



Cost and Cost-effectiveness of Large-scale Screening for Type 1 Diabetes in Colorado

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R. Brett McQueen,¹
Cristy Geno Rasmussen,² Kathleen Waugh,²
Brigitte I. Frohnert,² Andrea K. Steck,²
Liping Yu,² Judith Baxter,² and
Marian Rewers²

OBJECTIVE

To assess the costs and project the potential lifetime cost-effectiveness of the ongoing Autoimmunity Screening for Kids (ASK) program, a large-scale, presymptomatic type 1 diabetes screening program for children and adolescents in the metropolitan Denver region.

RESEARCH DESIGN AND METHODS

We report the resource utilization, costs, and effectiveness measures from the ongoing ASK program compared with usual care (i.e., no screening). Additionally, we report a practical screening scenario by including utilization and costs relevant to routine screening in clinical practice. Finally, we project the potential cost-effectiveness of ASK and routine screening by identifying clinical benchmarks (i.e., diabetic ketoacidosis [DKA] events avoided, HbA_{1c} improvements vs. no screening) needed to meet value thresholds of \$50,000–\$150,000 per quality-adjusted life-year (QALY) gained over a lifetime horizon.

RESULTS

Cost per case detected was \$4,700 for ASK screening and \$14,000 for routine screening. To achieve value thresholds of \$50,000–\$150,000 per QALY gained, screening costs would need to be offset by cost savings through 20% reductions in DKA events at diagnosis in addition to 0.1% (1.1 mmol/mol) improvements in HbA_{1c} over a lifetime compared with no screening for patients who develop type 1 diabetes. Value thresholds were not met from avoiding DKA events alone in either scenario.

CONCLUSIONS

Presymptomatic type 1 diabetes screening may be cost-effective in areas with a high prevalence of DKA and an infrastructure facilitating screening and monitoring if the benefits of avoiding DKA events and improved HbA_{1c} persist over long-run time horizons. As more data are collected from ASK, the model will be updated with direct evidence on screening effects.

Type 1 diabetes currently affects an estimated 1.25 million people (1), including 132,000 children and adolescents in the U.S. (2). The lifetime risk now exceeds 1%, and the incidence increases by 3% annually (2–4). Patients often experience a delay in diagnosis and care because 90% have no family history of type 1 diabetes and are less likely to recognize disease symptoms (5). As a consequence, patients experience complications that could have been avoided with a more timely diagnosis. Studies of high-risk children have led to the consensus that presymptomatic type 1 diabetes in

¹Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus, Aurora, CO

²Barbara Davis Center for Diabetes, University of Colorado School of Medicine, Aurora, CO

Corresponding author: R. Brett McQueen, robert.mcqueen@cuanschutz.edu

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children should be identified early to educate caregivers with regard to symptoms of hyperglycemia and to allow timely diagnosis before onset of potentially life-threatening diabetic ketoacidosis (DKA) (6–9). Diabetes awareness and minimal home blood glucose monitoring can prevent >80% of hospitalizations for DKA, including life-threatening complications such as cerebral edema (10). In Colorado, during the past two decades, the proportion of children presenting with DKA at initial diagnosis has increased from ~30% to 58% (11,12). While mortality has decreased, children in the U.S. die every year as the result of delayed diagnosis of type 1 diabetes. Prevention of DKA at diagnosis is associated with improved long-term glycemic control and a decreased risk of vascular complications and memory deficits (13,14).

The Autoimmunity Screening for Kids (ASK) program detects presymptomatic type 1 diabetes (15) (stage 1 or stage 2) and celiac disease in participating children at <\$100 per child screened. The ASK program is a research study aimed at 1) preventing complications as a result of delayed diagnosis of type 1 diabetes and celiac disease, 2) increasing awareness and education surrounding type 1 diabetes and celiac disease, and 3) rigorously developing the evidence to assess the feasibility of universal screening for these common childhood autoimmune diseases.

