Online Supplement for "The Impact of Biomarker Screening and Cascade Genetic Testing on the Cost-Effectiveness of MODY Genetic Testing"

	HNF1A/HNF4A – mean (SD)	GCK – mean (SD)	T1D – mean (SD)	T2D – mean (SD)
Gender – female (%)	68.1[1]	46.0[1]	49.7[2]	62.9[3]
Race – black (%)*	34.1[1]	37.7[1]	10.9[2]	60.7[3]
Smokers (% in given age group)[4,5]	≤12:**0%;** (12, 14):**2.2%;** [14, 18):**8.0%**; [18, 25):**14.7%;** [25, 45):**20.6%;** [45, 65):**19.3%;** ≥65:**10.1%**			
Initial Age (years)	14.1 (3.1)[1] Min 10, Max 20	12.3 (3.7)[1] Min 10, Max 20	10.8 (3.9)[2] Min 10, Max 20	14.8 (2.0)[3] Min 10, Max 20
Diabetes duration (years)	1.4 (1.7)[1] Min 0.5, Max 3.0	1.1 (1.8)[1] Min 0.5, Max 3.0	0.7 (0.5)[2] Min 0.5, Max 3.0	1.6 (1.5)[3] Min 0.5, Max 3.0
SBP (mm Hg)	99 (12)[2] Min 85, Max 145	99 (12)[2] Min 85, Max 145	99 (12)[2] Min 85, Max 145	115.6 (13.3)[3] Min 85, Max 160
Updated†	***124 (8)***[6] ***Min 90, Max 180***	***127 (19)***[7] ***Min 90, Max 180***	***124 (10)***[6] ***Min 90, Max 180***	***143 (20)***[8] ***Min 90, Max 180***
Total cholesterol (mg/dl)	159 (27)[2] Min 100, Max 300	159 (27)[2] Min 100, Max 300	159 (27)[2] Min 100, Max 300	N/A
Updated†	***167 (35)***[6] ***Min 100, Max 300***	***188 (34)***[7] ***Min 100, Max 300***	***166 (29)***[6] ***Min 100, Max 300***	**N/A**
HDL (g/dl)	56 (13)[2] Min 30, Max 85	56 (13)[2] Min 30, Max 85	56 (13)[2] Min 30, Max 85	41.6 (9.7)[9] Min 25, Max 60
Updated†	***53 (17)***[6] ***Min 30, Max 85***	***63 (21)***[7] ***Min 30, Max 95***	***53 (15)***[6] ***Min 30, Max 85***	***46 (11.6)***[8] ***Min 25, Max 65***
HbA1c (%)	7.0 (1.6)[1] Min 5.6, Max 10.2	6.4 (0.4)[1] Min 5.6, Max 7.6	7.6 (1.5)[2] Min 5.0, Max 12	7.7 (2.3)[3] Min 5.0, Max 12
BMI (kg/m^2)				32.4 (10.4)[1]‡ Min 15, Max 50
Updated†				***30.5 (6)***[8] ***Min 15, Max 50***
LDL (mg/dl)				102.6 (28.3)[9] Min 50, Max 180
Updated†				***116 (23.2)***[8] ***Min 60, Max 190***
Heart Rate				78.7 (14.2)[10] Min 50, Max 120
Updated†				***72 (12)***[8] ***Min 50, Max 120***
eGFR (mL min^{-1} /1.73m^2)				117 (0.8)[11] Min 115, Max 119
Updated†		**N/A**		***77.6 (15)***[8] ***Min 0, Max 108***
Hemoglobin (g/l)				13.5 (1.3)[12] Min 9.5, Max 17.5
Updated†				***14.5 (1.3)***[8] ***Min 10.5, Max 18.5***
WBC (10^6/ml)				9.0 (1.8)[12] Min 3.6 Max 14.4
Updated†				***6.8 (1.8)***[8] ***Min 1.4, Max 12.2***
Atrial fibrillation (%)				0
Updated†				***0.5***[8]
PVD (%)				0
Updated†				***2.7***[13]
Microalbuminuria (%)				6.3[14]
Updated†				***17.7***[8]

Supplementary Table 1: Baseline and updated characteristics.

