











Cost–effectiveness and budget impact analysis of screening strategies for maturity-onset diabetes of the young in three European countries

László Szilberhorn^{*1} , Tamás Zelei¹ , Heleen Vellekoop² , Simone Huygens² , Matthijs Versteegh² , Maureen Rutten-van Mölken^{2,3} , Rositsa Koleva-Kolarova⁴ , Apostolos Tsiachristas⁴ , Sarah Wordsworth⁴  & Balázs Nagy^{1,5} 

¹Syreon Research Institute, 1142, Budapest, Hungary

²Institute for Medical Technology Assessment, Erasmus University Rotterdam, P.O. Box 1738, 3000 DR, Rotterdam, The Netherlands

³Erasmus School of Health Policy & Management, Erasmus University Rotterdam, P.O. Box 1738, 3000 DR, Rotterdam, The Netherlands

⁴Health Economics Research Centre, University of Oxford, OX3 7LF, Oxford, UK

⁵Center for Health Technology Assessment, Semmelweis University, 1091, Budapest, Hungary

*Author for correspondence: laszlo.szilberhorn@syreon.eu

Background: Correct diagnosis of maturity-onset diabetes of the young (MODY), which is often misdiagnosed as Type 1 or 2 diabetes, is important for providing appropriate treatment. **Materials & Methods:** A diabetes model was adapted to Hungary, the Netherlands, and the UK to analyse the cost–effectiveness and budget impact of different screening strategies for MODY with 20 years time horizon. **Results:** Compared with no screening, screening with the MODY calculator then genetic testing is considered cost-effective with respect to each country's willingness to pay threshold. The addition of autoantibody testing dominated the no screening strategy. The budget impact of the strategies ranges between 0.001 and 0.025% of annual public healthcare spending. **Conclusion:** The analysed strategies are considered good value for money with potential cost savings in the long term.

First draft submitted: 6 February 2023; Accepted for publication: 21 April 2023; Published online: 4 September 2023

Keywords: adaptation • budget impact • cost–effectiveness • diabetes • economic evaluation • maturity onset diabetes of the young • MODY • screening

Introduction

Maturity-onset diabetes of the young (MODY) is a heterogeneous group of disorders that result in β -cell dysfunction causing insulin secretion impairment and is often misdiagnosed as Type 1 or Type 2 diabetes. Although the molecular genetic basis of MODY was recognized in the 1990s [1], limited data are available today. The overall prevalence of MODY in Europe is estimated to be 1–5 per 10,000 people, accounting for 1–5% of all diabetes mellitus cases. The most common subtypes of MODY in Europe are *HNF1A*-MODY, *GCK*-MODY and *HNF4A*-MODY. Various European countries including the UK, Norway, The Netherlands, Germany and Poland have a comparable subtype distribution [2].

Diabetes patients with the MODY subtype need different treatment than Type 1 or 2 diabetes patients. For *GCK*-MODY patients, dietary intervention alone is usually sufficient. *HNF1A*-MODY and *HNF4A*-MODY patients are more responsive to sulphonylurea than insulin and hence should be treated with the former to maintain optimal glycemic control [3]. Reports suggest that optimal glycemic control without major hypoglycemia can be maintained for decades at 20–40 mg doses of sulphonylurea [4,5]. While correctly diagnosing the MODY subtype is therefore very important, it cannot be distinguished easily from Type 1 and Type 2 diabetes based on clinical characteristics. An accurate diagnosis of MODY can only be made based on genetic testing.

In a previous study we performed an economic evaluation of different screening strategies for MODY in Hungary [6]. The screening strategies were 1) MODY calculator followed by genetic testing and 2) MODY calculator followed by autoantibody testing and genetic testing. Due to differences in healthcare systems and pricing of the tests and subsequent treatments, the optimal MODY screening strategy may differ between countries. The core Hungarian model was, therefore, adapted to the healthcare systems of The Netherlands and the UK. These countries differ with respect to the healthcare system (e.g., methods of financing, number of healthcare payors), price levels and the infrastructure for screening and genetic testing. For example, in The Netherlands, the price of genetic testing is more than twice as high as in the UK and Hungary [7,8].

This study aims to perform a cost-effectiveness and budget impact analysis of different MODY screening strategies in Hungary, The Netherlands and the UK. The model compares a strategy in which all patients are screened for MODY and those with a positive test result receive therapy changes (e.g., sulphonylurea instead of insulin for *HNF1A*-MODY and *HNF4A*-MODY patients, or diet instead of insulin for *GCK*-MODY patients) to a 'no screening' strategy, where every patient is treated with insulin.

Methods

Overview of the cost-effectiveness model

The original cost-effectiveness model [6] consists of a decision tree and a patient-level Markov simulation model that runs in 3-month cycles over a time horizon of 20 years. We are not using lifetime horizon owing to lack of data; the uncertainty of long-term extrapolation would make the results less robust. The model simulates different screening strategies to detect MODY patients and projects long-term outcomes of the diagnosed MODY patients. The decision tree model takes a cohort of patients through a screening process to have 10,000 patients at the end to simulate in the second part of the model, where diabetic patients younger than 35 years treated with insulin first fill out the MODY calculator. From that point on there are two scenarios: patients categorized as high risk (the recommended 40% cut-off value was used to define high risk of MODY) are tested with 1) massively parallel sequencing for MODY mutations, or 2) an autoantibody test to rule out Type 1 diabetes, after which autoantibody-negative patients are tested with massively parallel sequencing for MODY mutations. Both scenarios are compared with no screening. The core model structure including the decision tree and the patient-level Markov simulation model is described in detail in the original article [6]. The model considers six diabetic complications (*via* Markov submodels) and simulates the progress of these complications through a series of health states. The included complications are: 1) hypoglycemia, 2) neuropathy, 3) foot ulcer, 4) retinopathy, 5) macular oedema and 6) nephropathy. Patients on unnecessary insulin treatment can have more major hypoglycemic events; MODY patients with adequate treatment can have better glycemic control and consequently fewer complications; stopping unnecessary insulin treatment significantly reduces diabetic treatment costs and releasing the patient from unnecessary use of injectables can significantly improve health-related quality of life.

Data on screening (MODY calculator) and testing (autoantibody test and genetic test) effectiveness, state transition probabilities, treatment and complication-specific disutilities were derived from published literature and used for all three countries; see more details in the original article [6]. The patient characteristics of the diagnosed MODY patients was defined based on German registry data [9] and used for all three countries. General mortality, age- and sex-specific utility, and cost data that were used in the core model to estimate the cost-effectiveness of MODY screening in Hungary are described in the original article [6]. Country-specific input data for The Netherlands and the UK are presented in the following sections.