While the benefits of universal screening include prevention of hospitalizations for DKA and improvements in long-term glycemic control, there is a need to identify benchmarks for these clinical outcomes that meet cost-effectiveness thresholds over long-run time horizons. A previous short-term analysis suggested that price decreases to <\$1 for autoantibody testing would be required to reach a breakeven point of costs (16). However, that analysis was focused solely on the cost of avoiding DKA events in the short run and did not estimate the long-run cost-effectiveness of universal diabetes screening. Cost-effectiveness estimates, such as cost per case detected, do not provide a comprehensive assessment of the value of early diabetes screening given the potential impact of screening on lifetime survival and cost outcomes. This is particularly relevant in light of recent evidence for sustained improvement of glycemic

control from early detection and education, suggesting that the benefits of early diabetes screening may not materialize until later stages of the disease (13,17,18). The primary objective of the current study was to evaluate the costs and clinical benchmarks needed to meet commonly cited cost-effectiveness thresholds of ASK screening and, separately, routine screening for presymptomatic type 1 diabetes.

RESEARCH DESIGN AND METHODS

Study Participants

The ASK study started screening in January 2017 and will continue through 2020 with the intention of screening >50,000 general population Colorado children ages 2–17 years for islet autoantibodies to detect presymptomatic type 1 diabetes and for transglutaminase autoantibodies (TGAs) to detect celiac disease. The screening methods relevant to the results presented here are described below. Children are screened at pediatric and family practices, hospitals, and community events. The study protocol has been reviewed and approved by the Colorado Multiple Institutional Review Board (COMIRB #14–0553).

This report includes data for 10,029 children and adolescents screened by 11 July 2018. Their mean age was 9.3 years (SD 4.4); 50.3% were female. Hispanics accounted for 51.4%, non-Hispanic whites for 35.2%, non-Hispanic African Americans for 7.8%, and other races for 5.6% of the study population. Only 5.0% of the participants had a first-degree relative with type 1 diabetes. Cases were defined as children and adolescents with multiple islet autoantibodies (10-year risk of progression to clinical diabetes of 70% [19]) or a single high-affinity autoantibody detected by radio-binding and electrochemiluminescent assays after confirmation (20).

Data Collected During ASK

Our methodology to measure the cost per case detected consisted of the following steps: 1) identify all resource utilization events as part of the ASK program, 2) measure the amount of resources consumed in the relevant units (e.g., time), and 3) establish the cost per unit of resources. In addition, we stratify results that apply only to the ASK program and, separately, for results that

would apply to a routine screening setting. First, we report the resource utilization, costs, and effectiveness measures from the ongoing ASK program compared with usual care (i.e., no screening). Second, we report the resource utilization and costs that only would apply to a routine screening setting compared with usual care (i.e., no screening). Routine screening does not include research components such as time for consenting and questionnaires in addition to the outreach and media campaign costs that were included to increase the uptake of the ASK program.

Screening Activities and Time

The authors observed how the screening was performed at the ASK screening sites. On the basis of this observation and in consultation with program managers and screeners, there was agreement that the screening process could be divided into four activities: 1) recruitment, 2) consenting, 3) completing a screening questionnaire, and 4) blood sample collection and processing. Recruitment consisted of approaching families in the waiting area of the clinics or hospitals to describe the purpose of the screening. If a parent or legal guardian consented to the screening, a research questionnaire was administered to ascertain the family history and typical symptoms of type 1 diabetes and celiac disease as well as to document basic demographic data and contact information for two people. None of these activities would be needed if the screening were done in the context of routine primary care preventive screening supported by an electronic medical record. The final step consisted of sample collection, which was done by a finger prick or venipuncture.

To measure the average time required to complete the screening, we asked screeners to prospectively complete a time log measuring the start and end times for each of the four steps. The time it took to perform each activity varied depending on the number of screeners working together and the number of children screened together. This information and type of sample collection (i.e., finger prick, venipuncture) were also recorded. The screening tests included measurement of autoantibodies to insulin, GAD, tyrosine phosphatase-related islet antigen 2, and zinc transporter

8 for presymptomatic type 1 diabetes autoantibodies, and TGAs for celiac disease were also measured, but the TGA cost was excluded (21–23).

