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 | https://doi.org/10.2337/dc18-0261

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Received 3 February 2018 and accepted 12 October 2018

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc18-0261/-/DC1.

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OBJECTIVE

Maturity-onset diabetes of the young (MODY) is an autosomal dominant form of diabetes, with multiple causative genes. Some MODY subtypes can be treated with sulfonylureas instead of insulin, improving glycemic control, complication rates, quality of life (QoL), and costs. Using massively parallel sequencing (MPS), we recently determined the prevalence of pathogenic/likely pathogenic MODY variants in an Australian pediatric diabetes cohort. Here, these data are used to estimate cost-effectiveness of using MPS for MODY in all pediatric diabetes cases compared with standard practice (sequencing limited to individuals with specific clinical features).

RESEARCH DESIGN AND METHODS

A Markov decision model was developed to estimate incremental costs and quality-adjusted life-years (QALYs) of MPS screening, modeled over 30 years. We used our observed prevalence of 2.14% compared with 0.7% for standard practice, based on published data. The probabilities and utility weightings of long-term diabetes complications were based on HbA_{1c} and estimated from published data. A series of one-way sensitivity analyses were performed using the net monetary benefit framework.

RESULTS

Routine MPS screening for MODY was more effective and less costly than standard care screening, with 26 QALYs gained and 1,016,000 AUD (782,000 USD) saved per 1,000 patients. Cost of screening was fully offset within 10 years. Routine MPS screening remained dominant until MODY prevalence fell to <1.1%.

CONCLUSIONS

Routine MPS screening for MODY in the pediatric population with diabetes could reduce health system costs and improve patient QoL. Our results make a compelling argument for routine genetic screening in all children with presumed type 1 diabetes mellitus.

Maturity-onset diabetes of the young (MODY) is the commonest form of monogenic diabetes and can arise from heterozygous mutations in one of many genes (*HNF4A*, *GCK*, *HNF1A*, *PDX1*, *HNF1B*, *NEUROD1*, *KLF11*, *CEL*, *PAX4*, *INS*, *BLK*, *ABCC8*, and *KCNJ11* [rev. in 1]). Individuals with four MODY subtypes (*HNF4A*, *HNF1A*, *KCNJ11*, and *ABCC8*) may be able to use oral sulfonylureas instead of insulin, resulting in improved metabolic control, fewer complications of diabetes (e.g., retinopathy, renal failure), lower hypoglycemia rates, lower cost, and improved quality of life (QoL) (2). Further, the *GCK* subtype is nonprogressive and requires no treatment and minimal follow-up (3). MODY is not an autoimmune condition; thus, affected individuals do not require annual screening for other autoimmune diseases as is standard in type 1 diabetes mellitus (T1DM).

MODY is frequently underrecognized and misdiagnosed as T1DM or type 2 diabetes mellitus (T2DM) (4). Currently, MODY screening is recommended based on clinical grounds alone—i.e., individuals with diabetes who lack classical features of T1DM (e.g., diabetes autoantibodies) or T2DM (e.g., obesity and insulin resistance) who have an autosomal dominant family history of diabetes (5). However, diabetes autoantibodies may occur in MODY (6), and the increasing prevalence of pediatric obesity means BMI alone is less useful for distinguishing between T2DM and MODY. Thus, screening for MODY on clinical grounds alone may underestimate its true prevalence, as is evident from differences between prevalence rates of MODY in databases where testing was prompted by clinical criteria (6) compared with comprehensive population screening (7).

Iterative screening for MODY using Sanger sequencing is expensive (750–2,500 AUD per gene) and inefficient. In contrast, massively parallel sequencing (MPS) enables simultaneous sequencing of all MODY genes at lower cost. MPS is rapidly translating into clinical practice (8). We recently screened an entire pediatric population with diabetes using targeted MPS, demonstrating a prevalence of pathogenic/likely pathogenic MODY variants of 2.10% (7). Considering only cases identified initially as T1DM or obvious monogenic cases, the prevalence was 2.14%. In contrast, prevalence of MODY was 0.65% in a German and Austrian pediatric diabetes database (German-Austrian Diabetes-Patienten-Verlaufsdokumentation [DPV] database) (6); here, screening appears to have been instigated only in children with specific clinical features, and only three MODY genes were sequenced.