Adapting the model to The Netherlands & the UK

The core Hungarian model was adapted to reflect the local costs, general utility and mortality in The Netherlands and the UK, the discount rates were set based on the local health technology assessment (HTA) guidelines [10,11]. Local cost data were used for screening and testing, treatment and adverse events. Country, age and sex-specific population utility and life tables for general mortality were used. The patient pathways were validated by local medical experts in all three countries. Costs for each analysis are reported in the national currency as well as in 2021 international euros (int€), which are Euros adjusted for purchasing power parity (PPP) [12]. PPP-adjusted Euros make cost inputs and results more comparable across the countries by adjusting for price level differences.

The Netherlands

In accordance with Dutch HTA guidelines, effects and costs were discounted at 1.5 and 4%, respectively [13]. The guidance recommends lifetime horizon; however, due to lack of longitudinal data we used a conservative 20 year-long time horizon to minimize uncertainty, as used in the original model [6]. We technically used only healthcare perspective; we did not include informal care and productivity loss costs as the main effect of treatment switch is on quality of life, therapy costs and Haemoglobin-A1c (HbA1c) driven complications, and we assumed that these factors have little effect on productivity. Due to the relatively short time horizon of the model (20 years), the initially young population and the minimal effect of screening and therapy switch on survival, future costs due to prolonged life were not included either. The screening, testing, treatment and adverse event costs were derived from the Dutch Healthcare Authority (Nederlandse Zorgautoriteit) database and from published literature. The costs (with their references) used in the model are presented in [Table 1](#). The age- and sex-specific general utility values were calculated based on a previous publication that reported regression coefficients for age and sex [14]. The probabilities of nondiabetes-related death in each cycle were calculated on the basis of Dutch life tables [15]. The age- and sex-specific utility values and mortality rates are presented in [Supplementary Table 1](#).

The UK

In the UK, the cost-effectiveness analysis was conducted from the perspective of the NHS. Quality-adjusted life years (QALY) and costs were discounted at 3.5%. Only direct costs as cost of treatment, complications and diabetes management were included in the analysis. The costs were derived from a previously published model that analyzed the economic value of self-monitoring in case of Type 1 and 2 diabetes [23], the National Schedule of NHS costs and The National Institute for Health Care Excellence British National Formulary [16,20]. The age- and sex-specific general utility values were based on population norms for the UK [35]. Probabilities of annual background mortality are based on data for the period 2018–2020 obtained from the Office of National Statistics in the UK [36]. The age- and sex-specific utility values and mortality rates are presented in [Supplementary Table 1](#).

The base-case outcomes are presented for Hungary, The Netherlands and the UK, and include total costs and QALYs, as well as incremental costs and QALYs and incremental cost-effectiveness ratios (ICER) in [Table 3](#). For both screening strategies, the incremental outcomes compared with the no screening comparator are presented.

Overview of the budget impact model

Only direct medical costs were considered for the budget impact (BI) analyses. The costs and resource utilization data for the budget impact model were derived directly from the cost-effectiveness model. The target population and the comparators were the same as in the cost-effectiveness models. The time horizon of the budget impact analyses was 5 years.

The size of the patient cohort in the budget impact analysis was estimated based on country-specific population estimates, point prevalence (for the first year) and annual incidence (for the subsequent years) of Type 1 diabetes from the Diabetes Atlas [42] to have all the data from the same source to make them comparable. Type 1 diabetes data were used because diabetic patients using insulin below 35 years of age are predominantly diagnosed as Type 1. The inputs used in the analyses are presented in [Table 2](#).

Population growth was directly considered in the model with the eligible population size for each year in each country (see [Table 2](#)). A schematic representation of the model structure is given in [Figure 1](#).

Sensitivity analyses

Probabilistic sensitivity analyses (PSA) were performed, sampling 1000 parameter sets from the distributions around the parameters in the model to generate a probability distribution of calculated cost-effectiveness ratios, reflecting the combined uncertainty in the underlying parameters of the models. The results of the PSAs are represented on cost-effectiveness planes and cost-effectiveness acceptability curves, which show the probability of MODY screening to be cost-effective compared to no screening at the recommended country-specific thresholds. The thresholds used in each country were obtained from local guidelines. The thresholds for Hungary, The Netherlands and the UK are 7,294,500 HUF (int€31,559) [43], €20,000 (int€17,416) [11] and £20,000 (int€19,764) [10], respectively. The uncertainty in the budget impact analyses was examined with one-way sensitivity analyses on the population and epidemiology data, the screening effectiveness, and the annual cost data derived from the cost-effectiveness models.

Table 1. Cost inputs for the three countries in local currencies and international Euros.