Outreach and Media Costs

An outreach campaign was implemented to increase community awareness and education surrounding type 1 diabetes and celiac disease. The campaign was led by a Denver-based branding and position company. An ASK logo and ASK marketing materials were created in addition to a study website, Facebook page, and various promotional items. ASK marketing materials were targeted to the community at large, providers, and parents. ASK campaign communications and messaging were tailored to build community and provider investment in the ASK screening program. ASK promotional materials included print, radio, television, and social media outlets.

Unit Costs for Screening-Related Activities

Unit costs were assigned for the panel of screening tests, the screeners to complete the four-step screening process, the additional cost of communicating the results by mail to all participants and by phone and mail to parents of positive cases, and a repeat of the screening testing to confirm positive cases. The screening panel testing from ASK was a negotiated rate of \$15 that represents a lower unit price than observed across commercial health insurers. Therefore, we used the Centers for Medicare & Medicaid Services (CMS) laboratory fee schedule price of \$138 as an estimate of screening costs under routine screening settings. The CMS estimate was confirmed in the PharMetrics Plus (IMS Health Real-World Data Adjudicated Claims) commercial claims database by estimating the commercial and public paid amounts over the previous 5 years. All screeners were at a medical assistant level of education and training and, therefore, were applied a wage with fringe benefits derived from the U.S. Bureau of Labor Statistics (24). In addition, we assign a unit cost for a diabetes educator to communicate the results to all positive cases.

Estimating the Incremental Cost-Effectiveness Ratio

Results are reported from two separate analyses relying on similar data sources: 1) ASK screening using resource

utilization, costs, and effectiveness evidence from the first year of the ASK program and 2) routine screening that relies on nonnegotiated screening prices, as described above, and removes protocol-driven resources and costs from ASK. The routine screening scenario was designed to provide an expectation of resources used and potential value gained in routine clinical practice. Both ASK and routine screening analyses report the number of positive cases detected, total costs for all screened, cost per child screened, and cost per case detected. Cases were defined as children and adolescents with a single high-affinity autoantibody (5-year risk of progression to clinical diabetes of 30% [25]) or multiple islet autoantibodies (5-year risk of progression to clinical diabetes of 44% [19]) identified and confirmed from ASK screening. Finally, we project the potential costs and effectiveness from the U.S. payer perspective of both ASK and routine screening by varying potential clinical benefits (i.e., DKA events avoided, HbA_{1c} improvements vs. no screening) and identifying clinical benchmarks needed to meet commonly cited value thresholds of \$50,000–\$150,000 per quality-adjusted life-year (QALY) gained over a lifetime horizon (26,27). All cost estimates are expressed in 2018 U.S. dollars (USD). Cost and cost-effectiveness of simultaneous screening for celiac disease in ASK are not included in these analyses.

Within-Screening Analyses

The within-screening analysis includes all screening utilization, costs, and effectiveness up to 1 year from the start of the ASK Program. ASK screening estimates included all costs from ASK, including research and outreach and recruitment costs, while routine screening included the costs relevant to routine screening only. Results for both ASK and routine screening are reported as the number of positive cases detected, total costs for all screened, cost per child screened, and cost per case detected.

Lifetime Analyses

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 (Excel 2016; Microsoft Corporation, Redmond, WA) (28,29). The Markov

simulation model estimates long-run clinical and economic outcomes for the average patient with type 1 diabetes (Supplementary Material). 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: nephropathy, neuropathy, retinopathy, end-stage renal disease, cardiovascular disease, and acute complications, such as severe hypoglycemic episodes. The model approach links HbA_{1c} to the risk of long-term diabetes complications. 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 (30–33). The analyses were adapted from previous work and split into two models.

Model 1: Bridge Model

A bridge model was used to simulate patients through progression from risk of prediabetes (i.e., single antibody positive, multiple antibody positive) to a diagnosis of type 1 diabetes and death from ages 2 to 30 years. In model 1, screening and follow-up costs are assumed for all those screened up until age 18 years, and simulated patients are followed until age 30 years to track diagnosis of type 1 diabetes. The screening and follow-up costs include the following: initial screening costs for 10,029 children and adolescents screened (Table 2), communicating results, two follow-up visits a year until age 18 years, and repeat screening panel costs for all positive cases identified over the duration of the model time horizon.

