COQ6*) gene in patients affected by disease.[2] CoQ10 is an electron carrier in the mitochondrial respiratory chain, as well as a lipid-soluble antioxidant implicated in protecting cells from damage by reactive oxygen species. Its biosynthesis is still not well characterized in human cells. Mutations in CoQ10 biosynthesis genes, including *COQ4* and *COQ6*, cause primary CoQ10 deficiency. The manifestations of primary CoQ10 deficiency are very heterogeneous, and CoQ10 deficiency has been involved in many common disorders with increased oxidative stress, such as neurodegenerative diseases, cancer, cardiovascular diseases, diabetes mellitus, aging, and Alzheimer disease. It is well known that chronic increases in oxidative stress may trigger transformation and contribute to cancer progression by amplifying genomic instability. We proposed that the halpoinsufficiency of *COQ6* monooxygenase due to a loss-of-function mutation may lead to CoQ10 deficiency and chronic overproduction of reactive oxygen species in Schwann cells, thereby predisposing to schwannomatosis.

A critical issue of the hypothesis is whether heterozygous loss-of-function *COQ6* causes haploinsufficiency. A previous study of yeast found that haploinsufficiency of *COQ6* resulted in a mild reduction of fitness in a medium containing glucose.[3] Moreover, we assumed that the haploinsufficiency of the *COQ6* gene and CoQ10 deficiency may be conditional, dynamic, and tissue/cell specific. For example, one study found that cellular and tissue concentrations of CoQ10 decrease with age, and cellular concentrations below a critical threshold are incompatible with life. Furthermore, carcinogenesis is determined not only by genetic alterations but also gene–environment interaction, as well as metabolism, and not all transgenic mice with the exactly same genetic background and alterations may develop cancers. In addition, germ-line abnormalities associated with cancer may be detected in every cell in the body or only in the tumor cells. Interestingly, despite the presence of a constitutional genetic abnormality that might affect growth regulatory pathways in all cells, people are generally predisposed to only certain tumor types. The average age at disease onset was ~40 years for this familial schwannomatosis, indicating a chronic disease progression. In this particular family, we considered that the loss-of-function *COQ6* allele may lead to a chronic or conditional haploinsufficiency of *COQ6* in a cell/tissue-specific manner.

So far, the roles of mutations of CoQ10 biosynthetic genes in cancers are completely unknown. The association is only now coming of age, for example, the most recent cancer genomic studies identify *COQ2* gene mutations in human melanoma, colon and rectal cancers, ovarian carcinoma, and glioblastoma multiforme. In addition, more than 48 missense mutations of the *COQ6* gene have been identified in various human cancers (http://cancer.sanger.ac.uk/cancergenome/projects/cosmic). Furthermore, abnormally low plasma concentrations of CoQ10 have been found in a number of cancer types, including cervical cancer, breast cancer, and melanoma.[4] Although intensive research is needed to further explore the underlying mechanisms, increasing data have strongly indicated an undetermined implication of CoQ10 biosynthesis gene mutations in carcinogenesis.

Indeed, the exact oncogenic mechanism of the loss-of-function *COQ6* gene in disease remains a challenging question to be elucidated. Cancer is a complex multigenic disease

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

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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