T1D = type 1 diabetes; T2D = type 2 diabetes; SBP = systolic blood pressure; HDL = high density lipoprotein; HbA1c = hemoglobin A1c; LDL = low density lipoprotein; eGFR = estimated glomerular filtration rate; WBC = white blood cells; PVD = peripheral vascular disease.

*Although most studies included more than two race categories, white and black were normalized to 100% to be compatible with all models.

† Values updated starting at age 20.

‡ T2D patient information taken from Pihoker et al[1] assumed Ab (-) C-pep (+) non-MODY patients were similar to patients with T2D.

Cost (testing and treatment)	Mean Costs (2018 USD)*	References				
	CV Event	**Probability**[15]	**CVD Death**	**Probability**[15]		
HNF1A/HNF4A[15] **T1D**[15]	MI	0.53	MI hospital men	0.393		
			MI hospital women	0.364		
			MI within 1 year aged 0-65	0.1522		
			MI within 1 year aged 65-75	0.186		
			MI within 1 year aged 75-100	0.2508		
	Stroke	0.07	Stroke within 1 month	0.124		
			Stroke within 1 year	0.1063		
	Revascularization	0.12	Revascularization within 1 year	0.057		
	Angina	0.28	-	-		
T2D[8]	**CV complication rates per risk equations from UKPDS OM2**[8]					
GCK Age <20	**No CV complications (author assumption)**					
GCK Age 20 – 49[16] **(30-year Framingham)**	**CV Event***	**Probability (Male/Female)**[16]	**Demographics**	**Probability of Death Within 1 Year**[17]		
	Fatal/Nonfatal Stroke	0.230 / 0.393	Black, Female	0.14		
			Black, Male	0.08		
			White, Female	0.15		
			White, Male	0.11		
	Nonfatal MI	0.622 / 0.507	-	-		
	CVD Death	0.148 / 0.100	-	-		
GCK Age ≥50[17] **(ASCVD)**	**CV Event†**	**Probability**[17,18]	**Demographics**	**Probability of Death Within 1 Year**[17]		
				Age 50-64	**Age 64-65**	**Age ≥ 75**
	Fatal/Nonfatal Stroke	0.2523	Black, Female	0.14	0.21	0.27
			Black, Male	0.08	0.21	0.25
			White, Female	0.15	0.18	0.36
			White, Male	0.11	0.17	0.33
	MI	0.4246	Black, Female	0.10	0.21	0.31
			Black, Male	0.09	0.22	0.19
			White, Female	0.05	0.18	0.29
			White, Male	0.03	0.14	0.27
	CVD Death	0.3229	-	-	-	-

Supplementary Table 2: Probability of cardiovascular events and cardiovascular mortality.

MI = Myocardial infarction; T1D = Type 1 diabetes; T2D = Type 2 diabetes; CV = Cardiovascular; CVD = Cardiovascular disease.

* Pencina et al.[16] reported incident CVD events as either MI, fatal/nonfatal stroke, or cardiovascular death. Cardiovascular death was assumed to include death from MI. Given the young age and generally healthy nature of this cohort of GCK patients, no 1-year chance of death following MI was assumed. Stroke death probability estimates from the AHA represent data from patients aged 45-64 and are therefore most likely slight overestimates.[17]

† CV event probabilities for non-diabetic patients were from an Atherosclerosis Risk in Communities (ARIC) study.[18] ARIC is a multiethnic study drawn upon to create the ASCVD model. CVD events were reported as fatal/nonfatal stroke, CVD death, and fatal CHD/nonfatal MI. Based on national estimates from the AHA, 83.45% of the fatal CHD/nonfatal MI events were assumed to be MIs, and the remaining 16.55% fatal CHD events were added to the "CVD Death" category.[17]