Model 2: Lifetime Simulation Model

A lifetime simulation model from age ≥ 30 years for only those diagnosed with type 1 diabetes was used to estimate the impact of changes in HbA_{1c} from early detection of diabetes on clinical and economic outcomes (Supplementary Fig. 1). The benefits of the ASK program include early detection of presymptomatic type 1 diabetes. Further, previous evidence has suggested that avoidance of DKA events has a

sustained long-run benefit on HbA_{1c} levels (13). Model 2 estimates the long-run HbA_{1c} benefits (conditioned on avoiding DKA events at diagnosis and sustained over the model horizon) needed to offset upfront screening costs by avoiding long-term diabetic complications and associated health care expenditures. To link screening benefits to long-run complications, we vary different combinations of reductions in DKA events and resulting improvements in HbA_{1c} that are associated with diabetes-related complications. Costs and outcomes were discounted at 3% per year (34).

The outcomes of interest in model 2 include the reduction in DKA events alone in addition to improvements in HbA_{1c} associated with the reduction in DKA events required to meet value thresholds of \$50,000–\$100,000 per QALY gained over a lifetime. The QALY is a life expectancy estimate that is weighted in each time period and health state by a number ranging from 0 to 1, where 0 corresponds to death and 1 corresponds to perfect health. The weights are called health utilities and reflect the desirability of living in a health state such as type 1 diabetes (35). The QALY is the recommended estimate of effectiveness for cost-effectiveness studies by the Second Panel on Cost-Effectiveness in Health and Medicine because it is a combined metric of quality and quantity of life that can be used to compare the value of interventions across diseases (34). A detailed description of the model can be found in the Supplementary Material.

Sensitivity Analyses

To address the strength of the linked assumption between DKA avoidance and improvements in HbA_{1c} (13,17,18), we provide multiple risk reduction scenarios for DKA events and resulting HbA_{1c} changes. In Supplementary Table 6, we provide additional sensitivity analysis results. Specifically, using SE estimates from Duca et al. (13), we vary HbA_{1c} 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 HbA_{1c} from percentage reductions in DKA events.

RESULTS

Within-Screening Results

Direct Costs Measured During ASK

Initial investment in outreach and recruitment costs included campaign costs, development of the logo, design and production, website development, and ASK website monitoring. The total cost over this initial phase was ~\$90,000 (Table 1).

The total cost per person screened to recruit, consent, administer questionnaires, and draw a blood sample was estimated at ~\$22.50. To estimate a unit cost for routine screening that does not include research, consent, and questionnaires, we developed a survey to identify each screening component to isolate only costs relevant for routine screening. A total of 28 time logs were completed involving 44 participants. Of the parents or legal guardians approached, the majority (57%) of them were accompanying one child, although in some cases, there were two or three children (29% and 14%, respectively). The average time to conduct all screening activities was ~17 min (Table 1) for a mean time cost of ~\$6 per child screened using a medical assistant wage of \$39,740 with fringe benefits included (24). Including only screening time related to a blood draw resulted in a time cost for routine screening of \$1.79.

Cost Per Case Detected

ASK detected a single high-affinity islet autoantibody in 0.53% of the participants and multiple autoantibodies in 0.48%. Positive cases detected for all children screened was 101 (Table 2). The total costs for all children screened for ASK was \$471,000 and \$1,417,500 for routine care screening. Cost per child screened was \$47 for ASK screening and \$141 for routine screening. Cost per case detected was \$4,700 for ASK screening versus no screening and \$14,000 for routine screening versus no screening. The main driver of total cost differences between ASK and routine screening was the negotiated screening price of \$15 versus the CMS laboratory fee schedule price of \$138.

Lifetime Analyses

On the basis of model 1 predicted by age 30 years, among the initial 10,029 children and adolescents screened, 80 will progress to type 1 diabetes (36) (Table 3).

We assumed that the prevalence of DKA at diagnosis in routine care without screening was 46% and the subsequent population-level HbA_{1c} average was 9.1% (76 mmol/mol) using Colorado-specific data (13). Follow-up time costs for positive cases until age 18 years increased the screening intervention cost to \$560,000 and \$1,641,000 (discounted) for ASK and routine screening, respectively.