The aim of this study was to assess the long-term cost-effectiveness of targeted MPS screening for MODY in children presenting with diabetes, using population-based Australian prevalence data.

RESEARCH DESIGN AND METHODS

The cost-effectiveness analysis estimated expected costs and outcomes associated with routine targeted MPS screening for MODY at diagnosis for all children with presumed T1DM, using data from comprehensive MODY screening of the Western Australian Childhood Diabetes Database (WACDD). This database captures 99% of children with T1DM in Western Australia (state population 2.5 million). The comparator group was defined as "standard care," with ad hoc sequencing for MODY on clinical grounds as directed by physicians. Prevalence was determined using published data of the DPV database, which includes all children with diabetes in Germany and Austria (40,757 patients diagnosed before 18 years of age). The standard care arm was not drawn from WACDD, as our previous research caused a high local awareness of MODY (MODY prevalence 1.2% in WACDD, considering only those cases identified through clinical suspicion [i.e., prior to entire cohort screening] compared with 0.65% in the DPV database).

Costs were estimated from the Australian health care system perspective and included treatment costs plus costs associated with complications of diabetes over a 30-year time horizon. The net effectiveness of each strategy was valued in terms of quality-adjusted life-years (QALYs). Incremental cost-effectiveness was measured in terms of cost per QALY gained. A discount rate of 3% was applied to all future cost and QALY outcomes.

We performed a series of one-way sensitivity analyses to explore the impact of varying the modeled assumptions within plausible ranges of uncertainty.

Model Structure, Cohort, and Assumptions

The decision tree for the initial diagnosis and treatment pathways for a cohort of pediatric patients with presumed T1DM is shown in Fig. 1. We assumed that MPS was 100% specific and 100% sensitive in detecting pathogenic variants in MODY genes (9) and that the presence of a pathogenic variant was diagnostic of MODY. Characteristics of the modeled cohort were based on 1,259 pediatric patients with diabetes whose data were entered into WACDD between December 2013 and December 2015, including 1,242 children diagnosed with T1DM and 17 children diagnosed with MODY (testing instigated by their treating clinician).

Key model parameters included clinical features and MODY prevalence (Table 1). Mean age at diagnosis and mean HbA_{1c} were based on WACDD data. The underlying prevalence of MODY was taken from our previous study of this cohort (7). For this current study, it was assumed that all pathogenic/likely pathogenic MODY variants result in the clinical phenotype of MODY. Neonatal diabetes (NDM) constitutes another clinical subgroup of monogenic diabetes, and >50% of NDM cases are due to variants in MODY genes (10). Thus, these calculations include subjects with NDM, as these cases would also be detected by targeted MPS for MODY genes.

In the standard care arm, we assumed that patients were diagnosed with MODY following clinical suspicion and Sanger sequencing, with prevalence of 0.65% (6).

Successful conversion from insulin to sulfonylureas for MODY cases with mutations in *HNF1A*, *HNF4A*, *ABCC8*, or *KCNJ11* was estimated as 80%, extrapolated from studies in NDM and limited studies in MODY (2,11–13). Failure of sulfonylurea responsiveness over time was not modeled, as there is no long-term data in MODY. However, it was assumed that patients successfully converted to sulfonylureas would maintain a lifetime HbA_{1c} of 6.9% (52 mmol/mol) (2,11), which, it was assumed, would contribute to fewer long-term diabetes complications (many of which are directly proportional to HbA_{1c} [14]).