Proband Genetic Testing	3732.96 (includes 1 outpatient visit at 112.96)	Commercial Reference Laboratory Pricing (Bureau of Labor Statistics 2017†)
Cascade Genetic Testing	612.96 (includes 1 outpatient visit at 112.96)	Commercial Reference Laboratory Pricing (Bureau of Labor Statistics 2017†)
Biomarker screening (C-peptide and GAD65 + IA-2 Abs)	C-peptide: 12.25 GAD65: 14.75 IA-2: 14.75	Commercial Reference Laboratory Pricing
Sulfonylurea therapy‡	658.43	Laiteerapong et al.[19]
Metformin therapy‡	985.48	Laiteerapong et al.[19]
Other oral therapy‡ §	3321.46	Laiteerapong et al.[19]
Metformin/sulfonylurea‡	1544.21	See above (additive)
Metformin/other oral dual therapy‡	4207.24	See above (additive)
Insulin therapy (not including per kg amount)	5250.79	**See Supplementary Table 4**
Metformin/insulin dual therapy (not including per kg amount)	6136.57	See above (additive) (includes SMBG cost from insulin therapy)
HNF1A/HNF4A control treatment	3,759.83 + 16.56 per kg	**See Supplementary Table 4**
HNF1A/HNF4A treatment following sulfonylurea failure | |	1698.92 + 13.44 per kg	**See Supplementary Table 4**
GCK control treatment	1621.43 + 2.21 per kg	**See Supplementary Table 4**
T1D Treatment	5250.79 + 35.62 per kg	**See Supplementary Table 4**
T2D Treatment[19]	1,334.03 + 3.40 per kg	Medication breakdown and costs from Laiteerapong et al.[19]; **see Supplementary Table 4** for insulin cost calculations

Supplementary Table 3: Screening and treatment costs.

Abs = autoantibodies; SMBG = self-monitoring of blood glucose; T1D = type 1 diabetes; T2D = type 2 diabetes.

*Costs converted to 2018 USD (https://www.bls.gov/data/inflation_calculator.htm).

† Calculated based on hourly mean wages in Outpatient Care Centers (https://www.bls.gov/oes/current/oes291069.htm).

‡ Oral therapies include $99.70 for SMBG.[19]

§ Other oral therapy: alpha-glucosidase inhibitor, DPP-4 inhibitor, meglitinide, and thiazolidinedione averaged together.

| | Treatment change assumed due to suboptimal glycemic control: 62.5% sulfonylurea + insulin, 25.0% sulfonylurea + metformin, 12.5% sulfonylurea + DPP-4 inhibitor.[6] Due to presumably increased necessity of SMBG, this cost includes $306.51 for SMBG calculated for T2D insulin users.[19] Improved glycemic control relative to baseline despite sulfonylurea failure suggested that this SMBG cost would be more appropriate than the SMBG costs associated with total insulin therapy.

¶ T2D oral meds: metformin 51%, sulfonylurea 33%, thiazolidinedione 7%, DP4-inhibitor 7%, GLP1R-agonist 0.4%, meglitinide 2%, alpha-glucosidase inhibitor 1%; includes $99.70 for SMBG. For patients with T2D on insulin: 5% basal insulin only, 13% basal+bolus insulin; includes $306.51 for SMBG.[19]

<table>
<tr><th colspan="6">Annual cost for insulin treatment (not including insulin)*</th></tr>
<tr><td></td><td colspan="2">CGM + Pump</td><td>CGM + MDI</td><td>SMBG + Pump</td><td>SMBG + MDI</td></tr>
<tr><td>Annual equipment costs (2018 USD)</td><td colspan="2">CGM: 6,945.57[20]
Pump: 4,694.17[20]</td><td>6,945.57 for CGM[20]</td><td>4,694.17 for Pump[20]</td><td>N/A</td></tr>
<tr><td># glucose testing strips/day</td><td colspan="2">2.8[22]</td><td>2.8[22]</td><td>5.5[23]</td><td>4.1[21]</td></tr>
<tr><td>Annual cost assuming $1.15 cost per strip[21]</td><td colspan="2">Included in CGM cost</td><td>Included in CGM cost</td><td>2308.63</td><td>1720.98</td></tr>
<tr><td>Total annual cost (2018 USD)†</td><td colspan="2">11,639.74</td><td>6,945.57</td><td>7002.80</td><td>1,720.98</td></tr>
<tr><td>Proportion of insulin treated population[24] (%)</td><td colspan="2">7.29</td><td>2.02</td><td>51.14</td><td>39.55</td></tr>
<tr><td>Average cost of insulin use (2018 USD)†</td><td colspan="5">5250.79</td></tr>
<tr><th colspan="6">Insulin amounts/costs</th></tr>
<tr><td></td><td colspan="2">HNF1A/HNF4A – mean‡</td><td>GCK – mean‡</td><td>T1D – mean</td><td>T2D – mean</td></tr>
<tr><td>Insulin amount (u/(kg x day))</td><td colspan="2">0.52[1]</td><td>0.14[1]</td><td>0.61[25]</td><td>0.57[1]§</td></tr>
<tr><td>Insulin cost (2018 USD)†</td><td><u>Baseline</u>
0.16/unit[21]</td><td><u>Sulf Fail</u>
Basal insulin: 113.33/1000 units[19| |]</td><td>0.16/unit[21]</td><td>0.16/unit[21]</td><td>Basal insulin: 113.33/1000 units
Basal + bolus insulin: 82.22/1000 units[19]</td></tr>
<tr><td>Insulin cost per kg (2018 USD)†</td><td><u>Baseline</u>
30.34</td><td><u>Sulf Fail</u>
21.51</td><td>8.18</td><td>35.62</td><td>Basal: 23.57
Basal + bolus: 17.11</td></tr>
<tr><td>Proportion of patients on insulin (%)</td><td><u>Baseline</u>
54.54[1]</td><td><u>Sulf Fail</u>
62.50[6]</td><td>27.00[1]</td><td>100</td><td>5% basal
13% basal + bolus[19]</td></tr>
<tr><td>Adjusted Insulin cost per kg (2018 USD)†#</td><td><u>Baseline</u>
16.56</td><td><u>Sulf Fail</u>
13.44</td><td>2.21</td><td>35.62</td><td>3.40</td></tr>
</table>

