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

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We welcome the report by Johnson et al. (1) demonstrating cost-effectiveness of routine targeted massively parallel sequencing for known genes associated with monogenic diabetes in a pediatric cohort in Western Australia. This is an important approach that we hope can be implemented in other parts of Australia and beyond. Most of the benefit in this cohort was through the transition of therapy from insulin to sulfonylureas in patients with known variants of genes associated with sulfonylurea responsiveness such as *HNF4A*-diabetes.

However, not all patients with *HNF4A*-diabetes can be successfully transitioned to sulfonylureas from insulin (estimated at 80% for the Markov modeling [1]). We now report a case of a 24-year-old woman seen at our young adult service, diagnosed with type 1 diabetes at 6 years of age, subsequently found to have the p.R114 W variant in *HNF4A* at 21 years of age. Blood glucose levels were erratic (10–22.2 mmol/L), and she required almost 200 units of insulin daily. A sulfonylurea was trialled for unclear reasons a few years after the diagnosis of type 1 diabetes and caused severe hypoglycemia. After the *HNF4A*-diabetes was diagnosed, gliclazide was trialled but was inadequate as a single agent. The combination of a sodium–glucose cotransporter 2 inhibitor (first reported use in *HNF4A*-diabetes), glucagon-like peptide 1 agonist, metformin, and gliclazide allowed reduction of insulin doses and stabilization of her glucose levels, with $HbA_{1c}$ levels decreasing from 12.1% (109 mmol/mol) to 7.9% (63 mmol/mol). This patient is part of a large family of indigenous descent with an autosomal dominant history of young-onset diabetes and aggressive vascular disease. Her sister was diagnosed with type 1 diabetes at 16 years of age, her father was diagnosed with type 1 diabetes at 22 years of age, and all (except one) of her paternal aunts and uncles were diagnosed with diabetes (both type 1 and 2) at a young age. Cascade testing for family members is underway. The contribution of her Aboriginal background to the difficulty in managing her *HNF4A*-diabetes is unclear but raises the issue of wider complexities of other genetic modifiers and their potential contribution to the phenotype, such as that seen in our patient.

Molecular medicine is a constantly evolving landscape, with the pathogenicity of some variants questioned due to inconsistent clinical and laboratory data. The p.R114 W variant described here that caused this distinct *HNF4A* phenotype is one example (2). Furthermore, targeted massively parallel sequencing misses some as yet unknown genes that may cause monogenic diabetes in isolation or as part of a syndrome.

This case raised a number of issues for consideration, and we therefore wondered whether the following (usually provided by Clinical Genetics Services in Australia) were considered as part of "standard care" in the health economic modeling undertaken: *1*) cascade testing of family members of the proband, *2*) preimplantation genetic diagnosis and subsequent genetic counseling of probands who want an unaffected child in future, and *3*) interpretation, genetic counseling, and yearly follow-up of probands and their families with variants of unknown significance.

**Duality of Interest**. No potential conflicts of interest relevant to this article were reported.

## References

1. Johnson SR, Carter HE, Leo P, 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 quality of life. Diabetes Care 2019;42:69–76
2. Laver TW, Colclough K, Shepherd M, et al. The common p.R114W *HNF4A* mutation causes a distinct clinical subtype of monogenic diabetes. Diabetes 2016;65:3212–3217

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