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

Stephanie R Johnson*, FRACP [1,2,3,4]

Hannah E Carter*, PhD [5]

Paul Leo, PhD [2]

Samantha A Hollingworth, PhD [6]

Elizabeth A Davis, PhD [7,8,9]

Timothy W Jones, MD [7,8,9]

Louise S Conwell, PhD [1,4]

Mark Harris, MD [1,3,4]

Matthew A Brown, MD [2]

Nicholas Graves, PhD [5]

Emma L Duncan, PhD [2, 4,10]

* Denotes joint first authors

1. Department of Endocrinology and Diabetes, Lady Cilento Children's Hospital, 501 Stanley Street, South Brisbane, QLD 4101, Australia

2. Institute of Health and Biomedical Innovation, Faculty of Health, Queensland University of Technology, Translational Research Institute, Ipswich Rd Woolloongabba QLD 4102, Australia.

3. University of Queensland Diamantina Institute, University of Queensland, Translational Research Institute, 37 Kent St, Woolloongabba QLD 4102

4. Faculty of Medicine, University of Queensland, Herston, QLD 4006 Australia

5. Institute of Health and Biomedical Innovation, Faculty of Health, Queensland University of Technology, 60 Musk Ave Kelvin Grove QLD 4059 Australia

6. School of Pharmacy, University of Queensland, 20 Cornwall St Woolloongabba QLD 4102 Australia

7. Department of Diabetes and Endocrinology, Princess Margaret Hospital for Children, Perth, Western Australia, Australia

8. Telethon Kid's Institute, University of Western Australia Telethon Kids Institute, The University of Western Australia, Perth, Australia

9. The School of Paediatrics and Child Health, The University of Western Australia, Perth, Western Australia, Australia

10. Department of Endocrinology, Royal Brisbane & Women's Hospital, Butterfield St Herston QLD 4029

Corresponding author   Prof Emma Duncan

                              Department of Endocrinology and Diabetes

Royal Brisbane and Women's Hospital

Herston 4029

emma.duncan@qut.edu.au

Phone +61 7 36468111

Abstract

Objectives

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 glycaemic control, complication rates, quality of life, and costs. Using massively parallel sequencing (MPS), we recently determined the prevalence of pathogenic/likely pathogenic MODY variants in an Australian paediatric diabetes cohort. Here these data are used to estimate cost-effectiveness of using MPS for MODY in all paediatric diabetic cases, compared with standard practice (only sequencing 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, modelled over 30 years. We used our observed prevalence of 2.14% compared to 0.7% for standard practice, based on published data. The probabilities and utility weightings of long-term diabetes complications were based on HbA1c, 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 AU$1016000 (US$782000) saved per 1,000 patients. Cost of screening was fully offset within 10 years. Routine MPS screening remained dominant until MODY prevalence fell below 1.1%.

Conclusion

Routine MPS screening for MODY in the pediatric diabetes population could reduce health system costs and improve patient quality of life. Our results make a compelling argument for routine genetic screening in all children with presumed T1DM.

Maturity-onset diabetes of the young (MODY) is the commonest form of monogenic diabetes and can arise from heterozygous mutations in multiple genes (*HNF4A*, *GCK*, *HNF1A*, *PDX1*, *HNF1B*, *NEUROD1*, *KLF11*, *CEL*, *PAX4*, *INS*, *BLK*, *ABCC8* and *KCNJ11;* reviewed in [1]). Individuals with four MODY subtypes (*HNF4A, HNF1A, KCNJ11, ABCC8*) may be able to use oral sulphonylureas 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 non-progressive 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 under-recognized 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 antibodies) or T2DM (e.g. obesity and insulin resistance) who have an autosomal dominant family history of diabetes [5]. However, diabetes antibodies 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 to comprehensive population screening (Johnson *et al*. [accepted] *Pediatric Diabetes*).

Iterative screening for MODY using Sanger sequencing is expensive (AU$750-2500 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 [7]. We recently screened an entire pediatric diabetes population using targeted MPS, demonstrating a prevalence of pathogenic/likely pathogenic MODY variants of 2.10% (Johnson *et al.* [accepted] *Pediatric*

Diabetes). Considering only cases identified 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.

Methods

This 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. This database captures 99% of children with T1DM in WA (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 <18 years of age). The standard care arm was not drawn from WACDD as our previous research caused a high local awareness of MODY (1.2% identified through clinical suspicion in WACDD, compared to 0.65% in the DPV database).

Costs were estimated based on the Australian health care system and included treatment costs plus costs associated with complications of diabetes over a 30 year time frame. 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 modelled 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 Figure 1. We assumed 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 modelled cohort were based on 1,257 pediatric diabetes patients 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 HbA1c were based on WACDD data. The underlying prevalence of MODY was taken from our previous study of this cohort [10]. For this current study, it was assumed 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 [11]. 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 sulphonylureas 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, 12-14]. Failure of sulphonylurea responsiveness over time was not modelled, as there is no long-term data in MODY. However, it was assumed that patients successfully converted to sulphonylureas would maintain a lifetime HbA1c of 6.9% (52 mmol/mol) [2, 12], which was assumed would contribute to fewer long-term diabetes complications (many of which are directly proportional to HbA1c [15]).