Model 2 projected discounted total costs over a lifetime for the 78 people with type 1 diabetes as \$19.5 million and \$20.3 million for diabetes-related complication costs and total costs, respectively (Table 3). Discounted QALYs over a lifetime for the 78 people with type 1 diabetes was projected as 2,573 QALYs or an average of 33 QALYs per person.

Incremental costs in Table 4 show changes in costs and QALYs over a lifetime by way of reducing DKA events at diagnosis and improving HbA_{1c} for ASK and routine screening. To achieve value thresholds of \$50,000–\$100,000 per QALY for ASK screening and routine screening, screening costs would need to be offset by cost savings through a minimum 20% relative reduction in DKA events at diagnosis in addition to a 0.1% (1.1 mmol/mol) subsequent improvement in HbA_{1c} over a lifetime compared with no screening for patients who develop type 1 diabetes (Table 4). Greater reductions in DKA events at diagnosis of at least 40% and a subsequent improvement in HbA_{1c} of 0.3% (3.3 mmol/mol) led to cost savings for ASK screening. Cost savings were not achieved from avoiding DKA events alone in either ASK or routine screening. Sensitivity analyses (Supplementary Table 7) display projected lower and upper ranges of cost and effectiveness from changes in DKA and HbA_{1c} over a lifetime horizon.

CONCLUSIONS

Emerging evidence suggests that screening and education for type 1 diabetes can avoid DKA events at diagnosis and provide persistent improvements in HbA_{1c}. The ongoing ASK program has screened >10,000 children and adolescents and has provided early education and awareness for the families of 1.0% children who were identified with presymptomatic type 1 diabetes. Early experience from ASK suggests that this

Table 1—Resource utilization and costs to run the ASK program

Category	ASK inputs	Routine screening inputs	Source
Initial outreach and recruitment costs			
Campaign costs	\$10,000	NA	ASK marketing consultants
Development of logo	\$25,000	NA	ASK marketing consultants
Design and production	\$15,000	NA	ASK marketing consultants
Website development and maintenance	\$30,000	NA	ASK marketing consultants
Monitoring ASK website	\$10,000	NA	ASK marketing consultants
Screening price for four tests	\$15	\$138	ASK program, CMS (38)
Time per patient screened (min), mean (SD)			
Recruiting	3.5 (2.0)	NA	ASK program, resource utilization survey
Consenting	3.0 (1.3)	NA	ASK program, resource utilization survey
Questionnaire	5.5 (1.9)	NA	ASK program, resource utilization survey
Sample	5.6 (3.0)	5.6 (3.0)	ASK program, resource utilization survey
Total	17.4 (3.4)	5.6 (3.0)	ASK program, resource utilization survey
Time cost per patient for recruiting, consenting, questionnaires, and sample			
	\$22.50	\$1.79*	ASK program, resource utilization survey
Communicating results and follow-up for cases (per follow-up)			
	\$20.73	\$20.73	Diabetes educator time cost (40)

Usual care was assumed to be a do-nothing approach and, therefore, does not include any screening costs. NA, not applicable. *For time cost of sample only.

approach can reduce the rate of DKA at diagnosis to <10%, consistent with previous reports (6,7,37).

We estimated and reported an ASK screening scenario, which includes a discounted screening price and research protocol costs. In addition, we provide an expectation of resources used and potential value gained in clinical practice through a routine screening scenario that uses a CMS paid price for the screening panels but removes protocol-driven resources and costs from ASK. The cost per case was \$4,700 in ASK. It would increase for a hypothetical routine screening program if CMS was unable to negotiate a price significantly <\$138 (38). The cost-effectiveness of routine screening will largely depend on the cost of laboratory testing, and further effort is needed to develop affordable high-throughput methods for detecting islet autoantibodies. While the ASK discounted laboratory research price of \$15 is likely unsustainable today for a mass screening, the costs of a routine screening would be completely offset with a

40% decrease in DKA and the laboratory price of \$80.