Supplementary Table 4: Insulin treatment costs.

CGM = continuous glucose monitoring; MDI = multiple daily injections; SMBG = self-monitoring blood glucose; Sulf Fail = sulfonylurea failure; T1D = type 1 diabetes; T2D = type 2 diabetes.

* The numbers in the top portion of this table do not apply to patient with T2D or patients with HNF1A/HNF4A-MODY after sulfonylurea failure.

† Costs converted to 2018 USD (https://www.bls.gov/data/inflation_calculator.htm).

‡ HNF1A/HNF4A baseline and GCK values describe treatments in the control arm.

§ T2D patient information from Pihoker et al.[1] assumes that Ab (-) C-pep (+) non-MODY patients are generally similar to patients with T2D.

| | In the case of sulfonylurea failure for HNF1A/HNF4A-MODY, insulin amounts assumed to be the same as the initial therapy for HNF1A/HNF4A-MODY. Due to the known MODY diagnosis, added insulin was assumed to be basal only.

¶ Basal insulin was assumed to be long-acting. Basal + bolus is the averaged cost of long-acting basal insulin and short acting bolus insulin.

Insulin cost per kg was adjusted based on proportion of patients on insulin.

	HNF1A/HNF4A			GCK		T1D	T2D
	Clinical Diagnosis	Testing	Sulf Fail	Clinical Diagnosis	Testing		
Baseline Utility Parameters*	0.905	0.910	0.904	0.986	1.00	0.900[26]	0.920[27]

Event/state	**Utility/Disutility†**	**Cost (2018 USD)‡**	**HNF1A/HNF4A**	**GCK**	**T1D**	**T2D**
MI, year 1	-0.129[28]	46,359.64[23]	X	X	X	X
MI, year 2+	0.904[28]	2,562.56[23]	X	X	X	X
Angina, year 1	0.838[28]	9,197.35[23]	X		X	
Angina, year 2	-	3,982.45[23]	X		X	
Stroke, year 1	-0.181[28]	61,392.55[23]	X	X	X	X
Stroke, year 2+	0.670[28]	20,489.05[23]	X	X	X	X
Microalbuminuria	-	23.07[23]	X		X	
Macroalbuminuria	1.000	33.95[23]	X		X	
ESRD	0.602[26]	115,938.49[29]	X		X	X
BDR	1.000	10,130.35[30]	X		X	
PDR	0.975[31]	14,638.31[30]	X		X	
Macular edema	0.975[31]	9,164.36[30]	X		X	
Blindness	0.902[28]	5,001.92[23]	X		X	X
Cataract	-0.01[32]	3,473.96[33]	X		X	
Neuropathy	0.767[31]	1,531.27[29]	X		X	
Amputation, year 1	-0.109[33]	59,063.00[29]	X		X	X
Amputation, year 2+	0.835[28]	2,078.14[29]	X		X	X
Revascularization, year 1	-0.129[34]	18,766.03[35]	X		X	
Revascularization, year 2+	0.904[34]	1,971.02[35]	X		X	
Severe hypoglycemia	-0.0052[36]	1,475.43[23]	X		X	
DKA with hospitalization	-0.001[37]§	16,605.74[23]			X	
Moderate hypoglycemia	-0.00045[36,38]||	21.55[39]			X	
CHF, year 1	0.778[28]	25,980.30[40]				X
CHF, year 2	-	2,082.10[40]				X
IHD, year 1	0.888[28]	23,408.29[40]				X
IHD, year 2	-	2,082.10[40]				X
Ulcer	0.737[41]	2,347.83[40]				X