A Markov cohort model was developed based on the Sheffield Type 1

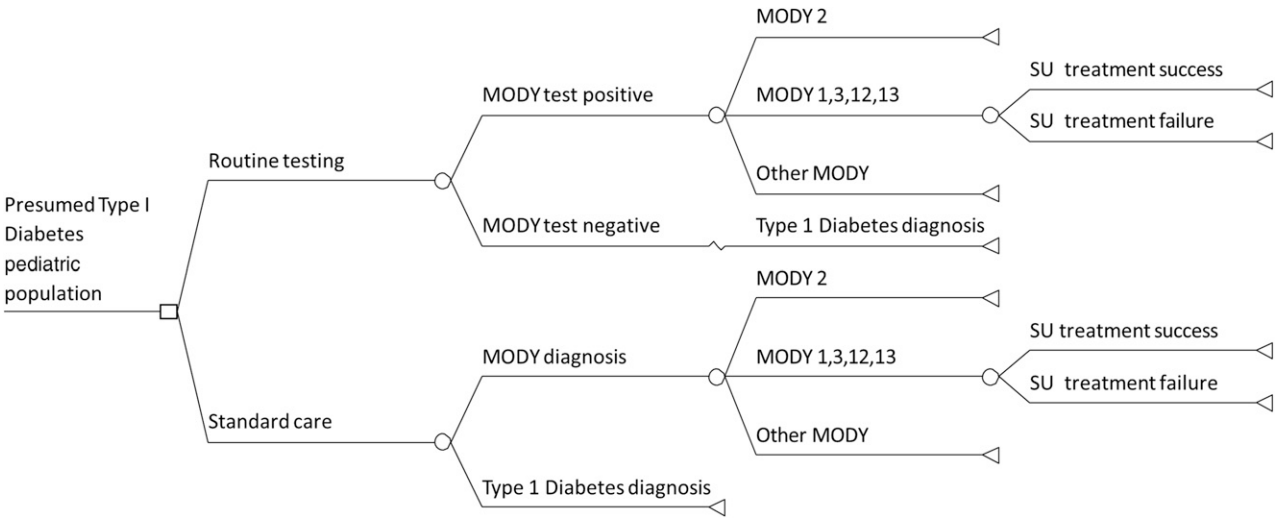

Figure 1—A decision model for genetic testing. MODY 1, *HNF4A*-MODY; MODY 2, *GCK*-MODY; MODY 3, *HNF1A*-MODY; MODY 12, *ABCC8*-MODY; MODY 13, *KCNJ11*-MODY; SU, sulfonylurea.

Diabetes Model (15) to examine the impact of long-term diabetes complications. We attached the model to the initial decision tree and characterized the progression of disease over time by assigning a series of annual probabilities of developing complications to both the routine and standard care cohorts. Modeled complications included nephropathy, neuropathy, retinopathy, cardiovascular disease, severe hypoglycemia, and diabetic ketoacidosis. Patients could die of end-stage renal disease, cardiovascular events, or other (non–diabetes-related) causes at any time in the model. The probabilities assigned to long-term complications accounted for each patient's age, duration of diabetes, treatment type, and HbA_{1c} (14). Assumptions and transition probabilities associated with long-term complications are presented in Supplementary Table 2.

Resource Use and Costs

Resources and costs associated with MODY testing and ongoing treatment of diabetes were determined (Supplementary Table 1). MPS laboratory costs were estimated at 500 AUD (383 USD) per sample. Sanger sequencing costs were current average per-gene sequencing costs (750 AUD [574 AUD]) and assumed that one MODY gene was sequenced per case and that all sequenced cases had a mutation identified.

Table 1—Clinical characteristics of the modeled cohort: base case and lower and upper estimates

	Base case	Lower	Upper	Source
MODY prevalence (as detected by MPS)	2.14%	1%	6.5%	Refs. 7,20
MODY prevalence (as detected by standard care)	0.65%	0.1%	1.5%	Ref. 6
Proportion of MODY that is MODY 2 (MPS)	48%	20%	83%	Refs. 7,20,21
Proportion of MODY that is MODY 2 (standard care)	62%	20%	83%	Refs. 6,20,21
Proportion of MODY that is MODY 1, 3, 12, or 13 (MPS)	41.4%	4.4%	53%	Refs. 7,20,33
Proportion of MODY that is MODY 1, 3, 12, or 13 (standard care)	35%	4.40%	53%	Refs. 6,21
Rate of successful conversion to SU in MODY 1, 3, 12, and 13	80%	50%	100%	Refs. 2,10
Lifetime HbA_{1c} for insulin-treated individuals#	7.8%, 62 mmol/mol	7.3%, 56 mmol/mol	8.9%, 74 mmol/mol	Data from WACDD and ref. 22
Lifetime HbA_{1c} for SU-treated individuals	6.9%, 52 mmol/mol	5.5%, 37 mmol/mol	7.0%, 53 mmol/mol	Ref. 2
Health utility of insulin-treated individuals#	0.86	0.69	0.96	Ref. 10
Health utility of SU-treated individuals and those with MODY 2	0.96	0.86	1.00	Ref. 10
Discount rate	3%	0%	5%	
Cost of MPS test (AUD)	500	80	1,000	