Input parameter	Hungary (HUF)	The Netherlands (€)	UK (£)	Ref.
Screening and testing				
MODY calculator	723 (int€ 3.13)	30.00 (int€ 26.12)	131.20 (int€ 129.66)	[8,16,17]
Autoantibody test	1346 (int€ 5.83)	10.24 (int€ 8.92)	44.10 (int€ 43.58)	[17–19]
MODY genetic test	256,655 (int€ 1,110.40)	1768.05 (int€ 1539.65)	650.00 (int€ 642.35)	[7,8]
Treatment				
Insulin (daily)	310 (int€ 1.34)	4.27 (int€ 3.72)	3.26 (int€ 3.22)	[20–22]
Sulfonylurea (daily)	28 (int€ 0.12)	0.18 (int€ 0.16)	0.06 (int€ 0.06)	[20–22]
Cost of HbA1c control (/3 months)	2376 (int€ 10.28)	30.03 (int€ 26.15)	122.11 (int€ 120.67)	[16–18]
Retinopathy and macular edema				
Cost of treatment of BDR (/3 months)	19,907 (int€ 86.13)	22.50 (int€ 19.59)	79.30 (int€ 78.36)	[18,23,24]
Cost of follow-up of BDR (/3 months)	3254 (int€ 14.08)	22.50 (int€ 19.59)	79.30 (int€ 78.36)	[18,23,24]
Cost of treatment of PDR (/3 months)	560,776 (int€ 2426.17)	1000.50 (int€ 871.26)	270.08 (int€ 266.90)	[18,23,24]
Cost of follow-up of PDR (/3 months)	4961 (int€ 21.46)	22.50 (int€ 19.59)	270.08 (int€ 266.90)	[18,23,24]
Cost of blindness (/3 months)	42,866 (int€ 185.46)	136.35 (int€ 118.74)	1484.32 (int€ 1,466.84)	[23,25–27]
Cost of macular edema therapy (first 3 months)	955,515 (int€ 4133.98)	283.64 (int€ 247.00)	788.43 (int€ 779.15)	[23,24,28]
Cost of macular edema follow-up (/3 months)	2517 (int€ 10.89)	50.65 (int€ 44.11)	788.43 (int€ 779.15)	[23,24,28]
Cost of eye screening	10,678 (int€ 46.20)	90.00 (int€ 78.37)	108.38 (int€ 107.10)	[16–18]
Neuropathy				
Cost of neuropathy	18,339 (int€ 79.34)	0 [†]	99.47 (int€ 98.30)	[23,29]
Cost of neuropathy testing	236 (int€ 1.02)	0 [†]	187.17 (int€ 184.97)	[16,17]
Nephropathy				
Cost of MA treatment (/3 months)	3007 (int€ 13.01)	0.90 (int€ 0.78)	9.51 (int€ 9.40)	[8,21,23]
Cost of GPR treatment (/3 months)	365,855 (int€ 1582.85)	1.80 (int€ 1.56)	1035.10 (int€ 1,022.91)	[8,21,23]
Cost of diagnosis of end stage (Ft/event)	15,535 (int€ 67.21)	232.22 (int€ 202.22)	1307.26 (int€ 1,291.86)	[8,16,17]
Cost of transplantation (months 16+; Ft/3 months)	671,301 (int€ 2904.35)	1016.00 (int€ 884.75)	2093.06 (int€ 2,068.41)	[18,23,30]
Cost of transplantation (months 13–15)	770,301 (int€ 3332.67)	1016.00 (int€ 884.75)	2093.06 (int€ 2,068.41)	[18,23,30]
Cost of transplantation (months 10–12)	770,301 (int€ 3332.67)	1016.00 (int€ 884.75)	2093.06 (int€ 2,068.41)	[18,23,30]
Cost of transplantation (months 7–9)	859,808 (int€ 3719.91)	1016.00 (int€ 884.75)	2093.06 (int€ 2,068.41)	[18,23,30]
Cost of transplantation (months 4–6)	1,197,493 (int€ 5180.89)	1016.00 (int€ 884.75)	2093.06 (int€ 2,068.41)	[18,23,30]
Cost of transplantation (months 1–3)	7,789,808 (int€ 33,702.17)	35,639.00 (int€ 31,035.17)	22,416.56 (int€ 22,152.58)	[18,23,30]
Cost of dialysis (/3 months)	916,211 (int€ 3963.93)	19,634.50 (int€ 17,098.12)	8179.41 (int€ 8,083.09)	[18,23,31]
Cost of lab tests	2635 (int€ 11.40)	3.27 (int€ 2.85)	169.88 (int€ 167.88)	[8,16,17]
Hypoglycemia				
Cost of treatment of major hypoglycemia	49,799 HUF (int€ 215.45)	912.26 (int€ 794.42)	241.93 (int€ 239.08)	[23,32,33]
Foot ulcer				
Not infected ulcer cost	12,041 (int€ 52.10)	396.87 (int€ 345.60)	1489.88 (int€ 1,472.33)	[17,23,34]
Infected ulcer cost	105,533 (int€ 456.58)	667.07 (int€ 580.90)	1489.88 (int€ 1,472.33)	[17,23,34]
Amputation cost	440,885 (int€ 1,907.46)	15,885.75 (int€ 13,833.63)	9560.26 (int€ 9,447.68)	[16,17,34]
Amputation follow-up cost	34,780 (int€ 150.47)	54.64 (int€ 47.58)	478.94 (int€ 473.30)	[17,23,34]

[†]The Dutch guidelines do not prescribe additional healthcare for patients with neuropathy.

int€: 2021 international euros, which are Euros adjusted for purchasing power parity.

BDR: Background diabetic retinopathy; GPR: Gross proteinuria; HbA1c: Hemoglobin A1c; HUF: Hungarian Forint; MA: Macroalbuminuria; MODY: Maturity-onset diabetes of the young; PDR: Proliferative diabetic retinopathy.

Results

Cost-effectiveness analyses

Over a horizon of 20 years, screening diabetic patients younger than 35 years of age on insulin with the MODY calculator and then testing them with massively parallel sequencing for MODY mutations resulted in a QALY gain

Table 2. Patient cohort estimates for the budget impact analyses.

Input parameter	Hungary	The Netherlands	UK	Ref.
Population size ≤35, 2022	3,599,307	6,831,000	28,848,000	[37,38]
Population size ≤35, 2023	3,559,159	6,805,000	28,785,000	[37,38]
Population size ≤35, 2024	3,520,328	6,774,000	28,709,000	[37,38]
Population size ≤35, 2025	3,481,283	6,740,000	28,617,000	[37,38]
Population size ≤35, 2026	3,440,974	6,715,000	28,574,000	[37,38]
T1DM prevalence	0.35%	0.64%	3.16%	[39–41]
T1DM incidence	0.04%	0.07%	0.35%	[39–41]

T1DM: Type 1 diabetes mellitus.

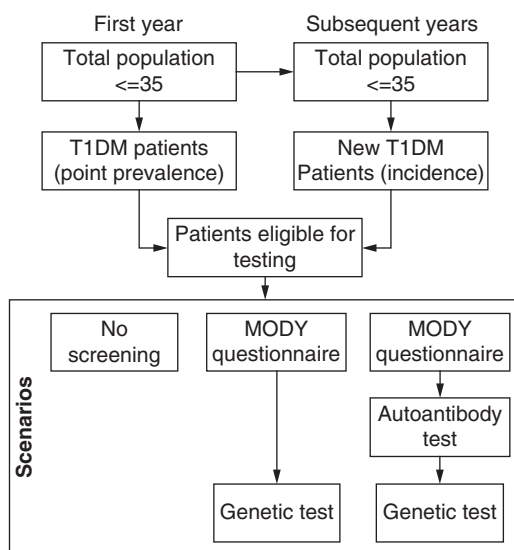


Figure 1. Structure of the budget impact model.
MODY: Maturity-onset diabetes of the young; T1DM: Type 1 diabetes mellitus.

Table 3. Base-case result of the screening strategies compared to no screening.

Scenario	Cost (int€)	QALY	Incremental cost	Incremental QALY	ICER (int€)
Hungary					
No screening	11,419	12.1488			
MODY screening with autoantibody test	11,400	12.1535	-19	0.0047	Dominant
MODY screening without autoantibody test [†]	11,507	12.1536	88	0.0048	18,602
The Netherlands					
No screening	22,968	14.6121			
MODY screening with autoantibody test	22,914	14.6177	-54	0.0056	Dominant
MODY screening without autoantibody test [†]	23,062	14.6177	95	0.0057	16,669
UK					
No screening	40,282	12.4433			
MODY screening with autoantibody test	40,280	12.4480	-2	0.0047	Dominant
MODY screening without autoantibody test [†]	40,325	12.4481	43	0.0048	9059

[†] MODY calculator followed by genetic testing.

