**Technical Appendix: Cost and Cost-Effectiveness of Large Scale Screening for Type 1 Diabetes in Colorado**

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The primary objective of this study was to evaluate the costs and clinical benchmarks needed to meet commonly cited cost-effectiveness thresholds of screening for pre-symptomatic type 1 diabetes. This technical appendix provides additional details on modeling inputs, structure, and validation.

**Markov Model Structure**

The Markov simulation model estimates long-run clinical and economic outcomes for the average type 1 diabetes patient (Appendix Figure 1). The model reflects the biological process of type 1 diabetes and is applicable to a wide range of treatment settings. The model structure includes the major diabetes complication states categorized by the American Diabetes Association (ADA): nephropathy, neuropathy, retinopathy, end-stage renal disease, coronary heart disease (CHD), and acute complications such as severe hypoglycemic episodes. The model approach links HbA1c to the risk of long-term diabetes complications. For the lifetime analysis, we extrapolated the findings from ASK and routine screening over the projected lifetime of patients using an adaptation from a previously published Markov simulation model (Microsoft Excel 2016, Redmond, WA).1,2 Specifically, annual transition probabilities were derived from the most recent microvascular and macrovascular follow-up evidence from the Diabetes Control and Complications Trial (DCCT), the Epidemiology of Diabetes Interventions and Complications (EDIC), and Pittsburgh Epidemiology of Diabetes Complications Experience studies.3-6 The analyses were adapted from previous work1,2 and split into two models.

**Model 1 – bridge model.** A bridge model was used to simulate patients through progression from risk of pre-diabetes (i.e., single antibody positive, multiple antibody positive) to a diagnosis of type 1 diabetes and death from ages 2 – 30. In model 1, screening and follow-up costs are assumed for all those screened up until age 18 and simulated patients are followed until age 30 to track diagnosis of type 1 diabetes.

**Model 2 – lifetime simulation model.** A lifetime simulation model from age 30 and over, for only those diagnosed with type 1 diabetes, was used to estimate the impact of changes in HbA1c from early detection of diabetes on clinical and economic outcomes (online Appendix Figure 1). The benefits of the ASK program include early detection of pre-symptomatic type 1 diabetes. Further, previous evidence suggests avoidance of DKA events has a sustained long-run benefit on HbA1c levels.7 Model 2 estimates the long-run HbA1c benefits (conditioned on avoiding DKA events at diagnosis) needed to offset up front screening costs by avoiding long-term diabetic complications and associated health care expenditures.

The outcomes of interest in model 2 include the reduction in DKA events alone in addition to improvements in HbA1c associated with the reduction in DKA events required to meet value thresholds of $50,000 to $150,000 per QALY gained over a lifetime.

A similar structure of disease progression has been used in many other validated diabetes modeling studies.8-12 The model structures use a cycle length of one year with varying time horizons based on each scenario. Due to methodological challenges related to the competing risks across categories of complications, we simulated separate cohort modules for complication paths. Therefore, for example, the percentage of the cohort experiencing CHD was not impacted (through mechanisms of competing risks) by the percentage of the cohort experiencing nephropathy. This method allows for population-level incidences across these four main categories of complications to be consistent with evidence-based risk predictors across all time horizons of the model.

In order to output average payoffs that were aggregated across the four complication modules, we assigned by model cycle, the module with the lowest proportion of the cohort alive to the no complication-related utility, cost, and severe hypoglycemic events. This is a conservative assumption within the Markov model related to mortality for interventions that improve survival in that we are assigning the mortality of the most severe module, but are not accounting for possible additional mortality from the other three modules. This method for aggregating across the main complications in diabetes is similar to other modeling approaches of this disease.8-11 For each complication state within each module, the disutility and cost was assigned to the proportion of the cohort experiencing the complication. Thus, for a given time cycle, if 5% of the cohort was assigned to end-stage renal disease (nephropathy module) and 10% of the cohort had macular edema (retinopathy module), the model is agnostic to the overlap in those that have both end-stage renal disease and macular edema, but assigns the disutility and cost associated with each complication at the percentage of the cohort who are experiencing that complication (for a given time cycle, the model would track the end-stage renal disease disutility and cost for 5% of the cohort with end-stage renal disease and the macular edema disutility and cost for 10% of the cohort with macular edema). In other words, a patient with end-stage renal disease and macular edema would be assigned a disutility (cost) equal to the disutility (cost) of end-stage renal disease plus the disutility (cost) of macular edema.



