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Detailed Description of Markov Simulation Modules

For retinopathy, we used the original DCCT prediction models for background diabetic retinopathy, macular edema, and proliferative retinopathy that relate glycated hemoglobin and duration of diabetes with the cumulative probability of developing these intermediate complications (courtesy Richard Eastman).[1, 2] For the transition from intermediate complications to blindness, we used annual probabilities from natural history studies of diabetic eye disease.[3, 4] For nephropathy, we again used the original DCCT prediction models microalbuminuria and gross proteinuria.[1, 2] For the transition from gross proteinuria to end-stage renal disease we used probabilities from a natural history study by Humphrey and colleagues.[5] For neuropathy, we used the DCCT prediction model for neuropathy. Once neuropathy developed, patients were subject to the risks of developing foot ulcers[6, 7] and amputation.[8] We assumed that the age at which risk of microvascular complications would begin was 17 years of age based on observations from epidemiological studies.[9]

For cardiovascular complications, there are no established prediction models for patients with type 1 diabetes in the literature. In lieu of such models, we employed prediction models for type 2 diabetes patients from the United Kingdom Prospective Diabetes Study for ischemic heart disease, myocardial infarction, congestive heart failure, and stroke.[10]

Hypoglycemic events are a major complication inherent to the treatment of type 1 diabetes.[11] Recent large studies have estimated the risk of severe hypoglycemic events (as defined in [12]) at 1.1 episodes per patient year in youth with insulin-treated type 1 diabetes.[13] In the hundreds of cases of NDM reported over the last five years after successful conversion to sulfonylureas, there is a consistent major decrease in the incidence of severe hypoglycemia, with only a single episode reported in the literature. We thus assume a rate of 1 episode per 1000 patient years, or 0.001 per patient year.

For diabetic ketoacidosis (DKA), we make a similar assumption that the risk of DKA is extremely low after successful conversion to sulfonylureas. While numerous patients before conversion have been reported to have experienced DKA (similar to type 1 diabetes patients) not a single case has yet been reported after switching off of insulin. We thus assume a rate of 0.01 per patient year based on the hypothetical concern that DKA could occur if a patient stopped all treatment. In contrast, DKA is a major cost of type 1 diabetes that has been suggested to occur 2-10 times per 100 patient-years. In those who are not screened or do not have a treatable mutation we assume a risk based on a recent large prospective study documenting 5.1 episodes of DKA per 100 patient-years. [14]

For mortality, first event mortality and diabetes mortality were based again on UKPDS models.[10] Background mortality rates were derived from National Vital Statistics Life Tables. As in prior diabetes modeling exercises, we subtracted the cardiovascular death rates from the overall death rates for the non-diabetes population (based on risk factor data from NHANES[15] and Framingham risk equations[16]) in order to obtain background death rates for the non-diabetes population. These mortality rates were then increased by 2.75 reflecting the increased risk of background mortality of diabetes patients compared to non-diabetes patients.[17-19]

Supplementary References

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Supplementary Table 1. Cost-effectiveness analysis base case model assumptions

