Short Running Title: Change in HbA1c over adolescents and young adults

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Title: Hemoglobin A1c (HbA1c) changes over time among adolescent and young adult participants in the T1D Exchange clinic registry

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Objective: HbA1c levels among individuals with type 1 diabetes influence the longitudinal risk for diabetes related complications. Few studies have examined HbA1c trends across time in children, adolescents and young adults with type 1 diabetes (T1D). This study examines changes in glycemic control across the specific transition periods of pre-adolescence-to-adolescence and adolescence-to-young adulthood, and the demographic and clinical factors associated with these changes.

Research Design and Methods: Available HbA1c lab results for up to 10 years were collected from medical records at 67 T1D Exchange clinics. Two retrospective cohorts were evaluated: the pre-adolescent-to-adolescent cohort consisting of 85,016 HbA1c measurements from 6,574 participants collected when the participants were 8-18 years old and the adolescent-to-young adult cohort, 2,200 participants who were 16-26 years old at the time of 17,279 HbA1c measurements.

Results: HbA1c in the 8-18 cohort increased over time after age 10 years until ages 16-17; followed by a plateau. HbA1c levels in the 16-26 cohort remained steady from 16-18, and then gradually declined. For both cohorts, race/ethnicity, income, health insurance, and pump use were all significant in explaining individual variations in age-centered HbA1c ($p<0.001$). For the 8-18 cohort, insulin pump use, age of onset, and health insurance were significant in predicting individual HbA1c trajectory.

Conclusions: Glycemic control among patients 8-18 years old worsens over time, through age 16. Elevated HbA1c levels observed in 18 year-olds begin a steady improvement into early adulthood. Focused interventions to prevent deterioration in glucose control in pre-adolescence, adolescence and early adulthood are needed.

Keywords: Diabetes Mellitus type 1, hemoglobin A1c, pediatric transition to adult care, insulin, retrospective studies

INTRODUCTION

Children and adolescents with type 1 diabetes often fail to achieve age-specific targets for glycemic control. Prior to the 2014 revision to American Diabetes Association (ADA) targets for children's glycemic control, 60-90% of children <6 years old achieved their target hemoglobin A1c (HbA1c). That number dropped to 13-29% among children >12 years old, whose previous ADA recommended HbA1c targets were stricter (1-3). The ADA recently adopted the ISPAD HbA1c target of 7.5% (58 mmol/mol) for all children (4, 5), making it likely that even fewer youth will achieve their target in the near term. Cross-sectional data from the SEARCH for Diabetes in Youth Study reveal the highest HbA1c levels among pediatric patients with type 1 diabetes are seen in adolescents (6). Similarly, the T1D Exchange has recently reported cross-sectional data indicating that mean HbA1c levels are higher in 13-17 and 18-25 year-olds than in either younger or older registry participants (7).

Despite current evidence, exactly how individuals' HbA1c levels change across the developmental continuum from pre-adolescence to young adulthood remains poorly understood, due in part to the relatively scant longitudinal data in this population. Even less well understood are the demographic, psychological, social, and clinical care factors that predict future deterioration in blood glucose control. These issues highlight a critical gap in knowledge: identifying additional predictors of future deterioration in glycemic control is necessary before interventions designed to preclude future declines in disease control can be developed and tested.

We begin to address this gap in knowledge by applying growth curve models to characterize individual patient-level changes in glycemic control across the continuum from

childhood to early adulthood, using longitudinal HbA1c data from the large population of pediatric and young adult patients enrolled in the T1D Exchange clinic registry (7). We hypothesize that age at diagnosis, race/ethnicity, gender, household income, insulin delivery method, and insurer/insurance status are each associated with changes in glycemic control across the specific transitions of pre-adolescence-to-adolescence and adolescence-to-young adulthood.

RESEARCH DESIGN AND METHODS

The T1D Exchange Clinic Network includes 75 U.S.-based pediatric and adult endocrinology practices (7). Each clinic received approval from an institutional review board (IRB). Informed consent was obtained according to IRB requirements from adult participants and parents/guardians of minors; assent from minors was obtained as required. Data were collected for the registry's central database from the participant's medical record and by having the participant or parent complete a comprehensive questionnaire, as previously described (7). This report includes data on participants from 67 T1D Exchange centers enrolled between September 2010 and July 2012.

Two retrospective cohorts were constructed from the registry of participants diagnosed to have type 1 diabetes prior to 8 years old with type 1 diabetes duration 2 years or more: the pre-adolescent-to-adolescent cohort consisting of HbA1c measurements collected when the participant was 8-18 years old (N=6,574 with at least one HbA1c measurement collected in this age range), and the adolescent-to-young adult cohort, when the participant was 16-26 years old at HbA1c collection (N=2,200 with at least one HbA1c measurement collected in this age range).

Overlap between the populations at 16-18 years old was allowed (N=1,778 with at least 1 HbA1c measurement collected in both age ranges) so that the pre-adolescent-to-adolescent and adolescent-to-young adult cohorts could be more easily compared to the findings of previous studies (8-13). Mean age at type 1 diabetes onset was about 4 years in both cohorts. Clinical characteristics at enrollment in each age cohort are shown in Table 1.

HbA1c values (mainly measured with point-of-care (POC) devices via DCA, other POC, or lab) were obtained from the clinic medical record. For each participant, up to 10 years of HbA1c measurements were included. The median (25^{th} percentile, 75^{th} percentile [interquartile range]) number of years of HbA1c data from the earliest value to the last value was 3.5 years (1.6 to 5.9) for the 8-18 cohort and 1.9 years (0.8 to 3.7) for the 16-26 cohort. The median (interquartile range) number of HbA1c measurements per participant was 11 (5 to 19) for the 8-18 cohort and 6 (3 to 11) for the 16-26 cohort for a total of 85,016 and 17,279 HbA1c measurements, and 29,855 and 7,055 person years of follow up, respectively.

Statistical Methods

Growth curve models were employed to parameterize the patterns of HbA1c over time in each cohort. General linear mixed models were fit to repeated measurements of HbA1c by including only polynomial functions of age in the unconditional models. Linear age was specified as a random effect, thereby allowing variation in linear age among individuals. The age variable was centered at 13 for the 8-18 cohort and at 21 for the 16-26 cohort to alleviate potential multicollinearity. Likelihood ratio tests were used to compare alternative specifications

to arrive at a best fitting model. A multivariable model was then fit on demographic variables (gender, race/ethnicity), income, health insurance, age at onset, pump use at the time of HbA1c measurement, and annual mean number of HbA1c measurements. Effects of these factors were estimated on the polynomial age parameters by including interaction terms in the model. The interaction between each factor and the linear age term was assessed; interaction terms with $p>0.01$ were removed from the model using a backward elimination procedure. Interactions with higher power polynomial age terms were assessed if the lower power interaction terms remained in the model. Prototypical plots were used to illustrate the effects of factors on the trajectory of HbA1c for factors with significant interaction terms.