**Appendix Figure 1. Modeling framework for pre-type 1 diabetes and long-run type 1 diabetes disease progression.** The population includes children screened from ages 2 – 18 and followed until diagnosis of type 1 diabetes until age 30. All those diagnosed move to the long-run type 1 diabetes model and are followed over a lifetime. Treatment arms are split by screening and no screening with the impact of HbA1c changes from early detection and education as the primary driver of long-run complications. An example one year cycle has patients starting at no complications and moving into microvascular disease states (e.g., retinopathy, neuropathy, and nephropathy) or macrovascular disease states (e.g., myocardial infarction, congestive heart failure, ischemic heart disease, and stroke). Patients can die from all cause death or complication-related death.

**Model Inputs**

**Appendix Table 1. Key Bridge Model Inputs**

|  |  |  |
| --- | --- | --- |
| **Input parameter** | **Mean** | **Source(s)** |
| Diabetes incidence among 0-35 year olds in CO (per year) | Age dependent from 23/100,000 to 45.5/100,000 | 13 |
| Diabetes risk ratio single ab+ | 1.3 | 14 |
| Diabetes risk ratio multiple ab+ | 1.5 | 14 |
| Proportion of new diagnoses with severe DKA events  | 46% | 15,16 |
| Relative risk of DKA | 0.2 | 15,16 |
| Association of DKA events to HbA1c | Time since diagnosis dependent | 7 |
| Screening panel cost | $15; $139 | ASK program; Centers for Medicare & Medicaid Services17 |

**Varied in sensitivity**

**Appendix Table 2. Utility inputs**

|  |  |  |
| --- | --- | --- |
| **Input** | **Mean** | **Source(s)** |
| Utility diabetes with no complications (adults) | 0.90 | 18 |
| Utility healthy no diabetes (children) | 1.00 | 19 |
| Disutility DKA | 0.05 | 20 |
| Disutility major hypoglycemic event | 0.047 | 20 |
| Disutility minor hypoglycemic event | 0.005 | 20 |
| Diabetic retinopathy | 0.761 | 19 |
| Blindness | 0.718 | 19 |
| Neuropathy | 0.752 | 19 |
| Amputation | 0.721 | 19 |
| Nephropathy (micro) | 0.724 | 19 |
| End stage renal disease | 0.67 | 19 |
| Cardiovascular disease | 0.70 | 19 |

**Appendix Table 3. Health State Cost Inputs**

|  |  |  |
| --- | --- | --- |
| **Input** | **Mean(2018 USD)** | **Source(s)** |
| Cost to treat DKA event | $9,319 | 21 |
| Cost of managing diabetes | $12,919 | 22 |
| Cost of unrelated health care  | $2,831 | 23 |
| Cost to treat major hypo event | $19,676 | 24 |
| Cost to treat minor hypo event | $210 | 24 |
| Diabetic retinopathy event year | $733 | 24 |
| Blindness event year | $3,417 | 24 |
| Neuropathy event year | $1,048 | 24 |
| Amputation event year | $10,795 | 24 |
| Nephropathy (micro) event year | $94 | 24 |
| End stage renal disease event year | $85,630 | 24 |
| Cardiovascular disease event year | $67,398 | 24 |
| Diabetic retinopathy follow-up | $84 | 24 |
| Blindness follow-up | $3,417 | 24 |
| Neuropathy follow-up | $1,315 | 24 |
| Amputation follow-up | $0 | 24 |
| Nephropathy (micro) follow-up | $0 | 24 |
| End stage renal disease follow-up | $85,630 | 24 |
| Cardiovascular disease follow-up | $2,273 | 24 |

\*Mean estimates varied in one-way and probabilistic sensitivity analyses using 2.5 and 97.5 percentiles of evidence-based probability distributions

**Appendix Table 4. Time-Varying Transition Probability Sources**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Complication** | **Source** | **Hazard Ratio for 1% increase in HbA1c** | **Distribution** | **Shape** | **Scale** |
| Cardiovascular disease | 5 | 1.25(1.10, 1.43) | Gompertz | 0.21 | 0.0003 |
| Peripheral neuropathy | 4 | 1.53(2.12, 3.57) | Weibull | 1.57 | 28.48 |
| Microalbuminuria | 3 | 1.80(1.54, 2.10) | Log-normal | 5.41 | 1.47 |
| Proliferative diabetic retinopathy | 6 | 2.37(1.83, 3.06) | Weibull | 1.44 | 88.73 |