ICER: Incremental cost-effectiveness ratio; MODY: Maturity-onset diabetes of the young; QALY: Quality-adjusted life-year.

and cost increase in all three countries (Table 3). The incremental costs varied between int€43 and int€95 in the three countries, with additional QALYs between 0.0048 and 0.0057. The estimated ICERs are int€9059 for the UK, int€16,669 for The Netherlands and int€ 18,602 for Hungary. The estimated ICERs in all three countries are below the lowest of their respective cost-effectiveness thresholds, so this screening strategy could be considered cost-effective in all three countries (Table 3).

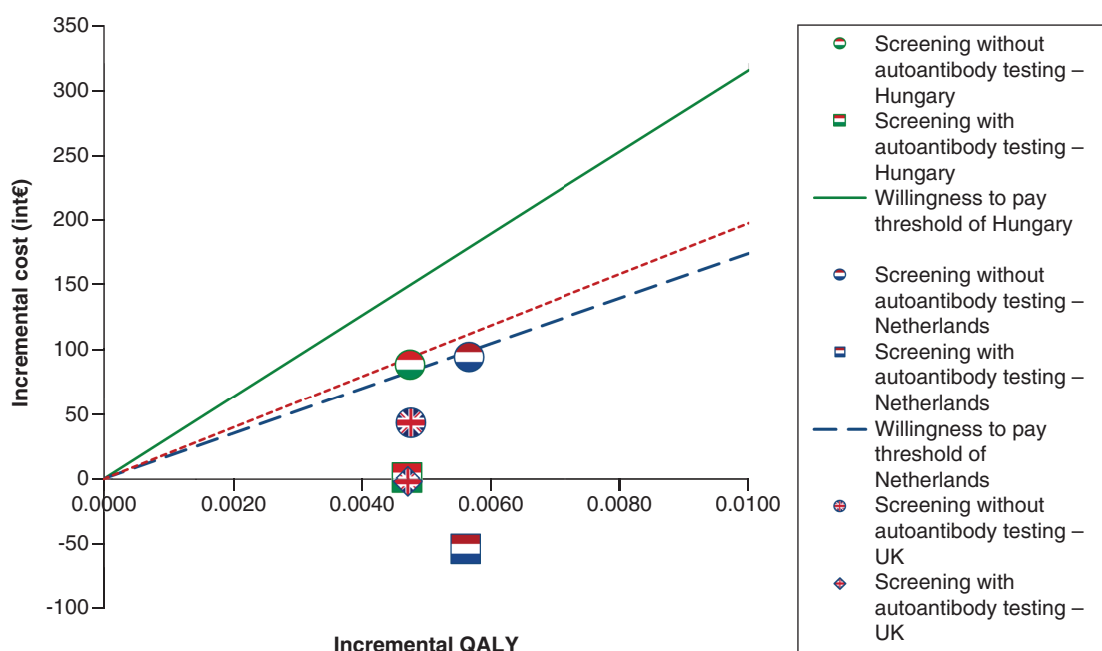


Figure 2. Cost-effectiveness plane for all scenarios and countries.
QALY: Quality-adjusted life-year.

Adding an autoantibody test between the MODY calculator and the genetic testing resulted in a substantial cost decrease with negligible QALY loss due to false-negative cases. The incremental costs compared to no screening became negative, making this scenario cost-saving with a QALY gain. This means that screening with the addition of autoantibody testing dominates the no-screening strategy in all cases (Table 3). The cost-effectiveness planes for each country and the two scenarios are shown in Figure 2.

Probabilistic sensitivity analyses

The outcomes of the probabilistic sensitivity analyses are shown in cost-effectiveness planes in Figure 3, and cost-effectiveness acceptability curves (CEAC) are presented in Figure 4. The cost-effectiveness planes look similar across the three countries. All iterations of the model resulted in QALY gains compared to no screening with additional costs or even cost savings, putting all points to the right quadrants of the planes. In the case of Hungary, screening with and without antibody testing is dominant in 83 and 18% of cases, respectively, and is considered cost-effective in 100 and 76% of cases at a willingness-to-pay threshold of int€31,559, respectively. In the case of The Netherlands, these numbers are 91 and 29% and 99 and 56%, respectively, at a willingness-to-pay threshold of int€17,416. In the UK, the scenarios are dominant in 63 and 24% and cost-effective in 99 and 77% of the cases at a willingness-to-pay threshold of int€19,764.

Budget impact analyses

For the screening scenarios, the total number of patients detected during the 5-year period was estimated to be 7996 and 7917 for the UK without and with autoantibody screening, respectively. The numbers for Hungary are 110 and 111, and for The Netherlands these are 378 and 381. The total 5-year budget impact of the no-screening scenario was estimated to be int€12,373,129,997 in the UK, int€51,259,025 in Hungary and int€422,516,450 in The Netherlands. These figures are 1.42, 0.12 and 0.14% of the annual public healthcare spending of these countries, respectively.

The 5-year budget impact figures for the two screening strategies and the no-screening strategy are reported in Table 4.

In Hungary, the incremental 5-year budget impact of screening without autoantibody testing is int€ 2,333,912; introducing autoantibody testing reduces the budget spent to int€ 373,996, which constitutes 0.005 and 0.001% of the annual public healthcare spending in Hungary, respectively. The screening scenario resulted in cost savings

