RESPONSE TO COMMENT ON JOHNSON ET AL.

Cost-effectiveness Analysis of Routine Screening Using Massively Parallel Sequencing for Maturity-Onset Diabetes of the Young in a Pediatric Diabetes Cohort: Reduced Health System Costs and Improved Patient Quality of Life. Diabetes Care 2019;42:69–76

Stephanie R. Johnson,[1,2,3,4] *Hannah E. Carter,*[5] *Paul Leo,*[2] *Samantha A. Hollingworth,*[6] *Elizabeth A. Davis,*[7,8,9] *Timothy W. Jones,*[7,8,9] *Louise S. Conwell,*[1,4] *Mark Harris,*[1,3,4] *Matthew A. Brown,*[2] *Nicholas Graves,*[5] *and Emma L. Duncan*[2,4,10]

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We thank Estrella and Simmons (1) for their letter regarding implications and limitations of our study (2).

We agree that most of the cost and health benefits from identifying maturity-onset diabetes of the young (MODY) mutations in children with diabetes is due to conversion from insulin to oral hypoglycemic agents, as discussed in our article. Further, we agree that conversion is not always possible, although, as illustrated in their case, substantial reduction in dose may be possible even if insulin cannot be ceased entirely. As shown in Table 1 and Fig. 2, our sensitivity analysis tested for uncertainty in conversion rates, varying this parameter from 50% to 100% (based on limited published data); routine testing remained beneficial within this range.

We agree that a limitation of targeted sequencing is an inability to screen genes not included in the target panel. An alternative would be whole-exome sequencing (WES), which we have demonstrated is sensitive and specific for MODY variant detection (3) and allows future reinterrogation of newly discovered genes. Several recent publications demonstrate improved diagnostic yield from reanalyzing exome data due to improved bioinformatics, updated genetic databases, new literature, and better phenotyping (4,5). Our sensitivity analysis showed cost benefits of routine screening with costs as high as AU$1,000/test. Although currently more expensive than panel-based approaches, WES costs are rapidly falling; WES may soon prove financially competitive, with added benefits of flexibility and reinterrogation.

Our modeling focused on per-individual cost of genetic testing in children with diabetes and did not include family cascade testing. It is reasonable to expect that identification of MODY in other family members with diabetes might result in similar clinical benefits (therapeutic change from insulin to sulfonylureas, improved quality of life, etc.). Relevantly, screening for a specific variant usually costs much less than the comprehensive initial screening of a proband.

However, whether cascade testing should be offered to all family members or limited to individuals with hyperglycemia is contentious. The benefit of cascade testing all family members depends in part on penetrance, which (as discussed) is difficult to establish for MODY. For some types of MODY with other clinical features (e.g., *HNF1B*-associated renal tract abnormalities), screening may be relevant even in the absence of diabetes. However, genetic testing of presymptomatic individuals raises the possibility of genetic

[1]*Department of Endocrinology and Diabetes, Lady Cilento Children's Hospital, South Brisbane, Queensland, Australia*
[2]*Institute of Health and Biomedical Innovation, Faculty of Health, Queensland University of Technology, Translational Research Institute, Woolloongabba, Queensland, Australia*
[3]*University of Queensland Diamantina Institute, Translational Research Institute, University of Queensland, Woolloongabba, Queensland, Australia*
[4]*Faculty of Medicine, University of Queensland, Herston, Queensland, Australia*
[5]*Institute of Health and Biomedical Innovation, Faculty of Health, Queensland University of Technology, Brisbane, Queensland, Australia*
[6]*School of Pharmacy, University of Queensland, Woolloongabba, Queensland, Australia*
[7]*Department of Diabetes and Endocrinology, Perth Children's Hospital, Perth, Western Australia, Australia*
[8]*Telethon Kids Institute, University of Western Australia, Perth, Western Australia, Australia*
[9]*School of Paediatrics and Child Health, University of Western Australia, Perth, Western Australia, Australia*
[10]*Department of Endocrinology, Royal Brisbane and Women's Hospital, Herston, Queensland, Australia*

Corresponding author: Emma L. Duncan, emma.duncan@qut.edu.au

S.R.J. and H.E.C. are joint first authors.

discrimination. In addition, the cost implications of cascade testing will vary from family to family due to varying family size. Thus, modeling costs of cascade testing would be extremely complex and were not included in this study. Similar issues pertain to prenatal testing; this too was not included in our model.

Lastly, the prevalence data for this analysis only included pathogenic/likely pathogenic variants based on American College of Medical Genetics and Genomics criteria (6); variants of uncertain significance were not included. We agree with Estrella and Simmons (1) that pathogenicity of variants—even those previously published as causative in particular families—is difficult to establish definitively (7). This lack of certainty, along with unknown penetrance, has important and time-consuming implications for genetic counseling. Again, these added complexities were not included in our modeling.

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