**Appendix Table 5. Other Transition Probability Sources**

|  |  |  |
| --- | --- | --- |
| **Complication** | **Source** | **Mean value** |
| Proliferative retinopathy to blindness | 25 | 0.0064 |
| Peripheral neuropathy to amputation | 26,27 | Varies from 0.028 to 0.14 dependent on duration of diabetes |
| Subsequent amputation | 26,27 | 0.1294 |
| Microalbuminuria to end-stage renal disease | 26,27 | Varies from 0.0042 to 0.074 dependent on duration of diabetes |

**Sensitivity Analyses**

Appendix Table 6 provides one-way sensitivity analysis results for lower and upper HbA1c projections from Duca et al.7 Due to a lack of long-run knowledge on the impact of the ASK screening program including the number of DKA events avoided and HbA1c among cases detected, we relied on assumptions using published evidence from Colorado. Specifically, we link DKA avoidance with recent evidence on the improvement in long-run HbA1c.7,28,29 To address the strength of this assumption, we provide multiple risk reduction scenarios for DKA events and resulting HbA1c changes. In Appendix Table 6, we provide additional sensitivity analysis results. Specifically, using standard error estimates from Duca et al., we vary HbA1c projections by lower and upper values for both populations within each DKA percentage reduction category, while holding all other input parameters constant in the model. This sensitivity analysis displays the impact on lower than expected and higher than expected changes in HbA1c from percentage reductions in DKA events. Note the incremental DKA treatment costs at diagnosis do not change as they are not conditional on changes in HbA1c. However, all other diabetes complication costs, incremental QALYs, and total costs change based on changes in HbA1c and associated complications and costs to manage and treat those complications. Please also note that upper and lower incremental cost estimates should not be interpreted as crossing a threshold of statistical significance. Rather, these results should be used as potential ranges of cost and effectiveness projections to address model limitations around projecting HbA1c over a lifetime horizon.

**Appendix Table 6. One-way sensitivity analysis for incremental lifetime population-level cost and clinical outcomes based on projected reductions in DKA events and resulting improved HbA1c from screening and follow-up**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| % Reduction in DKA events (Screening vs. no screening) | Proportion of Patients with DKA events in screening arm | Incremental average population HbA1c for type 1 diabetes patients(95% confidence interval from Duca et al.) | Incremental DKA treatment costs at diagnosis§ | Incremental other diabetes complication costs over a lifetime† | Incremental Effectiveness (QALYs) | Incremental total costs (ASK Screening vs. No Screening)‡ | Incremental total costs (Routine Screening vs. No Screening)‡ |
| 0% | 46% | 0.0% | $0 | $0 | 0 | $560,000 | $1,641,000 |
| 20% | 37% | -0.1%(-0.09%, -0.18%) | -$37,000 | -$506,000(-$662K, -$346K)  | 17(13, 21) | $18,000\*(-$138K, $177K)  | $1,098,000\*($942K, $1.3M)  |
| 40% | 28% | -0.3%(-0.18%, -0.36%) | -$73,000 | -$965,000(-$1.2M, -$670K) | 33(25, 40) | -$478,000\*\*(-$759K, -$182K) | $602,000\*($321K, $898K) |
| 60% | 18% | -0.4%(-0.27%, -0.54) | -$110,000 | -$1,384,000(-$973K, -$1.8M) | 49(36, 58) | -$934,000\*\*(-$1.3M, -$522K) | $147,000\*(-$235K, $558K) |
| 80% | 9% | -0.5%(-0.37%, -0.71%) | -$146,000 | -$1,769,000(-$2.2M, -$1.3M) | 64(48, 76) | -$1,355,000\*\*(-$1.8M, -$843K) | -$274,000\*\*(-$1.8M, $236K) |

§ All costs are in 2018 USD and rounded to the nearest $1,000; †Other diabetes complication costs include treatment and management of annual hypoglycemic events and long-run diabetes-related complications; ‡Total costs include screening costs for n=10029 children and adolescents, DKA treatment costs for cases that are diagnosed with type 1 diabetes and experience a DKA event, and all other diabetes complication costs over a lifetime for the predicted cases that convert to diabetes; \*Costs of screening offset enough for screening to be cost-effective at $150,000 per QALY or less; \*\*Costs of screening offset completely resulting in cost savings scenario

**Model Validation**

In previous versions, we have thoroughly tested the internal validation of the Markov model by investigating errors when adjusting inputs to extreme values. The process of internal validation included examination of all programming code, also known as “debugging.” We conducted an internal validation exercise to compare simulated percentages between the McQueen et al. model and the risk equations. We used the goal seek function to calibrate the model for precise estimation of cumulative incidence estimates shown in Appendix Table 7.