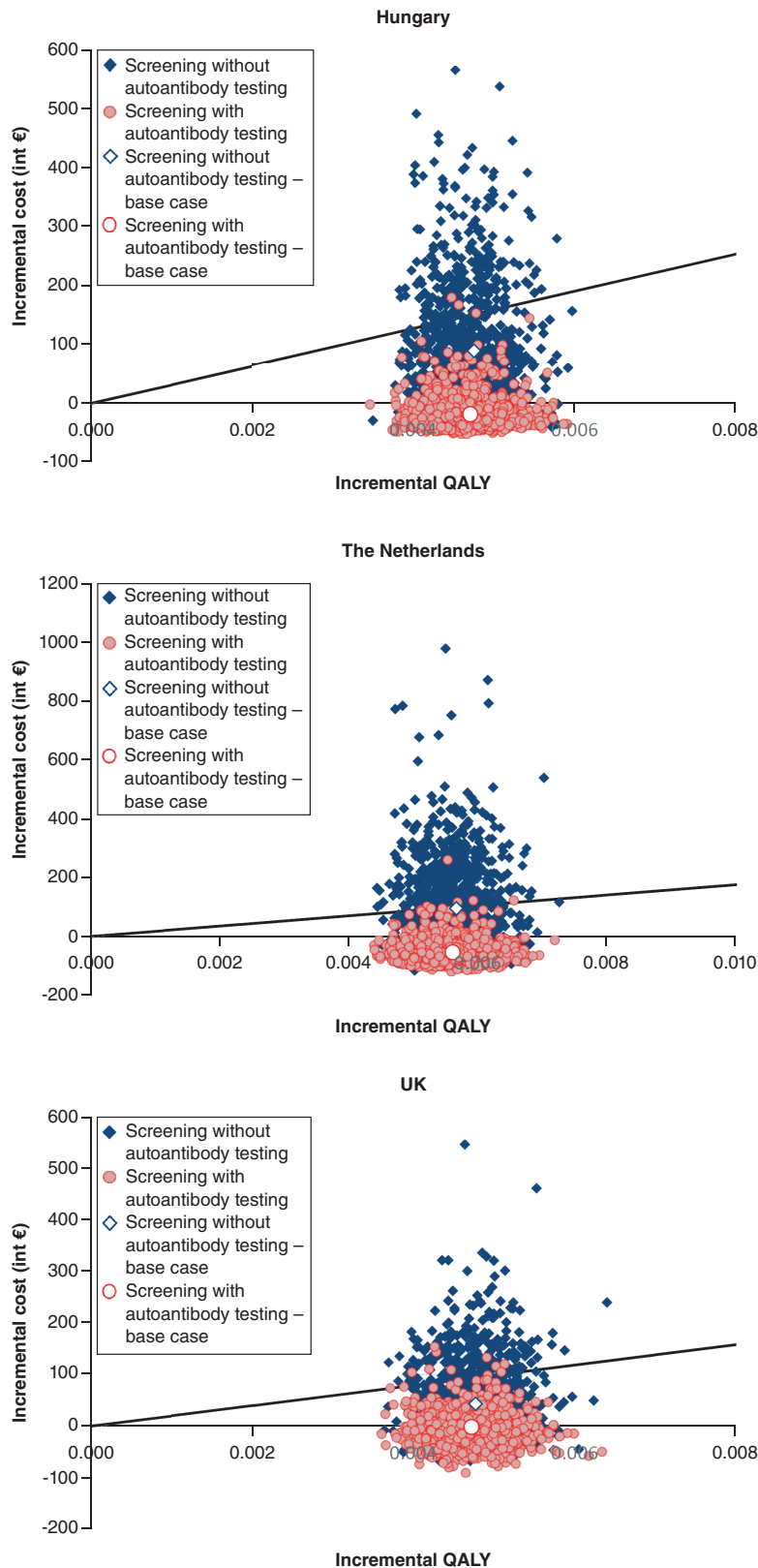


Figure 3. Cost-effectiveness planes.

int€: 2021 international euros, which are Euros adjusted for purchasing power parity.

QALY: Quality-adjusted life-year.

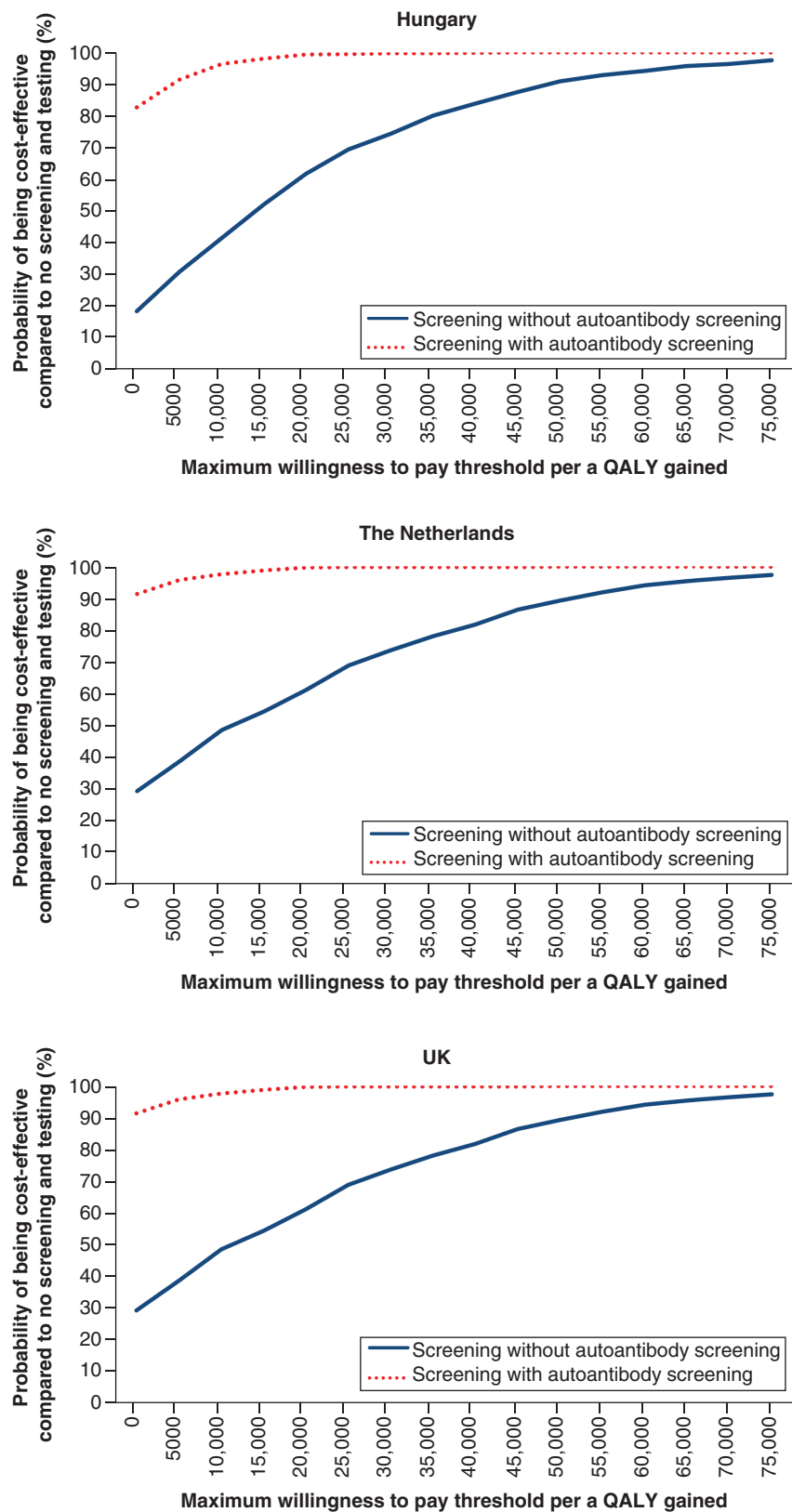


Figure 4. Cost-effectiveness acceptability curves. QALY: Quality-adjusted life-year.