Definition	Base-Case Value	References
Demographics		
Age at genetic testing	6	Pearson 2006[20], Stoy 2008[21]
Proportion women	0.5	Pearson 2006[20], Stoy 2008[21]
Proportion white	0.8	Chicago Neonatal Diabetes Registry
Clinical Characteristics		
Probability of having a genetic defect	0.416	Pearson 2006[20], Stoy 2008[21]
Probability of conversion to sulfonyurea (<14 years of age)	0.9	Pearson 2006[20], Stoy 2009
Probability of conversion to sulfonyurea (>14 years of age)	0.43	Chicago Neonatal Diabetes Registry
Duration of diabetes, years	0.25	Pearson 2006[20], Stoy 2008[21]
Blood pressure	Non-diabetic values	NHANES
Cholesterol	Non-diabetic values	NHANES; Wadwa 2005[22]
Body mass index	Age-gender based values	CDC Growth Charts
Smoking	0	Chicago Neonatal Diabetes Registry
A1C % if successfully converted to sulfonylurea	6.4	Pearson 2006[20], Stoy 2008[21]
A1C % if not successfully converted to sulfonylurea	8.1	Pearson 2006[20], Stoy 2008[21]
ANNUAL PROBABILITIES		
Diabetic retinopathy progression		
No retinopathy to background diabetic retinopathy (BDR)	DCCT equation intensive glucose arm	Eastman 1997[23]
BDR to Macular edema	DCCT equation intensive glucose arm	Eastman 1997[23]
BDR to Proliferative diabetic retinopathy (PDR)	DCCT equation intensive glucose arm	Eastman 1997[23]
Macular edema to blindness with photocoagulation	0.03	Vijan 2000[4]
PDR to blindness with photocoagulation	0.0148	Javitt 1994[3], Vijan 2000[4], ETDRS 1991[24]
Diabetic nephropathy progression		
Microalbuminuria	DCCT equation intensive glucose arm	Eastman 1997[23]
Microalbuminuria to Gross proteinuria	DCCT equation intensive glucose arm multiplied by 3 to obtain conditional probability	Eastman 1997[23], UKPDS 64[25]
Gross proteinuria to end-stage renal disease	0.0042 (0-11 years)	Humphrey 1989[5]
	0.0385 (12-24 years)	
	0.0740 (25 years+)	
Diabetic neuropathy progression		

Diabetic neuropathy	DCCT equation intensive glucose arm	Eastman 1997[23]
Neuropathy to foot ulcer	0.0075, without neuropathy	Young 1994[6], Gregg 2004[7]
	0.0435, with neuropathy	
Foot ulcer to amputation	0, no risk factors	Peters 2001[8]
	0, neuropathy	
	0.0067, neuropathy with foot deformity	
	0.095, history of foot ulcer	
Cardiovascular complications		
Ischemic heart disease	UKPDS equation	Clarke 2004[10]
Congestive heart failure	UKPDS equation	Clarke 2004[10]
Myocardial infarction	UKPDS equation	Clarke 2004[10]
Stroke	UKPDS equation	Clarke 2004[10]
Mortality		
First event mortality	UKPDS equation	Clarke 2004[10]
Diabetes mortality	UKPDS equation	Clarke 2004[10]
Background mortality	National Vital Statistics Life Tables ((non-cardiovascular death rate for non-diabetics)*2.75)	CDC, National Center for Health Statistics, 2004[15]; Patterson, 2007[17]; Skrivarhaug, 2006[18]; Dahlquist, 2005[19]
Diabetic ketoacidosis		
Sulfonylurea	0.001	Chicago Neonatal Diabetes Registry
Insulin	0.051	Karges, 2010[26]
Major hypoglycemic event requiring assistance		
Sulfonylurea	0.001	Chicago Neonatal Diabetes Registry; Rafiq, 2008[27]; Clarke, 2009[12]
Insulin	1.15	Cryer, 2008[11]
Other assumptions		
Prevalence of foot deformity	0.37	Rith-Najarian 1992[28]
Prevalence of peripheral vascular disease	0.15	Selvin, 2004[29]
Prevalence of atrial fibrillation	Gender and age specific prevalence from Kaiser population	Go at al, 2001[30]
TREATMENT COSTS	**2008 Dollars**	
Genetic testing and conversion		
Genetic testing of *KCNJ11*/*ABCC8*	$2,815	Athena Diagnostics, Inc. Price list
Transition to sulfonylurea costs	$4,366	Chicago Neonatal Diabetes Registry