Previous evidence on the cost-effectiveness of screening for type 1 diabetes risk focused on the cost-effectiveness of avoiding DKA events alone (16). Meehan et al. (16) proposed a screening program that is based on the screening and follow-up algorithm from The Environmental Determinants of Diabetes in the Young (TEDDY). The objective was to estimate the breakeven point for neutral costs between screening and no screening by varying the price of the screening tests. The authors found a price decrease to <\$1 (USD) would be required for a cost-neutral scenario. The focus of the Meehan et al. analysis was on avoiding short-run severe DKA events and the associated cost offsets. It is important to recognize, however, that type 1 diabetes is a lifetime, chronic disease whose trajectory is significantly affected not only by the events at onset but also by diabetic control over many years. Our analysis builds on previous work by adding a longer-term perspective by including

not only the cost offsets from avoiding DKA events but also the impact of DKA events on long-run glycemic control and the impact of glycemic control on long-run complications and associated costs. While the estimates from Meehan et al. are not directly comparable to our analysis, our results suggest that the value of screening materializes over longer-run time horizons more appropriate for a chronic condition.

If all 70 million U.S. children 1–17 years of age were screened today, an estimated 700,000 would be found with islet autoantibodies and a high risk for type 1 diabetes. To put our results in a broader context, the routine newborn screening for ~30 rare diseases costs the U.S. ~\$125–\$150 per child, depending on the panel requested (38). Fewer than 1 in 600 infants have one of these rare diseases detectable by testing a blood sample. The ASK program detects pre-symptomatic type 1 diabetes and celiac disease in participating children at <\$50 per child screened. One in 30 children has one of these conditions.

Table 2—Within-ASK screening program results during first year

Outcomes over 1-year time horizon	ASK screening vs. standard of care	Routine screening vs. standard of care
Number of positive cases detected	101	101
Total cost for all screened	\$471,000	\$1,418,000
Cost per screened	\$47	\$141
Cost per case detected	\$4,700	\$14,000

Research cost components removed include recruitment, consenting, and questionnaire. Data are rounded to the nearest \$1,000 (USD).

Table 3—Base-case predicted clinical and cost outcomes

	Predicted mean
Predicted cumulative incidence of diabetes by age 30 years (diagnosed cases per 10,029 children and adolescents screened)	78
Population average HbA _{1c} at age 30 years used to project long-term complications among those diagnosed with diabetes	9.1%
Discounted ASK screening and intervention costs*	\$560,000
Discounted routine screening and intervention costs*	\$1,641,000
Discounted DKA treatment costs at diagnosis†	\$240,000
Discounted other diabetes complication costs over a lifetime‡	\$19,500,000
Discounted total costs for cases diagnosed with type 1 diabetes over a lifetime	\$20,300,000
Discounted QALYs for cases diagnosed with type 1 diabetes over a lifetime	2,573

*Intervention costs include screening costs for the 10,029 children and adolescents screened, repeat confirmation screening costs for all positive cases, and two follow-up visits per year for prediabetes cases until patient is age 18 years. †Proportion of patients with a DKA event at diagnosis for all arms = 46%. ‡Other diabetes complication costs include treatment and management of long-term complications and minor and major hypoglycemic events for the patients that transitioned to have a diagnosis of diabetes.

There are important limitations of this analysis to consider. Given that this is the first general population screening program for type 1 diabetes in the U.S., we acknowledge that there is great uncertainty in our model projections. First, we do not address an age or screening schedule that optimizes value from a payer perspective. For example, what age(s) would optimize value, and what is the optimal repeat screening schedule to increase the sensitivity of identifying those with a high risk for developing type 1 diabetes? While we do not have enough evidence to answer these questions, we can posit that repeat screening would increase costs and identify fewer new subjects, thus requiring a higher benchmark on avoiding DKA events and improving glycemic control to meet commonly cited cost-effectiveness thresholds. Therefore, a critical next step is to identify the age and repeat screening

schedule that provide the highest value to patients, providers, and payers. Once ongoing birth cohort studies produce findings to help us to answer these questions, the model will be updated to reflect the most recent understanding of the value of screening at several ages and screening intervals.