Supplementary Table 5: Utilities and complication costs.

Sulf fail = sulfonylurea failure; T1D = type 1 diabetes; T2D = type 2 diabetes; MI = myocardial infarction; ESRD = end stage renal disease; BDR = background diabetic retinopathy; PDR = proliferative diabetic retinopathy; DKA = diabetic ketoacidosis; CHF = congestive heart failure; IHD = ischemic heart disease.

* HNF1A/HNF4A baseline utility values determined based on T1D utility values and proportion of patients on insulin vs. oral therapy. Multiplicative changes for different treatment regimens from Laiteerapong et al.[19]: 0.966 for insulin, 0.977 for oral meds. 100% insulin treatment assumed for patients with T1D. GCK testing arm utility of 1.00 assumed by authors given the young age of the population and lack of micro/macrovascular complications in this population.

† Positive values refer to multiplicative utility values applied annually. Negative values refer to disutility per episode. Utility and cost values relevant to T1D were derived from prior work by Wan et al.;[21] values relevant to T2D were derived from prior work by Laiteerapong et al.;[19] original sources utilized by these studies are reproduced here.

‡ Costs converted to 2018 USD (https://www.bls.gov/data/inflation_calculator.htm).

§ See Thokala et al.[15] for derivation.

|| See Wan et al.[21] for derivation.

Age	T1D Male	GCK Male	HNF1A/HNF4A Male	T2D Male	T1D Female	GCK Female	HNF1A/HNF4A Female	T2D Female
2	13.4	14.0	14.6	15.2	12.8	13.3	13.9	14.6
3	15.3	16.0	16.7	17.5	14.9	15.6	16.5	17.4
4	17.5	18.3	19.3	20.3	17.1	18.0	19.2	20.4
5	19.9	20.9	22.2	23.5	19.6	20.7	22.1	23.8
6	22.5	23.7	25.3	27.0	22.2	23.6	25.4	27.4
7	25.2	26.7	28.7	30.9	25.1	26.8	29.0	31.5
8	28.2	30.1	32.5	35.3	28.5	30.5	33.2	36.2
9	31.6	33.9	36.9	40.4	32.5	34.9	38.2	41.8
10	35.7	38.4	42.0	46.2	37.0	40.0	43.9	48.2
11	40.3	43.5	47.7	52.6	42.0	45.4	49.9	55.0
12	45.6	49.2	54.0	59.3	47.0	50.9	56.0	61.6
13	51.3	55.3	60.4	66.1	51.6	55.8	61.3	67.6
14	57.1	61.3	66.8	72.7	55.3	59.7	65.6	72.4
15	62.7	67.0	72.8	78.8	58.0	62.5	68.5	75.8
16	67.4	72.0	77.9	84.3	59.7	64.2	70.4	78.1
17	71.2	76.0	82.1	88.8	60.9	65.4	71.6	79.5
18	73.9	78.7	85.1	92.0	62.0	66.6	72.8	80.8
19	75.9	80.8	87.1	94.1	63.3	67.9	74.2	82.0
20	77.5	82.4	88.8	95.7	64.3	69.0	75.4	83.0

Supplementary Table 6: Updated weight values.[42]

T1D = type 1 diabetes; T2D = type 2 diabetes. All values shown in kg. Weights based on BMI z-scores reported for the various populations. T1D: 70th percentile, GCK: 80th percentile, HNF1A/HNF4A: 90th percentile, T2D: 95th percentile.