Data analysis used SAS version 9.3 (2011 SAS Institute Inc., Cary, NC). All p-values are two-sided. In view of the multiple comparisons and large sample size, only p-values<0.01 were considered significant.

RESULTS

For the 6,574 participants in the 8-18 cohort, the unconditional models of HbA1c trajectories indicated that among all age polynomials, a 4^{th} degree polynomial was best-fitting based on likelihood ratio tests. As illustrated in Figure 1A and 1B, the average HbA1c trajectory in the 8-18 cohort started from 8.2% (66 mmol/mol) at age 8, remained relatively stable until age 10 years, increased over time until between ages 16 and 17 years, followed by another stable period. The estimated trajectory closely follows the mean of the raw HbA1c data values at each time point (Figure 1A and 1B). Estimates of all age random effects were statistically significant

($p<0.001$), which indicates that individuals varied by their HbA1c growth trajectories. The best fitting specification of the data for the 16-26 cohort was a 3rd degree polynomial of age. In the 16-26 cohort (Figure 1C and 1D), HbA1c levels started from 8.9% (74 mmol/mol) at age 16 years, remained relatively stable until age 18 years, and then started a long decline to 8.2% (66 mmol/mol) at age 26 years. The estimated trajectory closely follows the mean of the raw HbA1c data values until about age 20 years, after which the estimated model tends to deviate from the decline seen in the raw HbA1c data values (Figure 1C and 1D). Similar to the findings for the 8-18 cohort, the age random effects also were significant ($p<0.001$). Individual subjects in the 16-26 cohort had considerable variations around the average cohort trajectory.

In both cohorts, race/ethnicity, income, health insurance, and pump use were all clinically and statistically significant in explaining individual variations in the age-centered HbA1c value (i.e. HbA1c at age 13 years and 21 years for the 8-18 cohort and 16-26 cohort, respectively) ($p<0.001$; Table 2). Table 2 shows the age-centered HbA1c average for each predictor category while adjusting for all other factors in the model. Non-Hispanic African Americans had the highest age-centered HbA1c among all racial/ethnic groups. A monotonic relationship was observed for household income with higher incomes associated with continually lower age-centered HbA1c values. Privately insured individuals also had lower age-centered HbA1c when compared with those with non-private insurance. Pump users had lower age-centered HbA1c compared with injection users. In both cohorts, results did not vary by the average number of available HbA1c measurements per year ($p=0.09$ and $p=0.24$ for the 8-18 and 16-26 cohorts, respectively).

For the 6,574 participants in the 8-18 cohort, insulin delivery method, age of onset, and type of health insurance were significant in predicting individual HbA1c trajectory (Figures 2A-2C). Participants on pumps tended to experience a slightly slower increase in HbA1c than participants using injections ($p=0.005$ for the interaction of pump use and cubic age); however the trajectories remained fairly parallel (Figure 2A). The older a participant was when diagnosed with type 1 diabetes, the faster the HbA1c values increased over the age range and the quicker the HbA1c values eventually plateaued ($p=0.009$ for the interaction of age of onset and quadratic age); however, HbA1c values remained fairly similar across the age range (Figure 2B). HbA1c values increased more slowly in participants with private insurance vs participants without private insurance ($p<0.001$ for the interaction of insurance status and quadratic age; Figure 2C).

DISCUSSION

We have shown that, in a large registry population from 67 centers across the United States, glycemic control among patients 8-18 years old worsens over time, except for short periods of relative stability (but different mean HbA1c levels) between ages 8-10 and 16-18. Data in the 16-26 year-old cohort extend these findings by demonstrating that the markedly elevated HbA1c levels observed in 16-18 year-olds begin a steady improvement into early adulthood. We further found that race/ethnicity, income, insulin delivery method, and type of insurance are each associated with mean age-centered HbA1c for both the 8-18 and 16-26 year-old cohorts, with non-Hispanic African American participants experiencing the highest mean age-centered HbA1c, while mean HbA1c values were similar among non-Hispanic White and

Hispanic/Latino individuals. In contrast, gender failed to show a clinically significant association with mean age-centered HbA1c. Importantly, insulin delivery method, age of onset, and type of insurance each demonstrated an association with change in glycemic control over time in the 8-18 year-old cohort, with injection use, older age at onset, and non-private insurance each associated with greater deterioration in HbA1c over time. Finally, we found that the number of HbA1c measurements per year was not associated with deterioration in glycemic control, although the average number of HbA1c measurements per year (<3) was lower than recommended.

Growth curve or "trajectory" analysis allows measurement of between-person differences in within-person change over time (14). Using this approach, the present study reveals a non-linear worsening of glycemic control from age 8 to age 16 years, with a period of relative stability form age 16 to age 18 years, followed by a continuous non-linear improvement in HbA1c from age 18 to age 26. These associations with trajectory of glycemic control have not been reported for a large U.S. type 1 diabetes population before. In fact, few national or multi-national registries have performed developmental growth curve analysis of patients' HbA1c change over time; previous large registry studies have primarily reported age-based differences in mean HbA1c across their populations. Several large non-U.S. population-based registry studies have previously demonstrated that population means for glycemic control by age increase across adolescence (15-18). One study found that among Danish children with T1D, mean glycemic control by age increased from 5-10 years old, 10-15 years old, and 15-18 years old, respectively, among individuals utilizing insulin pump therapy or multiple daily injections.

Glycemic control across the adolescent-to-adult transition was not analyzed. The authors further found that improvements in mean HbA1c from insulin pump therapy varied by duration of therapy (years) and by age. A longitudinal study of youth with T1D in Slovenia found an increase in median HbA1c among adolescents compared to younger children (19). That study did consider within-patient change in HbA1c over time, but continuous trajectories of HbA1c by age were not reported. Analysis of patients 1-19 years old from the SWEDIABKIDS registry revealed that individuals with the highest HbA1c were older and had a longer diabetes duration. Similarly, a study of children/adolescents in the German/Austrian DPV initiative revealed that mean HbA1c among children/adolescents varied by duration of diabetes and by age, with HbA1c remaining stable from ages 3-7 years, increasing from ages 7-16 years, and improving from ages 16-20 years (16). A second study derived from the DPV initiative found that mean glycemic control in children/adolescents worsened among two-thirds of children from "pre-puberty" (age <13 years) to "puberty" (age 13-20 years) and continued to worsen in one-third of teens from puberty to "post-puberty" (age >20 years) (17). Differences in mean HbA1c by age exist among these various population registries and the present study. For instance, in the DPV initiative, mean HbA1c at age 8 was approximately 7.5%, and rose to 8.6-8.7% by age 16, while in the present study those values were approximately 8.2% and 8.9%, respectively (16). This suggests that the trajectories in other populations may differ in some respects, with either greater or lesser change across the transitions from pre-adolescence to adolescence and from adolescence to young adulthood.