Table 4. 5-year budget impact of the screening strategies (in thousands int€).

	Year	2022	2023	2024	2025	2026
Hungary	No screening	7756.37	8942.12	10,218.73	11,529.19	12,812.60
	MODY screening without autoantibody test	9508.77	9099.76	10,368.45	11,670.44	12,945.53
	MODY screening with autoantibody test	8150.68	8946.68	10,217.10	11,520.84	12,797.73
	MODY screening without autoantibody test vs No screening	1752.39	157.64	149.71	141.24	132.93
	MODY screening with autoantibody test vs No screening	394.30	4.56	-1.63	-8.36	-14.87
The Netherlands	No screening	68,809.96	76,683.67	84,663.12	92,281.23	100,078.46
	MODY screening without autoantibody test	78,003.30	77,304.89	85,236.94	92,808.50	100,559.69
	MODY screening with autoantibody test	71,474.77	76,597.33	84,533.04	92,108.56	99,862.79
	MODY screening without autoantibody test vs No screening	9193.34	621.22	573.82	527.27	481.22
	MODY screening with autoantibody test vs No screening	2664.81	-86.35	-130.08	-172.66	-215.68
UK	No screening	1,960,957.34	2,208,838.82	2,464,518.56	2,730,768.88	3,008,046.39
	MODY screening without autoantibody test	2,143,786.21	2,220,248.16	2,474,771.27	2,739,858.44	3,015,918.56
	MODY screening with autoantibody test	2,091,597.37	2,214,567.64	2,469,116.92	2,734,233.42	3,010,313.94
	MODY screening without autoantibody test vs No screening	182,828.87	11,409.34	10,252.71	9089.55	7872.16
	MODY screening with autoantibody test vs No screening	130,640.02	5728.82	4598.36	3464.54	2267.54

int€: 2021 international euros, which are Euros adjusted for purchasing power parity.
MODY: Maturity-onset diabetes of the young.

from the third year onwards. These saving are attributable to substantial savings in therapy from switching to cheaper treatments and a slight reduction in complication costs due to better HbA1c control, which offsets the costs of screening and testing.

In The Netherlands, the incremental 5-year budget impact is int€11,396,869 and int€2,060,035 without and with autoantibody testing, respectively. These values are 0.004 and 0.001% of the annual public healthcare spending in the country, respectively. MODY screening with autoantibody testing becomes cost saving from the second year onwards.

The incremental 5-year budget impact in the UK is estimated to be int€221,452,636 and int€146,699,297 without and with autoantibody testing, respectively. These figures represent 0.025 and 0.017% of the annual public healthcare spending in the country, respectively. The higher budget spending in the UK compared to Hungary and The Netherlands resulted from a larger population being screened and higher prevalence and incidence rates. In the UK, savings in therapy and complication costs cannot offset the cost of screening in the first 5 years, but the incremental costs are decreasing over time.

The one-way sensitivity analyses conducted for the 5-year cumulative budget impact of the MODY screening with autoantibody test scenario for each country showed that the most influential parameter is the specificity of the MODY calculator. With lower specificity, more genetic testing is needed to find the patients making the budget impact higher; lowering the value by 10% translates to a 12, 76 and 87% increase to the 5-year budget impact in the UK, The Netherlands and Hungary, respectively. Other influential parameters are autoantibody test specificity and genetic test costs. In general, every change in parameter increases the need for genetic testing, which increases the budget impact of the screening programs.

Discussion

In the evaluation of personalised medicine interventions, it is important to include an accurate representation of the screening and testing pathways in the economic model [44]. In this study, we evaluated two screening strategies to detect MODY patients and subsequently switch their therapy to sulphonylurea or a diet based on their genetic subtype. We demonstrated how modelling of screening pathways can be approached and how HTA methods can be used to aid decision-making in three different countries.

Based on our results, similar conclusions can be reached in each country: screening without autoantibody testing can be considered cost-effective compared with no screening based on the national willingness-to-pay thresholds

in Hungary, The Netherlands and the UK. However, introducing autoantibody testing in the pathway between the MODY calculator and genetic testing substantially lowers the cost of detecting one patient, making these scenarios dominant over no screening in all three countries. Using autoantibody testing is the preferred option as it is dominant in all three countries. Testing more patients with genetic sequencing results in higher QALY outcomes but with substantial costs. Stratifying patients further to require fewer genetic sequences lowers the costs and the laboratory capacity needs as well.

The results of the budget impact analyses demonstrate that, in young diabetes mellitus patients, target population screening with the MODY calculator followed by genetic testing calls for high initial budget spending in the first year and more moderate budget resources in subsequent years. Using the autoantibody test after the MODY calculator can significantly reduce the need for expensive genetic testing. These scenarios can be cost saving from the year following the initial target population screening in Hungary and The Netherlands, and tend to reduce the annual costs in the UK, but the UK could not reach cost savings in the first 5 years of analysis.

The transferability of the cost–effectiveness and budget impact analysis results are limited between countries owing to different healthcare systems and economic development levels; however, based on our results, screening with adding autoantibody testing could be good value for money in other European countries. The main driver of the budget impact is the initial number of insulin users in the given country who are the target population of the screening program. Countries with a similarly high prevalence to the UK (Germany, France, Spain and Italy [42]) could face a high upfront cost to start the program. In Central–Eastern Europe, countries with similar prevalence to Hungary could expect a similar budget impact, but Poland (with 1.25% prevalence [42]) may consider the upfront costs of the program to high.

Publicly available data on MODY patient populations tend to be limited and insufficient, as MODY screening is not yet part of the general diabetes protocol in these three countries, and MODY patients have similar symptoms and characteristics to patients with Type 1 diabetes so it is hard to accurately diagnose them without genetic testing. As a result of the low number of diagnosed MODY patients, there are very few available clinical studies, and the results of existing studies are based on a small sample (i.e., a few patients or one family). Due to limited data availability, we used relevant data about Type 1 diabetes patients or expert assumptions on disease progression and complications instead. Our modelled population used the baseline characteristics of a population from a German registry data in all three cases due to lack of robust enough local data.