Second, recent and promising results on teplizumab in relatives at high risk for type 1 diabetes were not included in ASK or routine screening scenarios (39). We acknowledge that delaying progression to clinical type 1 diabetes with teplizumab could improve health benefits over and above screening and early detection, potentially improving the potential value of screening presented here. Our framework and analysis is all the more timely to address future questions around teplizumab. However, without approval and a market price, cost-effectiveness projections of screening with teplizumab

prevention would require even stronger assumptions than made in our current analysis. Combining our modeling framework with the use of teplizumab will be a future step in our understanding of value of screening and early detection.

Third, because of a lack of long-run knowledge on the impact of the ASK screening program, including the number of DKA events avoided and HbA_{1c} among cases detected, we relied on assumptions using published evidence from Colorado. Specifically, we link DKA avoidance with recent observational evidence on the improvement in long-run HbA_{1c} (13,17,18). We cannot, however, exclude the possibility that a causal effect of DKA on long-run HbA_{1c} is zero. Therefore, these results should not be interpreted as projections of actual ASK effects but, rather, of screening effects or benchmarks required to meet cost-effectiveness thresholds. In other words,

Table 4—Incremental lifetime population-level cost and clinical outcomes on the basis of projected reductions in DKA events and resulting improved HbA_{1c} from screening and follow-up

Percent reduction in DKA events (screening vs. no screening)	Proportion of patients with DKA events in screening arm	Incremental population average HbA _{1c} for patients with type 1 diabetes	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%	-\$37,000	-\$506,000	17	\$18,000*	\$1,098,000*
40%	28%	-0.3%	-\$73,000	-\$965,000	33	-\$478,000**	\$602,000*
60%	18%	-0.4%	-\$110,000	-\$1,384,000	49	-\$934,000**	\$147,000*
80%	9%	-0.5%	-\$146,000	-\$1,769,000	64	-\$1,355,000**	-\$274,000**

\$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 10,029 children and adolescents, DKA treatment costs for case patients diagnosed with type 1 diabetes and experience a DKA event, and all other diabetes complication costs over a lifetime for the predicted case patients who convert to diabetes. *Costs of screening offset enough for screening to be cost-effective at ≤\$150,000 per QALY. **Costs of screening offset completely, resulting in a cost savings scenario.

regardless of a causal impact between DKA episodes and long-run HbA_{1c}, a combined clinical benefit of avoiding DKA events and improved HbA_{1c} at a population level is associated with better value for money when screening large populations for presymptomatic type 1 diabetes. As more data are collected from ASK, the model will be updated with direct evidence on screening effects. Supplementary Table 7 provides additional sensitivity analyses around HbA_{1c} projections.

Finally, our results may not generalize to all clinical practice settings or to all patients with type 1 diabetes. The Barbara Davis Center for Diabetes is a tertiary care center with existing infrastructure for randomized and pragmatic clinical trials and a staff with experience in monitoring and following up with subjects at high-risk for developing type 1 diabetes. There would likely be some level of investment to expand screening to routine clinical practices around the country, which would increase the overall costs reported in this analysis, requiring higher clinical benchmarks to meet commonly cited cost-effectiveness thresholds. However, it is not clear what level of investment would be required at this time. Future research should use recent microcosting techniques at routine clinical practices to identify an initial investment required to expand screening. In addition, 51.4% of all screened in the ASK program were of Hispanic descent, which is not directly reflective of the overall population in the metropolitan Denver area (~30% of Hispanic descent). The majority of the ASK screening so far has been at hospital specialty clinics and emergency departments, with limited screening at primary care clinics, which has influenced the ethnic distribution of the screening. Efforts are under way to increase screening at primary care clinics as the ASK program strives to offer screening to all children aged 2–17 years in Colorado. In addition, we plan to identify and answer important questions that stratify effectiveness results by subpopulations such as race and ethnicity.

Despite these limitations, this analysis provides some of the first projections of clinical benchmarks needed to achieve good value for money when investing in large-scale screening programs for presymptomatic type 1 diabetes.

Specifically, presymptomatic type 1 diabetes screening may be cost-effective in areas with high prevalence of DKA and infrastructure facilitating screening and monitoring if the benefits of avoiding DKA events and improved HbA_{1c} persist over long-run time horizons. Ongoing findings from the ASK program will provide updated cost-effectiveness projections.

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