Health utility, where utility of 0 is equivalent to death and utility of 1 is equivalent to full health; MODY 1, *HNF4A*-MODY; MODY 2, *GCK*-MODY; MODY 3, *HNF1A*-MODY; MODY 12, *ABCC8*-MODY; MODY 13, *KCNJ11*-MODY; Ref., reference; SU, sulfonylurea. #Insulin-treated individuals include subjects with T1DM and with MODY for whom sulfonylureas were unsuccessful.

Ongoing treatment protocols were based on current Australian clinical practice. Specifically, individuals with MODY do not require annual screening for celiac or thyroid disease. Additionally, *GCK*-MODY cases require minimal follow-up (except during pregnancy). Rate of insulin pump use (48%) was obtained from WACDD.

Resource use items were valued using current Australian prices listed on the Medicare Benefits Schedule (16) and Pharmaceutical Benefits Schedule (17). Costs associated with long-term diabetes complications were derived from the literature and inflated to 2016 AUD (18) (Supplementary Table 3).

QoL Effects

QALYs were derived by weighting the time spent in a given health state by the health utility value associated with that state (where utility of 0 is equivalent to death and utility of 1 is equivalent to full health). We assigned a base case health utility for a life with complication-free T1DM of 0.86 (19). This improved to 0.96 for non–insulin-requiring diabetes, which included individuals with MODY successfully converted to sulfonylureas and those with *GCK*-MODY. Utility decrements associated with various diabetes complications were subtracted from these base case values accordingly (Supplementary Table 4).

Sensitivity Analyses

We conducted a series of one-way sensitivity analyses to examine the uncertainty around the base case parameters (Table 1 and Fig. 2). We considered the impact of testing a population with MODY prevalence ranging from 1 to 6.5%, reflecting the prevalence of MODY in an antibody-negative T1DM population (20). We used estimates from the published literature for ranges around proportions of each MODY subtype, based on reports from two population-based studies (one using traditional Sanger sequencing and one using MPS) (20,21).

Given the paucity of data on the percentage of individuals with MODY successfully converted to sulfonylureas, an arbitrary range of 50–100% was chosen. The range of HbA_{1c} in the insulin-treated group was taken from different cohorts in the Hvidore study (22), and HbA_{1c} in MODY cases treated with sulfonylureas was taken from various case reports and small case series (11–13).

The range of pump use in insulin-treated patients was 14–65%, reflecting differing clinical practices (23,24). Utility values for insulin-treated patients were varied from 20% below the base case of 0.86 (i.e., 0.69) up to the point where utility was equivalent to non–insulin-treated patients (0.96). Similarly, the utility value for non–insulin-treated patients ranged from a lower limit equivalent to that of insulin-treated patients (0.86) to an upper limit of 1.00 (i.e., full health).

MPS is not currently commercially available in many laboratories. To reflect the uncertainty in pricing, we considered cost of testing to be variable from a lower limit of 80 AUD (laboratory reagent cost price assuming batching) to an upper limit of 1,000 AUD (765 USD) with base case 500 AUD.