Several longitudinal observational studies in smaller cohorts have characterized trajectories of glycemic control during adolescence (8-10), but few have described the trajectory of glycemic control across the transition from childhood to adolescence (11). One study indicated that HbA1c rises modestly from ages 5-10 years old in healthy non-diabetic children (20). Similarly, only a few smaller studies (n=72 and n=117, respectively) have characterized change in glycemic control across the transition from adolescence to adulthood (12, 13). Our longitudinal data also agree with and extend the findings of previous studies regarding the impact of race/ethnicity and socioeconomic status on glycemic control in adolescence, since previous studies have examined the relationship between these factors using primarily cross-sectional data or data collected over brief periods of time (21-23). Notably, variables that often co-vary with race/ethnicity, like socioeconomic status, have been found in multiple studies to be more important determinants of glycemic control than race/ethnicity themselves (24, 25). Few studies have examined the impact of insulin pump therapy on longitudinal glycemic control in pediatric or young adult patients (19, 26, 27). Our data indicate that in a U.S. cohort, insulin pump therapy similarly improves HbA1c, although change in HbA1c over time is similar among those on pump or injection therapy. Our data further indicate a significant difference in the trajectory of glycemic control as a function of health insurance type (private versus non-private or no insurance). Most previous studies examining the influence of health insurance on glycemic control have been smaller and have been cross-sectional. One cross-sectional study of 295 youth found that HbA1c is higher among youth 12-19 years old with public insurance (28), while another found no increase in HbA1c among young people 1-21 years old with public insurance

(23). While the current finding is interesting, its generalizability to nations with free public health insurance may be limited. In Scandinavian countries, for instance, mean differences in HbA1c by ethnicity are still present, but diminished (29). Whether trajectories of glycemic in those nations are more similar to trajectories for those with public or private insurance in the U.S. remains to be determined. Finally, the current study is unique in its finding that age of diagnosis is a significant predictor of the trajectory of glycemic control for the pre-adolescent-to-adolescent cohort. While this finding may in part reflect duration of diabetes, differences in trajectory of glycemic control based on age at diagnosis while controlling for duration of diabetes have been reported elsewhere (30)

The present findings have important public health and clinical implications. First, they suggest that deterioration in glycemic control during adolescence does not completely ameliorate until age 25. Given the effect of elevated HbA1c at younger ages on future vascular complications (metabolic memory) in the Diabetes Complications and Control Trial (DCCT-EDIC) study (31-35), deterioration in glucose control and persistence of poor control into early adulthood may exert sustained deleterious effects on vascular complications into adulthood. Second, the present findings indicate that deterioration in glycemic control may precede adolescence. Many studies have verified that teenagers are particularly vulnerable to deterioration in glycemic control (8-10, 36, 37), but we have found that deterioration begins to emerge in patients as young as 10 years old. This suggests that novel therapeutic strategies and behavioral/educational interventions developmentally targeted to pre-teens may be necessary to effectively counteract the declines in glycemic control driven by early puberty (38, 39) and

continued loss of endogenous insulin production (40). Finally, the present study can also form the foundation for developing risk prediction models for deterioration in diabetes control across various developmental stages. We have shown that individual subjects' glycemic control trajectories exhibit considerable variation around the average cohort trajectory for both the childhood-to-adolescence cohort and the adolescence-to-young-adulthood cohort. Behavioral, social, and clinical care factors that influence glycemic control trajectories have been explored in several studies during adolescence (8-11, 36, 37). They should be further explored during the transitions from pre-adolescence to adolescence and from late adolescence to young adulthood while controlling for the effects of pubertal stage and endogenous insulin production.

There are several notable strengths of this study. The population we have studied from the T1D Exchange registry is considerably larger than that used by any other study to analyze longitudinal trends in glycemic control, as HbA1c data were available in each patient for up to 10 years. In addition, the cohort is characterized by considerable geographic and racial/ethnic diversity. Finally, the use of registry data may reflect "real-life" conditions more so than data from clinical trials or small observational studies during which participants experience an increased level of attention compared with that typically provided by the health care team during routine care. Certain limitations of the study also must be acknowledged. Income and health insurance were reported at the time of registry enrollment but were used to predict historic HbA1c growth curves. These variables can be dynamic; so their status at registry enrollment may not accurately represent patient status at the time of initial HbA1c measurement. Despite that gender, race/ethnicity, income, health insurance, and age of onset each helped to explain

individual variation in age-centered HbA1c and/or slope, sizable variances remained. There remains a great need to explore and collect data on potential factors that explain such variations. It is also important to recognize that the cohort is not population-based and participation in the cohort is predicated on being followed by an endocrinologist. Thus, the data may not be representative of all patients with T1D in the US.

These results add to the literature by providing a more comprehensive picture of glycemic control trends across the continuum from childhood to young adulthood. It is particularly notable that most teenagers with type 1 diabetes do not emerge as well-controlled adults with type 1 diabetes until their mid-twenties. Moreover, even at this age, HbA1c levels remain above the target values of <7.0% (<53 mmol/mol) for most. Nevertheless, it is encouraging that, in our population, there was a slow but steady decline in HbA1c levels as patients developmentally transitioned from adolescence to early adulthood. Focused interventions to prevent deterioration in glucose control from early adolescence through early adulthood and to enhance and accelerate the improvement in control in young adults are needed and could have a dramatic public health impact.

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M.A.C. research data, contributed to discussion, and wrote the manuscript. N.C.F. researched data, contributed to discussion, performed statistical analyses, and wrote the manuscript. D.M.M., D.A.S., B.A.O., E.T., J.M.L., C.N.B.S., W.V.T., V.C., K.M.M., and R.W.B. researched data, contributed to discussion, and reviewed/edited the manuscript.