Conclusion

Our cost–effectiveness analyses show that introducing the MODY calculator prior to genetic testing for MODY patients in Hungary and in the UK is cost-effective. The addition of autoantibody testing in the pathway between the MODY calculator and genetic testing makes the screening strategy dominant compared with no screening in each country, making it the preferred option to implement MODY screening in all three countries. Introducing autoantibody screening cannot fully offset the initial high cost of screening in any of the countries, but in Hungary and The Netherlands it starts to save costs from the third and the second year onwards, respectively.

Open access

This work is licensed under the Creative Commons Attribution 4.0 License. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/pme-2023-0017

Author contributions

L Szilberhorn and B Nagy initiated the research and developed the economic model. T Zelei, M Rutten-van Mölken and B Nagy supported the development of conceptual modelling framework. L Szilberhorn, S Huygens, H Vellekoop and R Koleva-Kolarova collected the model input parameters, L Szilberhorn run the base case and scenario analyses. H Vellekoop, S Huygens and R Koleva-Kolarova reviewed the model. L Szilberhorn, T Zelei and B Nagy interpreted the model results and developed the draft manuscript. H Vellekoop, S Huygens, M Versteegh, M Rutten-van Mölken, R Koleva-Kolarova, S Wordsworth and A Tsiachristas reviewed and commented on the draft manuscript. L Szilberhorn, T Zelei and B Nagy finalized the manuscript. All authors read and approved the current version of the manuscript.

Financial & competing interests disclosure

The HEcoPerMed project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No. 824997. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Data sharing statement

The datasets supporting the conclusions of this article are included in the main text and in its supplementary materials, including model description and input data with data sources. All other datasets used and analyzed in the current study are available from the corresponding author upon request.

Summary points

- Cost-effectiveness and the budget impact of different hypothetical multi-step maturity-onset diabetes of the young (MODY) screening strategies were assessed in three European countries: Hungary, The Netherlands and UK.
- The target population was patients with diabetes mellitus under 35 years of age who receive insulin treatment.
- Two patient stratification strategies were followed:
 1. Screening strategy 1: patients were first categorized with the MODY calculator then high-risk patients were tested with massively parallel sequencing for MODY mutations;
 2. Screening strategy 2: patients were first categorized with the MODY calculator, then high-risk patients were tested for the presence of autoantibodies against islet cell antigens, followed by massively parallel sequencing for MODY mutations of autoantibody-negative patients.
- A simulation model was used that combined a decision tree and an individual-level Markov model to assess the costs and quality-adjusted life years of each screening strategy and compared the two screening strategies with no screening.
- The budget impact of these two strategies was compared with no screening in a 5-year time horizon.
- Stratifying patients based on age and insulin treatment followed by a risk assessment questionnaire, a laboratory test and genetic testing appeared to be the dominant strategy in each country, by saving costs and generating quality-adjusted life years.
- Population screening with the MODY calculator followed by genetic testing calls for high initial budget spending in the first year and more moderate budget resources required in the subsequent years.
- Using an autoantibody test after the MODY calculator can significantly reduce the need for expensive genetic testing.
- These results draw attention to the potential benefits of personalization *via* well-designed patient stratification, resulting in cost savings and improved quality of life.
- A multistep screening strategy for MODY patients could be considered for reimbursement in the examined countries.

References

1. Gardner DS, Tai ES. Clinical features and treatment of maturity onset diabetes of the young (MODY). *Diabetes Metab. Syndr. Obes.* 5, 101 (2012).
2. Nkonge KM, Nkonge DK, Nkonge TN. The epidemiology, molecular pathogenesis, diagnosis, and treatment of maturity-onset diabetes of the young (MODY). *Clin. Diabetes Endocrinol.* 6(1), 1–10 (2020).
3. Urakami T. Maturity-onset diabetes of the young (MODY): current perspectives on diagnosis and treatment. *Diabetes Metab. Syndr. Obes.* 12, 1047 (2019).
4. Fajans SS, Brown MB. Administration of sulfonylureas can increase glucose-induced insulin secretion for decades in patients with maturity-onset diabetes of the young. *Diabetes Care* 16(9), 1254–1261 (1993).
5. Shepherd M, Shields B, Ellard S, Rubio-Cabezas O, Hattersley AT. A genetic diagnosis of *HNFLA* diabetes alters treatment and improves glycaemic control in the majority of insulin-treated patients. *Diabetic Med.* 26(4), 437–441 (2009).
6. Kovács G, Nagy D, Szilberhorn L *et al.* Cost-effectiveness model of genetic testing strategies for Maturity Onset Diabetes of the Young (MODY). *Pers. Med.* (2023).
7. DiabetesGenes.org A new test for all MODY genes (2021). www.diabetesgenes.org/tests-for-diabetes-subtypes/a-new-test-for-all-mody-genes/
8. Dutch Healthcare Authority [Nederlandse Zorgautoriteit] NZA tariffs (2022). <https://zorgproducten.nza.nl>