The discount rate was tested over a range between 0 and 5%. All other costs,

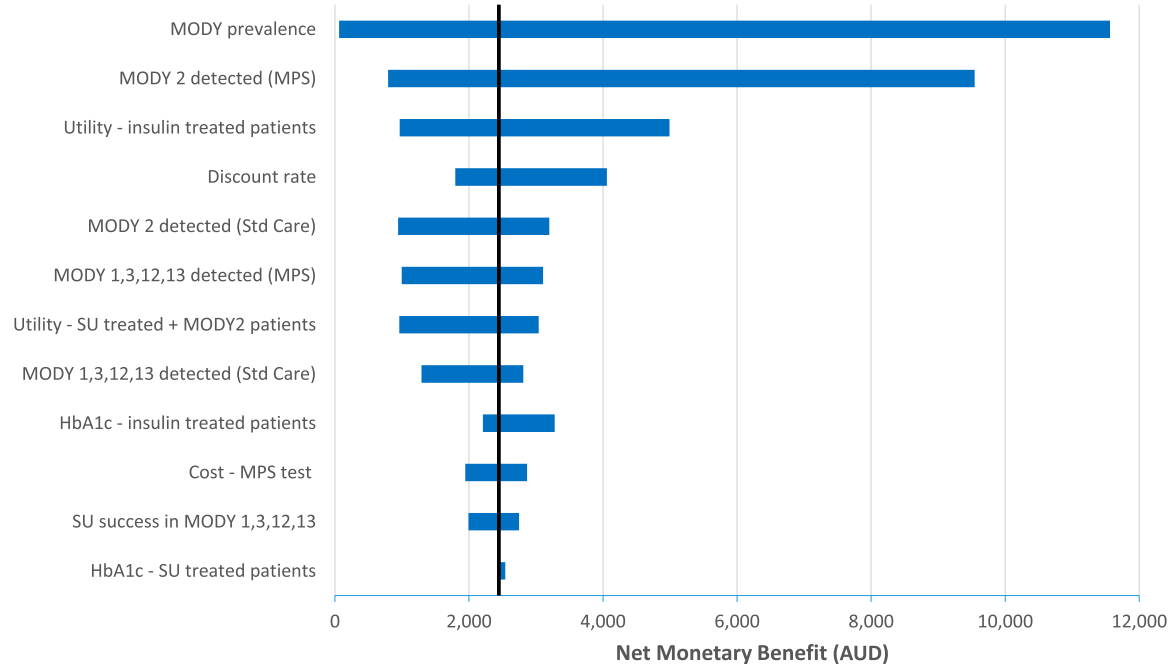

Figure 2—Sensitivity analysis for 30-year NMB associated with routine genetic testing. Base case NMB = 2,702 AUD based on WTP threshold of 64,000 AUD. MODY 1, *HNF4A*-MODY; MODY 2, *GCK*-MODY; MODY 3, *HNF1A*-MODY; MODY 12, *ABCC8*-MODY; MODY 13, *KCNJ11*-MODY; Std Care, standard care; SU, sulfonylurea. Ranges for bars: MODY prevalence, 1.0–6.5%; MODY 2 detected by standard care or MPS, 20–83%, and discount rate, 0–5%; MODY 1, 3, 12, and 13 detected using MPS or standard care, 4–53%; probability of SU success, 50–100%; baseline utility for insulin-treated subjects, 0.69–0.86; baseline utilities for non–insulin-treated subjects, 0.86–1.0; HbA_{1c} for insulin-treated subjects, 7.3–8.9% (56–74 mmol/mol); HbA_{1c} for non–insulin-treated subjects, 5.5–7.0% (37–53 mmol/mol); discount rate, 0–5%; and cost of MPS, 80–1,000 AUD. (A high-quality color representation of this figure is available in the online issue.)

utilities, and transition probabilities were varied by 20% above and below base case values.

The results of the sensitivity analyses are presented in terms of their net monetary benefits (NMBs) (Fig. 2). NMB is a summary statistic that represents the value of an intervention in monetary terms when a willingness-to-pay (WTP) threshold for a QALY is known (NMB = [WTP threshold × incremental effectiveness] − incremental costs). A positive NMB indicates that a strategy is cost-effective, while a negative NMB indicates that the costs outweigh the benefits. We adopted a WTP threshold of 64,000 AUD (48,969 USD) per QALY, based on a recent published estimate representing a standard WTP in the Australian context (25).

RESULTS

Routine MPS screening for MODY results in an average increase of 0.026 QALYs per patient over a 30-year time period (Table 2). The main drivers were QoL improvements in MODY subjects able to cease insulin therapy and modest reductions in the proportion of patients experiencing long-term complications.

In addition to producing health benefits, routine screening reduced total health system costs by an average of 1,016 AUD (782 USD) per patient over 30 years. This translated to an incremental cost-effectiveness ratio of −39,076 AUD (−30,076 USD) per QALY gained and was considered highly cost-effective. The costs of routine screening were fully offset within 10 years. Savings increased each year owing to the lower ongoing costs of sulfonylureas relative to insulin and the lower risk of long-term complications.