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Table 1. Participant Characteristics at Enrollment

	Ages 8-18 Cohort (N=6574)	Ages 16-26 Cohort (N=2200)
Gender: Female	3279 (50%)	1171 (53%)
Race/Ethnicity		
White Non-Hispanic	5236 (80%)	1826 (84%)
Black Non-Hispanic	339 (5%)	97 (4%)
Hispanic or Latino	624 (10%)	173 (8%)
Other Race/Ethnicity	336 (5%)	88 (4%)
Age of onset *(years)*		
mean±standard deviation	4.2±2.0	4.2±2.1
0-<2	885 (13%)	292 (13%)
2-<4	1572 (24%)	490 (22%)
4-<6	2042 (31%)	690 (31%)
≥6	2075 (32%)	728 (33%)
Body Weight*		
Normal/underweight	4066 (63%)	1094 (55%)
Overweight	1450 (23%)	597 (30%)
Obese	866 (14%)	291 (15%)
Household Income		
Less than $35,000	929 (20%)	354 (25%)
$35,000 - <$50,000	492 (11%)	177 (13%)
$50,000 - <$75,000	758 (16%)	225 (16%)
$75,000 - <$100,000	848 (18%)	224 (16%)
e$100,000	1597 (35%)	416 (30%)
Health Insurance		
Private	4238 (73%)	1351 (78%)
Other	1506 (26%)	412 (23%)
No insurance	29 (<1%)	18 (1%)

Insulin Delivery Method		
Pump	4088 (62%)	1312 (60%)
Injection	2457 (38%)	878 (40%)
Average Number of A1c per Year[†]		
mean±standard deviation	2.7±0.8	2.3±0.9

[*] Body weight categories defined from body mass index (BMI) percentiles calculated based on body weight, height, gender, and age from the Centers for Disease Control and Prevention growth charts from 2000. The following body weight categories were assigned as follows: obese if BMI percentile e95, overweight if BMI percentile ≥85 but <95, and normal weight/underweight if BMI percentile is <85.

[†] The variable was a single unweighted value for each individual, derived by dividing total number of HbA1c measurements by total number of years with nonmissing HbA1c.

Table 2. Adjusted Age-Centered Mean HbA1c by Demographic Factor

	Ages 8-18 Cohort		Ages 16-26 Cohort	
	HbA1c Mean at Age 13 Years[†] (mmol/mol)	**95% Confidence Interval (mmol/mol)**	**HbA1c Mean at Age 21 Years[§] (mmol/mol)**	**95% Confidence Interval (mmol/mol)**
Gender				
Male	8.76 (72)	8.69, 8.82 (71, 73)	9.00 (75)	8.76, 9.16 (73, 77)
Female	8.83 (73)	8.77, 8.89 (73, 74)	9.07 (76)	8.89, 9.26 (74, 78)
P-value	0.009		0.39	
Race/Ethnicity				
White Non-Hispanic	8.53 (70)	8.49, 8.58 (69, 70)	8.79 (73)	8.67, 8.91 (71, 74)
Black Non-Hispanic	9.34 (78)	9.22, 9.47 (77, 80)	9.41 (79)	9.00, 9.83 (75, 84)
Hispanic or Latino	8.61 (71)	8.51, 8.70 (70, 72)	8.79 (73)	8.49, 9.09 (69, 76)
Other Race/Ethnicity	8.70 (72)	8.57, 8.82 (70, 73)	9.07 (76)	8.65, 9.48 (71, 80)
P-value	<0.001		0.002	
Household Income				
<$35,000	9.07 (76)	9.00, 9.15 (74, 76)	9.41 (79)	9.19, 9.62 (77, 82)
$35,000-<$50,000	8.90 (74)	8.80, 8.99 (73, 74)	9.08 (76)	8.82, 9.35 (73, 79)
$50,000-<$75,000	8.81 (73)	8.73, 8.90 (72, 74)	8.94 (74)	8.69, 9.20 (71, 77)
$75,000-<$100,000	8.70 (72)	8.61, 8.78 (71, 72)	8.89 (74)	8.62, 9.15 (71, 76)
≥$100,000	8.49 (69)	8.41, 8.56 (68, 70)	8.76 (72)	8.53, 9.00 (70, 75)
P-value	<0.001		<0.001	

Health Insurance				
Private	8.65 (71)	8.59, 8.71 (70, 72)	8.84 (73)	8.66, 9.03 (71, 75)
Other/No insurance	8.94 (74)	8.86, 9.02 (73, 75)	9.19 (77)	8.96, 9.41 (74, 79)
P-value		<0.001		<0.001
Insulin Delivery Method at HbA1c Measurement				
Pump	8.67 (71)	8.61, 8.73 (71, 72)	8.83 (73)	8.64, 9.02 (71, 75)
Injection	8.98 (74)	8.92, 9.04 (74, 75)	9.29 (78)	9.11, 9.48 (76, 80)
P-value		<0.001		<0.001

† Adjusted for remaining factors in the table in addition to: 4th degree age polynomials, age at diagnosis, age*age at diagnosis, age^2*age at diagnosis, insurance status, age*insurance status, age^2*insurance status, insulin delivery method, age*insulin delivery method, age^2*insulin delivery method, age^3*insulin delivery method

§ Adjusted for remaining factors in the table in addition to: 3rd degree age polynomials

Figure 1A. Mean HbA1c Trajectory from 8 to 18 Years of Age with Distribution of Raw HbA1c by Age

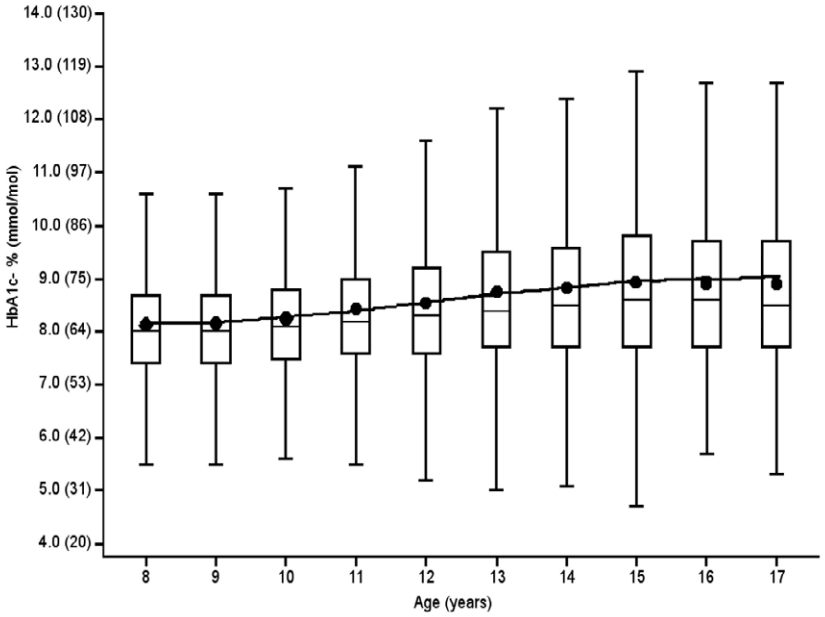

Figure Legend
White box= 25th and 75th percentiles
Line in middle of white box= Median
Black dot= Raw mean
Black line= Growth model mean HbA1c

Figure 1B. Mean HbA1c Trajectory from 8 to 18 Years of Age with Mean Raw HbA1c by Age