A Markov cohort model was developed based on the Sheffield Type 1 Diabetes Model [16] 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 relative probability of developing complications in any given year to each patient cohort. Modelled complications included nephropathy, neuropathy, retinopathy, cardiovascular disease, severe hypoglycemia, and diabetic ketoacidosis. Patients could die from 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 HbA1c [15]. Assumptions and transition probabilities associated with long-term complications are presented in Supplementary Table 1.

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 AU$500 (US$383) per sample. Sanger sequencing costs were current average per-gene sequencing costs (AU$750 [US$574]), and assumed that one MODY gene was sequenced per case and that all sequenced cases had a mutation identified.

Ongoing treatment protocols were based on current Australian clinical practice. Specifically, individuals with MODY do not require annual screening for coeliac and/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 (MBS) [17] and Pharmaceutical Benefits Schedule (PBS) [18]. Costs associated with long-term diabetes complications were derived from the literature and inflated to 2016 dollars [19] (Supplementary Table 3).

Quality of life (QoL) effects

Quality-adjusted life years (QALYs) were derived by weighting the time spent in a given health state by the utility value associated with that state (where utility of zero is equivalent to death and utility of one is equivalent to full health). We assigned a base case utility for a life with complication-free T1DM of 0.86 [20]. This improved to 0.96 for non-insulin requiring diabetes, which included individuals with MODY successfully converted to sulphonylureas [20] 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 Figure 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 [21]. 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 sequencing, and one using MPS [21, 22].

Given the paucity of data on the percentage of individuals with MODY successfully converted to sulphonylureas, an arbitrary range of 50-100% was chosen. The range of HbA1c in the insulin treated group was taken from different cohorts in the Hvidore study [23], and HbA1c in MODY cases treated with sulphonylureas was taken from various case reports and small case series [1, 2].

The range of pump use in insulin treated patients was 14% to 65%, reflecting different clinical practice [24, 25]. 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 this laboratory. To reflect the uncertainty in pricing, cost of testing was varied from a lower limit of AU$80 (laboratory reagent cost price assuming batching) to an upper limit of AU$1,000 ([US$765] base case AU$500).

The discount rate was tested over a range between 0% and 5%. All other costs, 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 (NMB; Figure 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 AU$64,000 (US$48969) per QALY, based on a recent published estimate representing a standard WTP in the Australian context [26].

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 AU$1,016 (US$782) per patient over 30 years. This translated to an incremental cost effectiveness ratio of - AU$39,076 (- US$30,076) per QALY gained and was considered highly cost-effective. The costs of routine screening were fully offset within 10 years. Savings increased each year due to the lower ongoing costs of sulphonylureas 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 years and 30 years. It was the dominant strategy for all the one-way sensitivity analyses and for underlying MODY prevalence of 1.1% and above.

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

Discussion

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 modelled parameters: routine testing remained dominant with prevalence as low as 1.1% and sequencing costs as high as AU$1,000 (US$765) per patient.

Most of the reduced cost and QoL benefits resulted from the use of sulphonylureas rather than insulin. The change in health utility for sulphonylurea use was extrapolated from data in adults with T2DM, as such data are not available for sulphonylurea-treated MODY (neither in adults nor children) nor in children with T2DM. We have modeled for this uncertainty within the sensitivity analysis (Figure 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 [27]. 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 [11]. 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 sulphonylureas than can MODY, the benefits of sulphonylureas are similar in both groups. Naylor *et al*. evaluated the cost effectiveness of genetic testing (using Sanger sequencing) for MODY in a young adult population with T2DM [28]. They based their assumptions on a theoretical prevalence of MODY of 2% in the T2DM population, which estimate is 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 T2DM populations.

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 entire of Western Australia); thus we provide an accurate estimate of benefit to the health services of this state [10].

A strength of the Markov modelling 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 and non-insulin treated patients. When combined 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 [29-31]. 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 downwards. 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 [32]). 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. Whilst the Framingham and Jackson cohort revealed a low prevalence of diabetes among those with a MODY variant [32], no study has reported penetrance in a population with a high pre-test probability, i.e. pre-existing 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. Sequencing remained dominant down to a prevalence of 1.1% (which is equivalent to a penetrance of <50%)

The probabilities of successful transfer from insulin to sulphonylureas were based on limited evidence drawn mainly from case reports [2, 12-14]. There is no large scale study of the efficacy of sulphonylureas in MODY and/or treatment failure over time. Nonetheless, the sensitivity analyses suggested that the cost-effectiveness result was robust to uncertainty around these parameters (modelled from 50% to 100% success). Modelling 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 [21]. 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 modelled this specifically). We have also not modelled costs and complication rates for a pediatric T2DM population. 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), acknowledging 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 sulphonylureas.