Routine MPS screening for MODY was dominant (i.e., the intervention costs less and is at least as effective as the comparator) at both 10 and 30 years. It was the dominant strategy for all of the one-way sensitivity analyses and for underlying MODY prevalence of ≥1.1%.

When we adopted a WTP of 64,000 AUD per QALY, the NMB of routine MPS screening was 2,702 AUD. This result was robust and remained positive across all the one-way sensitivity analyses (Fig. 2). The costs and QoL benefits of the change from insulin to sulfonylurea therapy accounted for 78% of the total NMB, far outweighing the benefits of reduced diabetes complications.

CONCLUSIONS

This is the first cost-effectiveness analysis of routine screening for monogenic diabetes using targeted MPS. Routine genetic testing for MODY using targeted MPS is both more effective and less costly over 10 and 30 years than current standard care (testing predicated on clinical recognition). Health benefits of routine MPS screening were apparent within a year, with costs fully offset within 10 years. These results were robust to the effects of uncertainty within the modeled parameters: routine testing remained dominant, with prevalence as low as 1.1% and sequencing costs as high as 1,000 AUD (765 USD) per patient.

Most of the reduced cost and QoL benefits resulted from the use of sulfonylureas rather than insulin. The change in health utility for sulfonylurea use was extrapolated from data in adults with T2DM, as such data are not available for

Table 2—Base case cost-effectiveness analysis results

	After 10 years			After 30 years		
Modeled cohort outcomes	Routine MPS testing	Testing based on clinical suspicion only	Difference	Routine MPS testing	Testing based on clinical suspicion only	Difference
Microalbuminuria (%)	16.20	16.33	−0.13	42.93	43.26	−0.33
Macroalbuminuria (%)	1.87	1.89	−0.02	13.36	13.50	−0.13
ESRD (%)	0.18	0.19	0.00	6.26	6.32	−0.06
Death from ESRD (%)	0.03	0.03	0.00	2.63	2.66	−0.03
Background retinopathy (%)	3.38	3.41	−0.03	10.30	10.40	−0.10
Proliferative retinopathy (%)	0.40	0.40	0.00	1.99	2.01	−0.02
Macular edema (%)	1.24	1.25	−0.01	6.09	6.14	−0.05
Blindness (%)	0.01	0.01	0.00	0.21	0.22	0.00
Neuropathy (%)	8.30	8.39	−0.07	24.18	24.39	−0.21
Amputation (%)	0.76	0.77	−0.01	5.50	5.55	−0.05
Myocardial infarction (%)	0.00	0.00	0.00	0.82	0.83	−0.01
Stroke (%)	0.00	0.00	0.00	0.19	0.19	0.00
Heart failure (%)	0.00	0.00	0.00	0.33	0.33	0.00
Death from CVD events (%)	0.00	0.00	0.00	0.14	0.14	0.00
Hypoglycemia (mean episodes per person)	0.55	0.55	−0.01	1.76	1.78	−0.02
Ketoacidosis (mean episodes per person)	0.45	0.46	−0.01	1.44	1.46	−0.02
Alive (%)	99.97	99.96	0.00	97.30	97.27	0.03
Total costs (AUD)	49,904	50,427	−522.53	147,431	148,448	−1,017
QALYs	7.5137	7.5030	0.0107	17.0793	17.0530	0.0263
ICER (AUD/QALY)	MPS test is dominant			MPS test is dominant		

CVD, cardiovascular disease; ESRD, end-stage renal disease; ICER, incremental cost-effectiveness ratio.

those with sulfonylurea-treated MODY (neither in adults nor children) or in children with T2DM. We modeled for this uncertainty within the sensitivity analysis (Fig. 2). Further, ceasing insulin as a child may have greater QoL benefits than ceasing in adulthood because the risk (and fear) of severe hypoglycemia with insulin is greater in children and their parents (26). We did not include any QoL benefits for parents and other family members; thus, the QoL benefits are conservative estimates; if there is improvement in QoL for other family members, this will be added gain for the community.