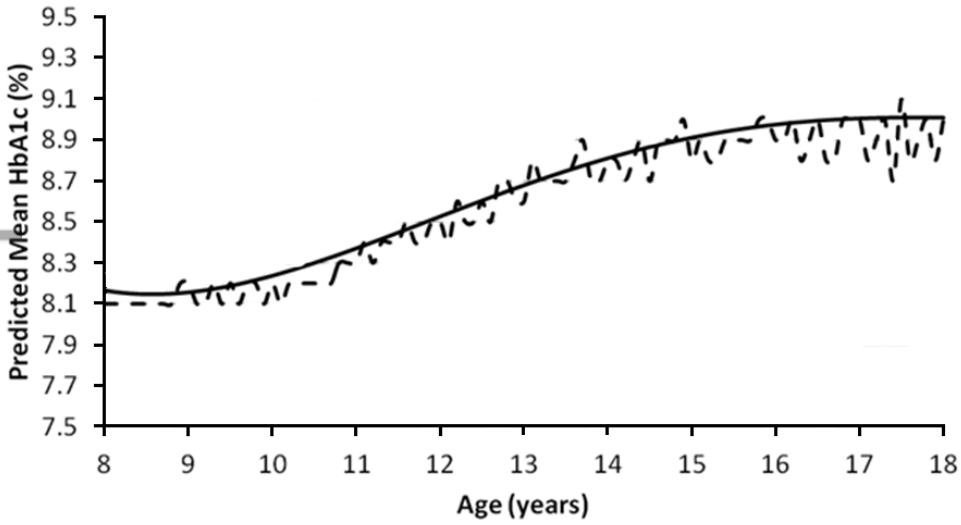

Figure Legend

Solid black line= Growth model predicted mean HbA1c

Dotted black line= Participant mean HbA1c (raw data)

Figure 1C. Mean HbA1c Trajectory from 16 to 26 Years of Age with Distribution of Raw HbA1c by Age

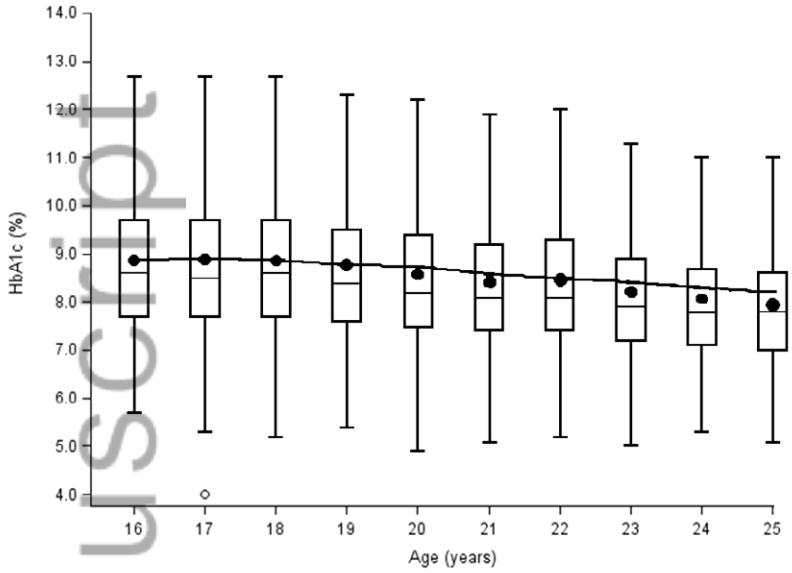

Figure Legend
White box= 25th and 75th percentiles
Line in middle of white box= Median
Black dot= Raw mean
Black line= Growth model mean HbA1c

Figure 1D. Mean HbA1c Trajectory from 16 to 26 Years of Age with Mean Raw HbA1c by Age

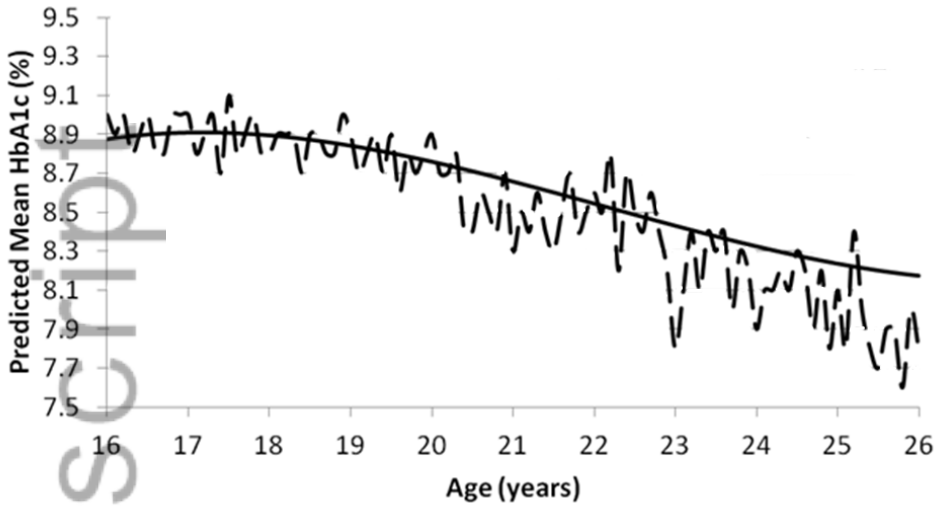

Figure Legend
Solid black line= Growth model predicted mean HbA1c
Dotted black line= Participant mean HbA1c (raw data)

Figure 2A. Prototypical HbA1c Trajectories for Method of Insulin Delivery among the 8-18 Cohort

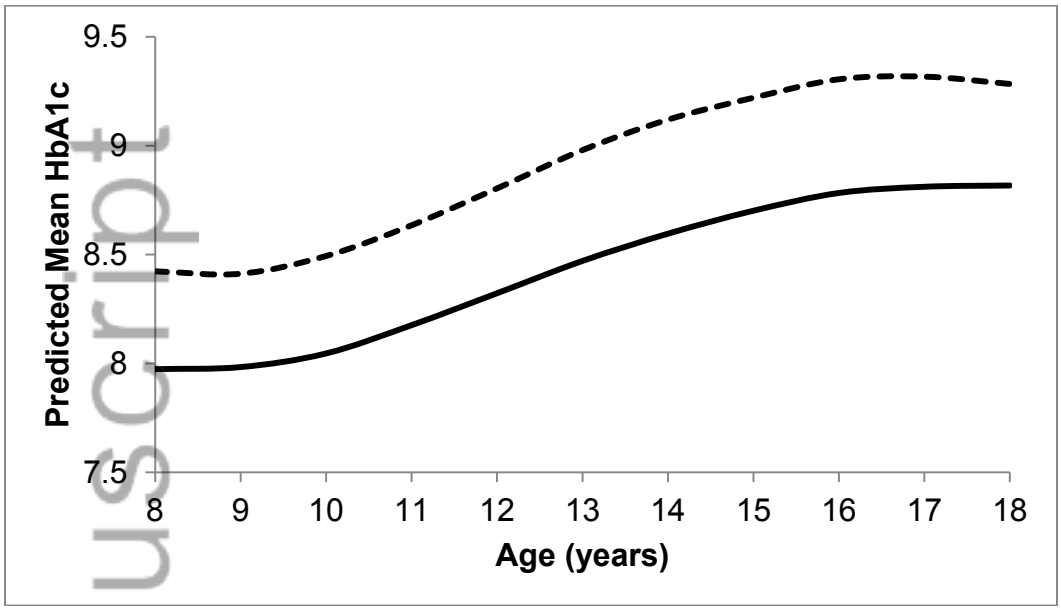

Figure Legend
Solid black line= Pump users
Dotted black line= Multiple daily injection users