9. Warncke K, Kummer S, Raile K *et al.* Frequency and characteristics of MODY 1 (*HNF4A* mutation) and MODY 5 (*HNF1B* mutation): analysis from the DPV database. *J. Clin. Endocrinol. Metab.* 104(3), 845–855 (2019).
10. National Institute of Health and Care Excellence. NICE, Health Technology Evaluations: the Manual. www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741 (2022).
11. Zorginstituut Nederland. Guideline for Economic Evaluations in Healthcare. <https://english.zorginstituutnederland.nl/publications/reports/2016/06/16/guideline-for-economic-evaluations-in-healthcare> (2016).
12. OECD. Purchasing power parities (PPP) (2022). <https://data.oecd.org/conversion/purchasing-power-parities-ppp.htm#indicator-chart>
13. Zorginstituut Nederland. Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg. www.zorginstituutnederland.nl/publicaties/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg (2016).
14. Heijink R, Van Baal P, Oppe M, Koolman X, Westert G. Decomposing cross-country differences in quality adjusted life expectancy: the impact of value sets. *Popul. Health Metr.* 9(1), 1–11 (2011).
15. Centraal Bureau voor de Statistiek (CBS). StatLine – Overlevingskansen 2018; geslacht, leeftijd. <https://opendata.cbs.nl/statline/#/CBS/nl/dataset/70701ned/table?dl=29BD5>
16. National Schedule of NHS Costs Year: 2019-20 – All NHS trusts and NHS foundation trusts – HRG Data. www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/
17. ICPM. ICPM list of 37/2020. (X. 30.) of the Ministry of Human Resources, in force from 2020.11.02 [Törzslista a 37/2020. (X. 30.) EMMI rendelet alapján, hatályos 2020. nov. 2.-étől]. www.hbcs.hu/uploads/jogszabaly/3243/fajlok/37_2020_X_30_EMMI_rendelet.pdf
18. NZA. Opendisdata (2022). www.opendisdata.nl/msz/zorgproduct/079799036
19. NHS Immunology Laboratory. GAD antibodies (2022). www.ouh.nhs.uk/immunology/diagnostic-tests/tests-catalogue/gad-antibodies.aspx
20. The NICE British National Formulary (BNF) (2022). <https://bnf.nice.org.uk/>
21. NEAK. Public Drug Database 2021. 08.01 [Publikus Gyógyszertörzs 2021. Augusztus 1]. www.neak.gov.hu/felso_menu/szakmai_oldal/ak/gyogyszer_segedeszkoz_gyogyfurdo_tamogatas_egeszsegugyi_vallalkozasoknak/pupha/PUPHAarch/pupha_arc_2021 (2021).
22. Farmacotherapeutisch kompas voor gemiddelde dosering; medicijnkosten.nl voor medicijnprijzen. www.zorginstituutnederland.nl/Verzekerde+zorg/medicijnen-zvw
23. Mcqueen RB, Breton MD, Craig J *et al.* Economic value of improved accuracy for self-monitoring of blood glucose devices for type 1 and type 2 diabetes in England. *J. Diabetes Sci. Technol.* 12(5), 992–1001 (2018).
24. Tóth G, Nagy ZZ, Németh J. A cukorbetegség szemészeti szövődményeinek modellalapú költségtérhe Magyarországon. *Orvosi Hetilap* 162(8), 298–305 (2021).
25. Németh J, Nagyjánosi L, Nagystók S *et al.* Időskori vakság betegségterhe Magyarországon. *Lege Artis Medicinae* 21, 641–647 (2011).
26. Hakkaart-Van Roijen L VDLN, Bouwmans C, Kanters T, Tan SS. Costing manual: Methodology of costing research and reference prices for economic evaluations in healthcare [in Dutch: Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg] ce. [www.zorginstituutnederland.nl/binaries/zinl/documenten/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg/Richtlijn%2Bvoor%2Bhet%2Buitvoeren%2Bvan%2Beconomische%2Bevaluaties%2Bin%2Bde%2Bgezondheidszorg%2B\(verdiepingsmodules\).pdf](https://www.zorginstituutnederland.nl/binaries/zinl/documenten/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg/Richtlijn%2Bvoor%2Bhet%2Buitvoeren%2Bvan%2Beconomische%2Bevaluaties%2Bin%2Bde%2Bgezondheidszorg%2B(verdiepingsmodules).pdf) (2015).
27. Lafuma A, Brezin A, Fagnani F, Mimaud V, Mesbah M, Berdeaux G. Nonmedical economic consequences attributable to visual impairment. *Eur. J. Health Econ.* 7(3), 158–164 (2006).
28. Goossens L, Knoester P, Rutten-Van Mölken M. Avastin (bevacizumab), Macugen (pegaptanib) en Lucentis (ranibizumab): vergelijking van medicatiekosten. *Pharmaceut. Weekb.* 2(4), 75–79 (2008).
29. Csákvári T, Elmer D, Németh N *et al.* A diabeteses polyneuropathia okozta epidemiológiai és egészségbiztosítási betegségterhe elemzése egészségbiztosítási adatok alapján. *Orvosi. Hetilap.* 162(Suppl. 1), 38–45 (2021).
30. Kaló Z, Kiss Z, Gerendy P, Nagyjanosi L, Voko Z. Cost of renal replacement therapy in Hungary: 2749. *Transplantation* 90, 735 (2010).
31. NEAK. Dialysis care annual fee, 2021 [Dialízis ellátások éves alapdíja 2021]. www.neak.gov.hu/pfile/file?path=/felso_menu/szakmai_oldal/alk/gyogyito_meglelozo_ellatas/szakellatas_muvese_kezeles/Dializis_ellatasok_eves_alapdija_2021.&inline=true (2021).
32. Drg. DRG 5.0 (in force from 2020.11.01) [HBCS 5.0 (Érv. 2020.11.01.)]. www.neak.gov.hu/felso_menu/szakmai_oldal/alk/gyogyito_meglelozo_ellatas/szabalykonyvek/bsorolo
33. De Groot S, Enters-Weijnen CF, Geelhoed-Duijvestijn PH, Kanters TA. A cost of illness study of hypoglycaemic events in insulin-treated diabetes in the Netherlands. *BMJ Open* 8(3), e019864 (2018).
34. Redekop WK, McDonnell J, Verboom P, Lovas K, Kalo Z. The cost effectiveness of Apligraf® treatment of diabetic foot ulcers. *Pharmacoeconomics* 21(16), 1171–1183 (2003).
35. Kind P, Hardman G, Macran S. UK population norms for EQ-5D (1999). www.york.ac.uk/che/pdf/DP172.pdf
36. Office for National Statistics. National life tables – life expectancy in the UK: 2018 to 2020. www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2018to2020

37. [Central Statistics Office]. [Population of Hungary by sex and age] (2022). www.ksh.hu/interaktiv/korfak/orszag.html
38. United Nations Department of Economic and Social Affairs Population Division. World Population Prospects 2019, custom data acquired via website. <https://population.un.org/wpp/> (2019).
39. Diabetes Atlas. Hungary Diabetes report 2000–2045 (2021). <https://diabetesatlas.org/data/en/country/91/hu.html>
40. Diabetes Atlas. Netherlands Diabetes report 2000–2045 (2021). <https://diabetesatlas.org/data/en/country/139/nl.html>
41. Diabetes Atlas. United Kingdom Diabetes report 2000–2045 (2021). <https://diabetesatlas.org/data/en/country/209/gb.html>
42. Diabetes Atlas (2021). <https://diabetesatlas.org/>
43. Ministry of Human Capacities. Professional guideline of Ministry of Human Capacities on conducting health-economic analyses [Az Emberi Erőforrások Minisztériuma szakmai irányelve az egészség-gazdaságtani elemzések készítéséhez]. EüK LXXI 21 (2021). www.neak.gov.hu/pfile/file?path=/letoltheto/EOSZEF_letoltheto_doku/002194-2021_Az_egeszseg-gazdasagtan_i_elemzesek_keszitesehez_es_ertekelesehez&inline=true
44. Vellekoop H, Huygens S, Versteegh M *et al.* Guidance for the harmonisation and improvement of economic evaluations of personalised medicine. *Pharmacoeconomics* 39(7), 771–788 (2021).