The first analysis of the benefits of genetic testing in monogenic diabetes was performed for NDM (10). Genetic testing was cost saving, with increased QALYs, even though testing was with Sanger sequencing of two genes, which cost more than targeted MPS. Although a greater proportion of NDM can be treated by sulfonylureas compared with MODY, the benefits of sulfonylureas are similar in both groups. Naylor et al. (27) evaluated the cost-effectiveness of genetic testing (using Sanger sequencing) for MODY in a young adult population with T2DM. They based their assumptions on a theoretical prevalence of MODY of 2% in the T2DM population—an estimate yet to be verified. Routine genetic screening in this population was not as cost-effective as we have shown here, mainly due to lower rates of insulin use in populations with T2DM.

The current study is based on real-world data from a pediatric diabetes clinic with essentially complete case ascertainment for T1DM for a large catchment population (i.e., the entirety of Western Australia); thus, we provide an accurate estimate of benefit to the health services of this state.

A strength of the Markov modeling approach is the ability to synthesize the best available evidence in a systematic and transparent manner to estimate costs and benefits associated with alternative treatment protocols across patient subgroups. We could also estimate the relative rates of long-term diabetes complications for insulin-treated and non–insulin-treated patients. In combination with data on patient-rated preferences and health system costs, we had an evidence-based means of projecting the long-term cost-effectiveness of routine screening.

We made a number of assumptions in our model, including 100% sensitivity and specificity of targeted MPS. To date, all studies of targeted sequencing have identified all previously identified variants (28–30). Other assumptions include prevalence of MODY gene variants of 2.14% and complete penetrance. The prevalence figure may be an underestimate: two-thirds of subjects in WACDD had both consent and DNA to allow MPS, but the denominator used for prevalence was the entire T1DM and MODY population. Furthermore, only pathogenic or likely pathogenic variants were included; variants of unknown significance were excluded, again potentially biasing the prevalence figure downward. Conversely, this prevalence figure may be an overestimate, as penetrance may not be 100% (i.e., the presence of a MODY variant does not necessarily result in a MODY phenotype [31]). It is very difficult to assess penetrance of MODY; most testing to date has been in families with a clear history supportive of autosomal dominant diabetes, which clearly biases the outcome. While the Framingham Heart Study and Jackson Heart Study cohorts revealed a low prevalence of diabetes among those with a MODY variant (31), no study has reported penetrance in a population with a high pretest probability, i.e., preexisting diabetes. Until a complete population has been sequenced for MODY genes, with subsequent in-depth clinical assessment of MODY phenotype, exact penetrance of MODY variants remains unknown. Routine sequencing remained dominant down to a prevalence of 1.1% (equivalent to a penetrance of ≈50%).

The probabilities of successful transfer from insulin to sulfonylureas were based on limited evidence drawn mainly from case reports (2,11–13). There is no large-scale study of the efficacy of sulfonylureas in MODY or treatment failure over time. Nonetheless, the sensitivity analyses suggested that the cost-effectiveness result was robust to uncertainty around these parameters (modeled from 50 to 100% success). Modeling mainly focused on the benefits of switching treatment regimens. Other benefits of identifying MODY include screening for and treatment of clinical features associated with specific subtypes (e.g., urogenital abnormalities in *HNF1B*-MODY), improved gestational management (particularly for *GCK*-MODY), and cascade screening for this autosomal-dominant disease in family members. None of these benefits were included in the model.

Screening might be of greater cost benefit in populations with higher prevalence of MODY, e.g., those with antibody-negative T1DM (20). However, as routine testing is so dominant in terms of cost and QALY, it may prove unnecessary to assess antibody status for routine screening to remain cost-effective (although we have not modeled this specifically). We have also not modeled costs and complication rates for a pediatric population with T2DM. Our previous study in a pediatric population showed that prevalence of pathogenic/likely pathogenic variants in MODY genes was higher in presumed T2DM than in presumed T1DM (both antibody-positive and antibody-negative cases), though we acknowledge that far fewer T2DM cases were sequenced. Although prevalence of MODY variants may be higher in T2DM, the lower use of insulin in this cohort may offset cost benefits, as most of the benefit in this analysis was derived from switching from insulin to sulfonylureas.