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 AU$750. There are no data on the sensitivity of Sanger sequencing in standard care, nor 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 [7] but availability is far from universal and costs vary greatly. We used a base case cost of AU$500 (US$383) per MPS test to reflect the likely true costs of reagents, bio-informatics 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 AU$1,000 (US$765) 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 modelled outcomes. Our results may be able to be 'fine-tuned' over time as long-term clinical outcome data in MODY becomes available – and as sequencing becomes more routine in clinical care generally.

The current International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines for MODY recommend genetic testing in three situations: a) a family history of diabetes in one parent and one other first-degree relative; b) when a patient with diabetes lacks characteristics of T1DM (no antibodies, low or no insulin requirement) c) 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 and/or incomplete penetrance [33]) or the generalized obesity epidemic. Moreover, the

DPV cohort showed 17% of MODY cases had antibodies. 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 presumed T1DM children 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.

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, sulphonylurea.

Figure 2: Sensitivity analysis for 30 year net monetary benefit (NMB) associated with routine genetic testing.

Base case NMB = AU$2,702 based on willingness to pay of AU$64,000.

MODY 1, *HNF4A*-MODY; MODY 2, *GCK*-MODY; MODY 3, *HNF1A*-MODY; MODY 12, *ABCC8*-MODY; MODY 13, *KCNJ11*-MODY; MPS, massively parallel sequencing; NMB, net monetary benefit; Std Care, standard care; SU, sulphonylurea.

Ranges for bars:

- MODY prevalence 1.0 – 6.5%

- MODY 2 detected by standard care or MPS 20 – 83%; discount rate 0% to 5%

- MODY 1,3,12,13 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

- HbA1c for insulin treated subjects 7.3% – 8.9% (56 – 74 mmol/mol)

- HbA1c for non-insulin treated subjects 5.5% – 7.0% (37- 53 mmol/mol)

- Discount rate 0 – 5%

- cost of MPS AU$80 – AU$1,000

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Table 1

Clinical characteristics of the modelled cohort: base case, lower and upper estimates

Variable	Base case	Lower	Upper	Source
MODY prevalence (as detected by MPS)	2.14%	1%	6.5%	[21] Johnson et al. [accepted] *Pediatric Diabetes*
MODY prevalence (as detected by standard care)	0.65%	0.1%	1.5%	[6]
Proportion of MODY that is MODY 2 (MPS)	48%	20%	83%	[21, 22] Johnson et al. [accepted] *Pediatric Diabetes*
Proportion of MODY that is MODY 2 (standard care)	62%	20%	83%	[6, 21, 22]
Proportion of MODY that is MODY 1,3,12,13 (MPS)	41.4%	4.4%	53%	[21, 34] Johnson et al. [accepted] *Pediatric Diabetes*
Proportion of MODY that is MODY 1,3,12,13 (Standard care)	35%	4.40%	53%	[6, 22]
Rate of successful conversion to SU in MODY 1,3,12,13	80%	50%	100%	[2, 11]
Lifetime HbA1c for of insulin-treated individuals[#]	7.8% 62mmol/mol	7.3% 56mmol/mol	8.9% 74mmol/mol	Data from WACDD and [23]
Lifetime HbA1c for of sulphonylurea-treated individuals	6.9% 52mmol/mol	5.5% 37mmol/mol	7.0% 53mmol/mol	[2]
Health utility of insulin-treated individuals[#]	0.86	0.69	0.96	[11]
Health utility of sulphonylurea -treated individuals and MODY 2	0.96	0.86	1.00	[11]
Discount rate	3%	0%	5%	
Cost – MPS test (AUD)	$500	$80	$1000	

[#] Insulin-treated individuals include Type 1 diabetes and MODY subjects for whom sulphonylureas were unsuccessful

MODY, maturity-onset diabetes of the young; MODY 1, *HNF4A*-MODY; MODY 2, *GCK*-MODY; MODY 3, *HNF1A*-MODY; MODY-12, *ABCC8*-MODY; MODY 13, *KCNJ11*-MODY; MPS, massively parallel sequencing

Table 2: Base case cost-effectiveness analysis results

Modelled cohort outcomes	After 10 years			After 30 years		
	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
Macroalbuminiura (%)	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 (AU$)	49,904	50,427	−522.53	147,431	148,448	−1,017
QALYs	7.5137	7.5030	0.0107	17.0793	17.0530	0.0263
ICER (AU$/QALY)	MPS test is dominant			MPS test is dominant		

CVD, cardiovascular disease; ESRD, End stage renal disease; ICER, incremental cost effectiveness ratio; MPS, massively parallel sequencing; QALY, quality adjusted life years.