	HNF1A/HNF4A-MODY*	
Outcomes	**Control**	**Testing**
BDR	11.17%	5.46%
PDR	6.26%	3.51%
Macular Edema	0.36%	0.17%
Blindness	0.00%	0.00%
Macroalbuminuria	27.98%	19.53%
ESRD	16.22%	11.15%
Neuropathy	4.90%	3.15%
Amputation	0.00%	0.00%
Angina	1.54%	1.31%
Stroke	0.38%	0.32%
MI	2.85%	2.49%
Revascularization	0.66%	0.58%

Supplementary Table 7: **Probabilities of major complications for HNF1A/HNF4A-MODY in the base case (30-year) analysis.**

BDR = background diabetic retinopathy; PDR = proliferative diabetic retinopathy; ESRD = end stage renal disease; MI = myocardial infarction.

*Complication rates are not shown for patients with T1D and T2D because these patients were modelled with no changes between the control arm and testing arm. For patients with GCK-MODY, there were negligible differences in complication rates between the control arm and testing arm.

	Outcome	Control	Testing	**Difference** [95% CI]
10-year analysis	Cost (USD)	90,771.32	91,318.49	+547.17 [542.21; 552.06]
	LE (Years)	9.9458	9.9459	+0.0001 [0.0001; 0.0002]
	QALY	7.7308	7.7319	+0.0011 [0.0011, 0.0012]
	ICER (USD/QALY)	-	-	**507,700** [481,488; 555,796]
30-year analysis (Base case)	Cost (USD)	300,091.42	299,900.57	-190.84 [-209.83; -171.23]
	LE (Years)	27.9299	27.9329	+0.0030 [0.0027; 0.0034]
	QALY	16.3556	16.3608	+0.0052 [0.0050; 0.0054]
	ICER (USD/QALY)	-	-	**Dominant**
Lifetime analysis	Cost (USD)	477,671.46	477,068.57	-602.89 [-631.11; -574.02]
	LE (Years)	45.9724	46.0052	+0.0328 [0.0312; 0.0344]
	QALY	20.0295	20.0427	+0.0133 [0.0128; 0.0137]
	ICER (USD/QALY)	-	-	**Dominant**

Supplementary Table 8: **Cost, LE, and QALY outputs for 10-year, 30-year, and lifetime time horizons.**

LE = life expectancy; QALY = quality adjusted life year; ICER = incremental cost-effectiveness ratio.

	Number of relatives with diabetes, prediabetes, or hyperglycemia (children and siblings)							Avg per proband
	0	**1**	**2**	**3**	**4**	**5**	**6**	
Total* n=221(%)	95 (42.99)	74 (33.48)	26 (11.76)	13 (5.88)	8 (3.62)	4 (1.81)	1 (0.45)	1.01

Supplementary Table 9: Number of relatives with diabetes, prediabetes, or hyperglycemia per MODY positive proband in the University of Chicago National Monogenic Diabetes Registry.

*Total includes data from HNF1A-, HNF4A-, and GCK probands. Total proportions were applied to both the HNF1A-/HNF4A-MODY and GCK-MODY models .

Sector	Type of impact	Included in this reference case analysis		Notes on evidence sources
		Health Care Sector	Societal	
Formal health care sector				
Health	**Health outcomes (effects)**			
	Health-related quality of life effects	Yes	-	See Supplementary Table 5
	Longevity effects	Yes	-	
	Other health effects*	No	-	
	Medical costs			
	Paid for by third-party payers	Yes	-	See Supplementary Tables 3-5
	Paid for by patients out-of-pocket	No	-	
	Medical care related costs including:		-	
	Healthcare services	Yes	-	
	Medication costs	Yes	-	
	Genetic testing and biomarker screening costs	Yes	-	
	Future unrelated medical costs	No	-	
Informal health care sector				
Health	Patient-time costs	NA	-	
	Unpaid caregiver costs	NA	-	
	Transportation costs	NA	-	
Non-health care sectors				
Productivity, Consumption, Social Services, Legal/Criminal Justice, Education, Housing, Environment	See Sanders et al. for examples[43]	NA	-	

Supplementary Table 10: Impact inventory for cost-effectiveness analysis.[43]

* Other health effects were monitored as they pertained to health utility effects (see Supplementary Table 5), which is reflected in the "health-related quality of life effects" field.

References

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