**Appendix Table 7. Internal Validation Results**

|  |  |  |  |
| --- | --- | --- | --- |
| **Complication** | **Validation estimate** | **Model estimate** | **Source** |
| Cardiovascular disease | 3% | 3% | Nathan et al. 2005 Figure 1A intensive treatment group |
| Peripheral neuropathy | 25% | 25% | Martin et al. 2006 Figure 1 intensive treatment group |
| Microalbuminuria | 21% | 21% | de Boer et al. 2008 Figure 1 intensive treatment group |
| Proliferative diabetic retinopathy | 10% | 10% | Nathan et al. 2009 Figure 2A intensive treatment group |

PDR: baseline age at 27, cumulative incidence estimated at duration of diabetes of 21 years; estimates through EDIC year 12

PN: baseline age at 33, cumulative incidence estimated at duration of diabetes of 19 years; approximated from Albers et al. with incidence of 25% after baseline group began with incidence of 7%

Micro: baseline age at 33, cumulative incidence estimated at duration of diabetes of 21 years

CVD: baseline age at 27, cumulative incidence estimated at duration of diabetes of 21 years

In addition to the internal validation, we conducted an external validation exercise comparing direct medical cost differences between our model and the IMS CORE model based on changes in HbA1c.30 Due to methodological differences in modeling approaches, the results are not directly comparable, but rather give an indication of whether the model cost estimates are in reasonable ranges compared to other validated models. The IMS CORE model also includes additional health states not included in the McQueen et al. model. Therefore, caution must be exercised when comparing the McQueen et al. model estimates with the Baxter et al. estimates. Each column in Appendix Table 8 presents cost savings at the patient level from reducing HbA1c.

**Appendix Table 8. Comparison of type 1 diabetes cost reductions per person from avoided complications**

|  |  |  |
| --- | --- | --- |
|  | Baxter et al. model (IMS CORE) | McQueen et al. |
| HbA1c | 5 years | 10 years | 5 years | 10 years |
| *Per-person cost reductions* |  |  |   |  |
| Reduction from 8% to 7.5% | £89 | £358 | £23 | £199 |
| Reduction from 9% to 8% | £103 | £494 | £45 | £395 |

Notes: Validation uses costs for complications (2014 pound sterling) from Baxter et al.; Baxter et al. model includes other health states not included in McQueen et al. model and therefore not directly comparable

For example, after 10 years, a reduction in HbA1c from 9% to 8% resulted in a cost savings per patient of £494 and £395 from the IMS CORE and McQueen et al. models, respectively. Over a 5 year period, a reduction in HbA1c from 9% to 8% resulted in a cost savings per patient of £103 and £45 from the Baxter et al. and McQueen et al. models, respectively. The McQueen et al. model estimates are in similar ranges, but underestimate cost savings compared to the IMS CORE model estimates. For the purposes of estimating cost savings from HbA1c improvements, one could interpret the cost savings projected by the McQueen et al. model as being conservative.

Methodological differences between Baxter et al. and McQueen et al. are likely the driver of these differences. First, the IMS CORE model is a patient-level model that requires direct input of patient-level data. The McQueen et al. model relies on a population-level cohort analysis. Second, as mentioned previously, the IMS CORE model includes additional health states and costs not included in the McQueen et al. model. For example, IMS CORE includes additional costs for laser treatment and cataract operation for blindness; separate costs for Angina; a range of different ulcer costs (broken down by infected vs. not infected); and multiple renal complication states and costs. Third, Baxter et al. included the concept of excess bed days for people with diabetes. This inclusion of excess bed days totaled nearly 25% of their total cost estimates. This concept was not included in the cost inputs of the McQueen et al. analysis. Even with the different approach taken by the IMS CORE and McQueen et al. model, the estimates are in reasonable ranges that move in the expected direction of higher differences in HbA1c equating to higher differences in complications and costs.

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