Figure 2B. Prototypical HbA1c Trajectories for T1D Onset at 2, 4, 6 Years of Age among the 8-18 Cohort

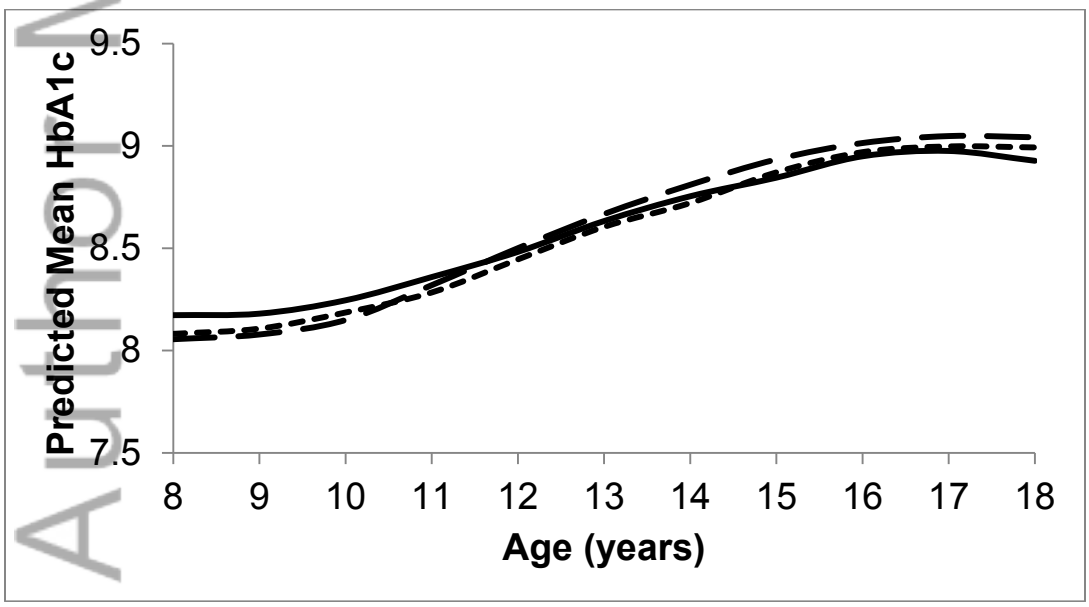

Figure Legend
Solid black line= 2 years age at onset
Short dotted black line= 4 years age at onset
Long dotted black line= 6 years age at onset

Figure 2C. Prototypical HbA1c Trajectories for Type of Health Insurance among the 8-18 Cohort

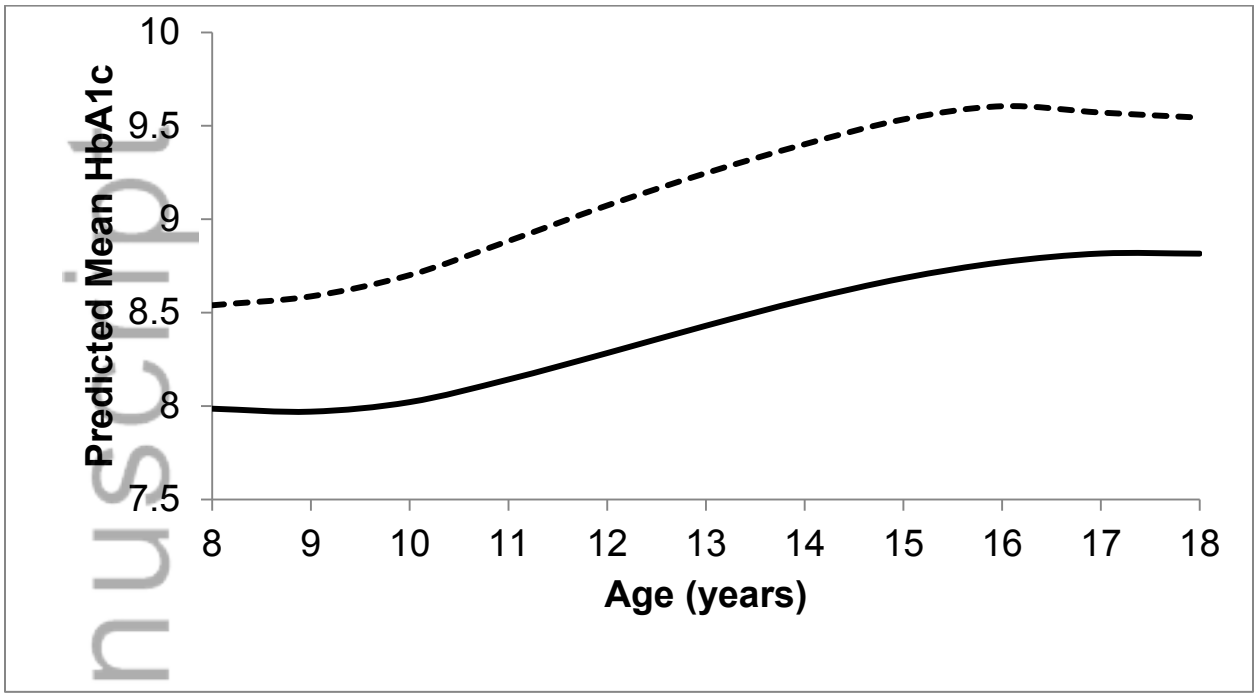

Figure Legend

Solid black line= Private insurance

Dotted black line= Other/no insurance

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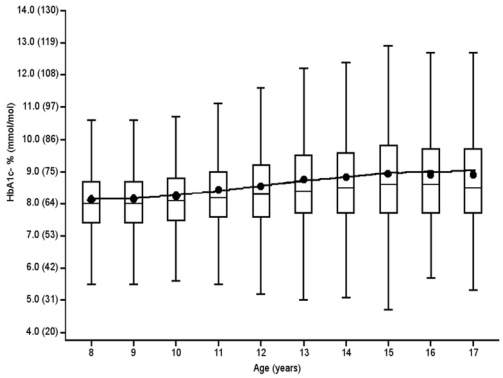