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Glucometer costs		
Lancet (each)	$0.07	Redbook 2009
Annual lancet use on sulfonylurea	6	Chicago Neonatal Diabetes Registry
Annual lancet use on insulin	12	Chicago Neonatal Diabetes Registry
Strip (each)	$0.72	Redbook, 2009
Annual strip use on sulfonylurea	1095	Chicago Neonatal Diabetes Registry
Annual strip use on insulin	2190	DCCT, 1993, 2000[31, 32]
Minutes per Test Strip	5	Expert opinion
Pump and syringe costs		
Pump (annual)	$1,371.00	Weintrob, 2003[33]
Proportion pump	0.7	Chicago Neonatal Diabetes Registry
Multiple daily injections, syringe cost (annual)	$377.78	Redbook, 2009
Syringe utilization per day	4	Chicago Neonatal Diabetes Registry
Drug Costs		
Insulin - Glargine (Lantus) - per unit	$0.10	Redbook, 2009
Insulin Use (unit / kg / day)	0.70	Chicago Neonatal Diabetes Registry
Sulfonylurea - Glyburide 1.25mg - per tablet	$0.12	Redbook, 2009
Sulfonylurea - Glyburide 2.5mg - per tablet	$0.19	Redbook, 2009
Sulfonylurea - Glyburide 5mg - per tablet	$0.28	Redbook, 2009
Sulfonylurea Use	2-5 tablets 2-4 times/day	Pearson 2006[20], Stoy 2008[21]
Sulfonylurea Use (mg / kg / day)	0.73	Chicago Neonatal Diabetes Registry
Year of age - switch from small to medium tablets	10	Chicago Neonatal Diabetes Registry
Year of age - switch from medium to large tablets	14	Chicago Neonatal Diabetes Registry
COMPLICATION COSTS (2008 Dollars)		
Eye related costs		
Macular edema (event)	$951.48	O'Brien 2003[34]
Macular edema (state)	$93.77	O'Brien 2003[34]
Proliferative diabetic retinopathy (event)	$1,051.51	O'Brien 2003[34]
Proliferative diabetic retinopathy (state)	$93.77	O'Brien 2003[34]
Blindness (state)	$4,608.63	O'Brien 2003[34]
Kidney related costs		
Microalbuminuria (event)	$78.77	O'Brien 2003[34]
Microalbuminuria (state)	$18.75	O'Brien 2003[34]
Proteinuria (event)	$83.77	O'Brien 2003[34]
Proteinuria (state)	$27.51	O'Brien 2003[34]
ESRD (state)	$46,288.89	O'Brien 2003[34]

Neuropathy related costs		
Neuropathy (state)	$465.11	O'Brien 2003[34]
Foot ulcer (event)	$11,313.44	Singh 2005[35]
Lower extremity amputation (event)	$37,951.84	O'Brien 2003[34]
Lower extremity amputation (state)	$1,364.09	O'Brien 2003[34]
Cardiovascular complication costs		
Acute myocardial infarction (event)	$37,964.35	O'Brien 2003[34]
Acute myocardial infarction (state)	$2,098.02	O'Brien 2003[34]
Angina (event)	$7,531.85	O'Brien 2003[34]
Angina (state)	$1,945.48	O'Brien 2003[34]
Ischemic stroke (event)	$50,273.63	O'Brien 2003[34]
Ischemic stroke (event)	$16,777.88	O'Brien 2003[34]
Diabetic ketoacidosis	$4,237	Ellis, 2008[36]
Major hypoglycemic event requiring assistance	$1,300.91	Bullano 2005[37]
INDIRECT COSTS		
Caregiver time	Age and sex specific median hourly wage	Bureau of Labor Statistics 2007
Caregiver - Gender	Female	
Caregiver - Age	40	
UTILITIES		
Blindness	0.69	Dasbach, 1992[38]
End-stage renal disease	0.61	DCCT, 1996[39]
Foot ulcer	0.75	Redekop, 2004[40], Tennvall 2001[41]
Lower extremity amputation	0.68	Redekop, 2004[40]
Myocardial infarction or arrest	0.88	CDC, 2002[42]
Angina (Ischemic heart disease)	0.97	CDC, 2002[42]
Stroke	0.64	Rosen, 2005[43]
Life with sulfonylurea	0.96	Chin, 2008[44]
Life with insulin	0.86	Chin, 2008[44]
DISCOUNT RATE	0.03	

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Supplementary Figure 1. Cost-Effectiveness of Genetic Testing by Prevalence of Treatable Genetic Defects. Threshold analysis of the 30 year ICER ($/QALY) for a range of hypothetical lower prevalences of sulfonylurea-treatable mutations in *KCNJ11* and *ABCC8*, with all other base case assumptions held constant.