We assumed that standard care (i.e., genetic testing based on clinical suspicion) would result in each clinically identified case having a mutation detectable by Sanger sequencing, of only one gene, at a cost of 750 AUD. There are no data on the sensitivity of Sanger sequencing in standard care, or the average number of genes screened before testing is either successful or abandoned. Thus, identification of MODY cases in standard care is likely to cost much more than we have estimated here.

The use of MPS in clinical diagnosis of many conditions has translated into clinical practice (8), but availability is far from universal and costs vary greatly. We used a base case cost of 500 AUD (383 USD) per MPS test to reflect the likely true costs of reagents, bioinformatics, and personnel time, acknowledging that these costs depend on throughput and expertise and that commercial costs usually build in a profit margin. Nonetheless, MPS testing remained cost saving up to 1,000 AUD (765 USD) per test.

Our study made some unavoidable assumptions given the dearth of literature in MODY (e.g., use of published data from T1DM or T2DM or from adult rather than pediatric cohorts). The deterministic sensitivity analysis allowed for the identification of threshold values to highlight scenarios where changes to key assumptions had the potential to change the overall cost-effectiveness result. This enables the reader to make judgements around the model's assumptions that are informed by their own experience, context, or the latest evidence and, in turn, to understand how these judgments may affect the modeled outcomes. It may be possible to fine-tune our results over time as long-term clinical outcome data in MODY become available and as sequencing becomes more routine in clinical care generally.

The current International Society for Pediatric and Adolescent Diabetes guidelines for MODY recommend genetic testing in three situations: *1*) a family history of diabetes in one parent and one other first-degree relative; *2*) when a patient with diabetes lacks characteristics of T1DM (no autoantibodies, low or no insulin requirement); and *3*) when a patient with diabetes lacks characteristics of T2DM (marked obesity, acanthosis nigricans). The guidelines were created at a time when testing was neither readily available nor inexpensive, and do not take into account the possibility of de novo mutations or incomplete penetrance (32) or the generalized obesity epidemic. Moreover, among the DPV cohort, autoantibodies were present in 17% of MODY cases. Our study challenges the restriction of genetic testing based on clinical criteria, as we have shown that, given the current low costs of sequencing, routine MPS in all newly diagnosed children presumed to have T1DM produces QALY gains while reducing health system costs. The adoption of this evidence-based and cost-effective approach will lead to individualization of therapy and improved patient outcomes—and may save some children from a lifetime of insulin.

Acknowledgments. The authors thank the participants, the research staff at the Telethon Kids Institute, in particular Adam Retterath and Wade Brownlee and the staff of the Brown laboratory at Queensland University of Technology, in particular Sharon Song, Lisa Anderson, and Jessica Harris for their assistance with MPS; Jessica Harris and Lawrie Wheeler for Sanger sequencing; Dr. Jonathan Ellis for bioinformatics analysis; Janelle MacFarlane and Nirubasini Paramalingam for invaluable assistance with the ethics submission process; and Dr. David Pennisi for help with proofreading and editing the manuscript.

Funding. S.R.J. was supported by a University of Queensland research scholarship. M.A.B. is supported by a National Health and Medical Research Council Senior Principal Research Fellowship.

Duality of Interest. The research for this study was supported by an Australasian Pediatric Endocrine Care research grant (WI205296), funded by Pfizer. No other potential conflicts of interest relevant to this article were reported.

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript.

Author Contributions. S.R.J. contributed to study design, sample acquisition, DNA processing, sequencing analysis, data acquisition, and model creation and analysis and led the writing. H.E.C. contributed to study design; was responsible for data acquisition, model creation, and running the model; contributed to data analysis; and also led the writing. P.L. provided bioinformatics support. S.A.H. contributed to study design, data acquisition, and running the model and data analysis. E.A.D. and T.W.J. were responsible for sample acquisition. L.S.C. and M.H. contributed to study design. M.A.B. contributed to study design and DNA processing. N.G. contributed to study design and model design. E.L.D. devised the study, contributed to study design and data analysis, and led the writing. S.R.J., H.E.C., P.L., S.A.H., E.A.D., T.W.J., L.S.C., M.H., M.A.B., N.G., and E.L.D. critically reviewed the manuscript and approved the manuscript. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. E.L.D. is the guarantor of this work and, as such, had full access to all the data in this study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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