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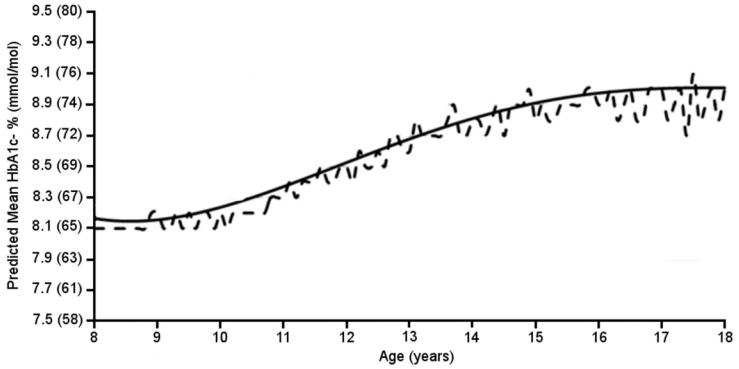

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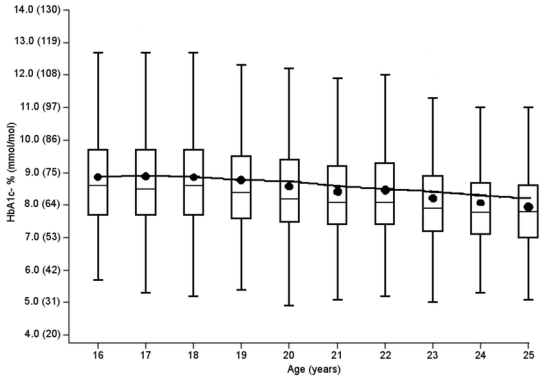

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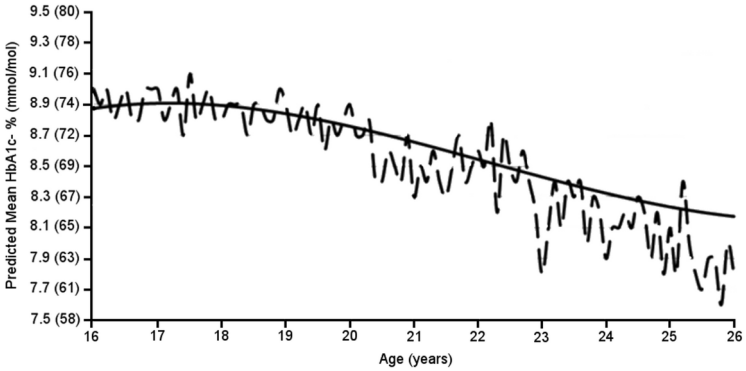

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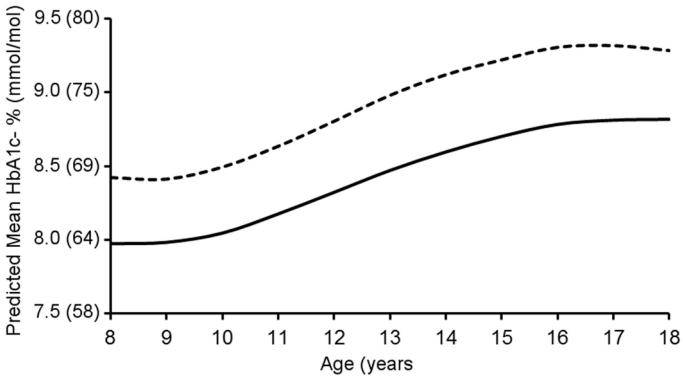

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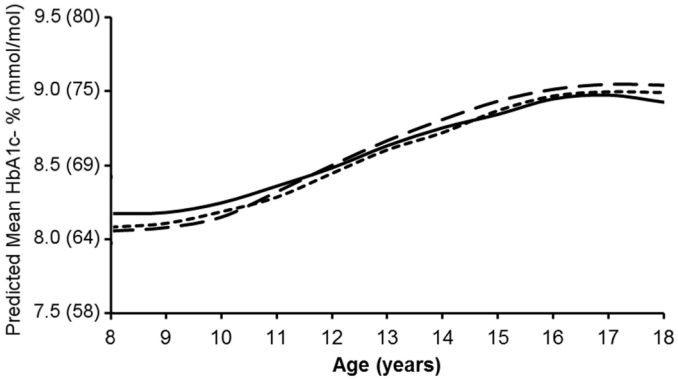

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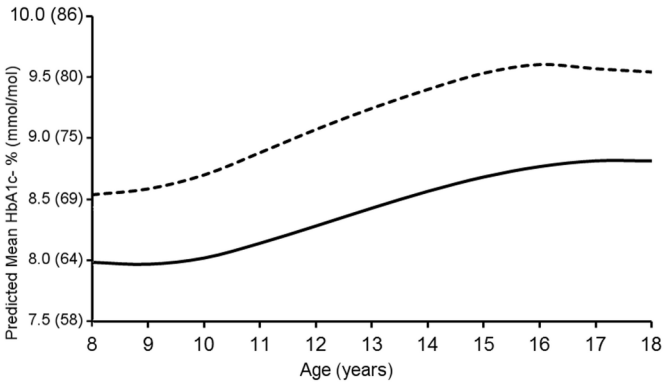

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Online Only Supplemental Material

Appendix 1

For the T1D Exchange Clinic Network author group, sites with participating principal investigators (PI), co-investigators (I) and coordinators (C) ordered by the number of participants recruited per site as of August 1, 2012 is included below:

Philadelphia, PA Children's Hospital of Philadelphia (n=1451) Steven Willi (PI); Terri Lipman (I); Tammy Calvano (C); Olena Kucheruk (C); Pantea Minnock (C); Chau Nguyen (C) **Aurora, CO Barbara Davis Center for Childhood Diabetes** (n=1440) Georgeanna Klingensmith (PI); Carolyn Banion (I); Jennifer Barker (I); Cindy Cain (I); Peter Chase (I); Rosanna Fiallo-Scharer (I); Sandy Hoops (I); Megan Kelsy (I); Georgeanna Klingensmith (I); David Maahs (I); Cathy Mowry (I); Kristen Nadeau (I); Marian Rewers (I); Arleta Rewers (I); Robert Slover (I); Andrea Steck (I); Paul Wadwa (I); Philippe Walravens (I); Philip Zeitler (I); Eric Cruz (C); Heidi Haro (C); Maria King (C) **Syracuse, NY SUNY Upstate Medical University** (n=1301) Ruth Weinstock (PI); Roberto Izquierdo (I); Suzan Bristol (C) **New York City, NY Naomi Berrie Diabetes Center, Columbia University P&S** (n=1249) Robin Goland (PI); Rachelle Gandica (I); Mary Chan (C); Ellen Greenberg (C); Amy Kurland (C) **Ann Arbor, MI University of Michigan** (n=927) Joyce Lee (PI); Brigid Gregg (I); Meng Tan (I); Ashley Eason (C) **Aurora, CO University of Colorado/Denver, Barbara Davis Center for Childhood Diabetes** (n=897) Satish Garg (PI); Aaron Michels (I); Audrey Morris (C); Haley Stewart (C); Sonya Walker (C) **Indianapolis, IN Riley Hospital for Children, Indiana University School of Medicine** (n=859) Linda DiMeglio (PI); Tamara Hannon (I); Donald Orr (I); Stephanie Woerner (C) **Boston, MA Children's Hospital Boston** (n=836) Joseph Wolfsdorf (PI); Maryanne Quinn (I); Kayla Fitch (C) **Portland, OR Harold Schnitzer Diabetes Health Center at Oregon Health and Science University** (n=793) Andrew Ahmann (PI); Jessica Castle (I); Farahnaz Joarder (I); Chris Bogan (C); Rebecca Fitch (C); Bethany Wollam (C) **Atlanta, GA Atlanta Diabetes Associates** (n=742) Bruce Bode (PI); Katie Gazaway (C); RaShonda Hosey (C) **Buffalo, NY University Pediatric Associates** (n=673) Kathleen Bethin (PI); Teresa Quattrin (I); Michelle Ecker (C) **Los Angeles, CA Children's Hospital Los Angeles** (n=605) Jamie Wood (PI); Lynda Fisher (I); Debra Jeandron (I); Francine Kaufman (I); Mimi Kim (I); Roshanak Monzavi (I); Pisit Pitukcheewanont (I); Anna Sandstrom (I); Marisa Cohen (C); Brian Ichihara (C); Megan Lipton (C) **Grand Rapids, MI Helen DeVos Children's Hospital Endocrinology and Diabetes** (n=576) Michael Wood (PI); Yaw Appiagyei-Dankah (I); Ayse Cemeroglu (I); Maala Daniel (I); Daniel Postellon (I); Michael Racine (I); Lora Kleis (C); Laura Wagner (C) **Seattle, WA University of Washington, Diabetes Care Center** (n=569) Irl Hirsch (PI); Anthony DeSantis (I); DC Dugdale (I); R Alan Failor (I); Lisa Gilliam (I); Mary Janci (I); Peggy Odegard (I); Dace Trence (I); Brent Wisse (I); Jan Ginsberg (C); Dori Khakpour (C); Christina Peterson (C); Pam Thomson (C) **Idaho Falls, ID Rocky Mountain Diabetes & Osteoporosis Center, PA** (n=557) David Liljenquist (PI); Mark Sulik (PI); Carl Vance (PI); Jean Halford (C); James Manning (C) **Morristown, NJ BD Diabetes Center at Goryeb Children's Hospital** (n=542) Harold Starkman (PI); Tymara Berry (I); Laurie Ebner-Lyon (I); Elaine Nussbaum (I); Christine Wagner (I); Marie Fox (C) **Stanford, CA Stanford University School of Medicine, Division of Pediatric Endocrinology** (n=525) Bruce Buckingham (PI); Avni Shah (I); Breanne Harris (C) **Minneapolis, MN International Diabetes Center/Park Nicollet Adult Endocrinology** (n=514) Richard Bergenstal (PI); Amy

Criego (I); Greg Damberg (I); Glenn Matfin (I); Margaret Powers (I); David Tridgell (I); Beth Olson (C) **Boston, MA Joslin Diabetes Center- Pediatric** (n=451) Sanjeev Mehta (PI); Lori Laffel (I); Camille Ratliff (C) **New Haven, CT Yale Pediatric Diabetes Program** (n=398) Eda Cengiz (PI); William Tamborlane (I); Melody Martin-Fredericksen(C); Amy Steffen (C) **Los Angeles, CA University of Southern California - Community Diabetes Initiatives** (n=365) Anne Peters (PI); Lucy Montoya (C); Valerie Ruelas (C) **Durham, NC Duke University Medical Center - Pediatric Endocrine Division** (n=364) Robert Benjamin (PI); Juanita Cuffee (C); Jean Litton (C); Amber Spruill (C) **Minneapolis, MN International Diabetes Center/Park Nicollet Pediatric Endocrinology** (n=357) Richard Bergenstal (PI); Amy Criego (I); Greg Damberg (I); Glenn Matfin (I); Margaret Powers (I); David Tridgell (I); Beth Olson (C) **Chicago, IL Northwestern University** (n=352) Grazia Aleppo-Kacmarek (PI); Elaine Massaro (C); Kimberly Webb (C) **Charlottesville, VA University of Virginia Health System** (n=342) William Clarke (PI); Christine Burt Solorzano (I); Mark DeBoer (I); Dianne Shifflett (C) **St. Louis, MO Washington University** (n=342) Janet McGill (PI); Lori Buechler (C); Mary Jane Clifton (C); Stacy Hurst (C); Sarah Kissel (C); Carol Recklein (C) **Iowa City, IA University of Iowa Children's Hospital** (n=327) Eva Tsalikian (PI); Michael Tansey (I); Joanne Cabbage (C); Julie Coffey (C); Sarah Salamati (C) **Kansas City, MO Children's Mercy Hospital** (n=323) Mark Clements (PI); Sripriya Raman (I); Angela Turpin (I); Jennifer Bedard (C); Cyndy Cohoon (C); Aliza Elrod (C); Amanda Fridlington (C); Lois Hester (C); Terri Luetjen (C) **Detroit, MI Henry Ford Health System** (n=316) Davida Kruger (PI); Andrew Hofmann (C) **Gainesville, FL University of Florida** (n=306) Desmond Schatz (PI); Michael Clare-Salzler (I); Colleen Digman (I); Becky Fudge (I); Mike Haller (I); Henry Rohrs (I); Janet Silverstein (I); Sujata Wagh (I); David Weinstein (I); Tamara Wright (I); Erica Dougherty (C) **Orange, CA Children's Hospital of Orange County** (n=305) Mark Daniels (PI); Susan Clark (I); Timothy Flannery (I); Nikta Forghani (I); Ajanta Naidu (I); Christina Reh (I); Peggy Scoggin (I); Lien Trinh (I); Rebeca Quintana (C); Heather Speer (C) **Columbus, OH Central Ohio Pediatrics Endocrinology and Diabetes Services** (n=303) William Zipf (PI); Diane Seiple (C) **Sioux Falls, SD Avera Research Institute** (n=281) Brad Uhing (PI); Julie Kittelsrud (C); Ashley Stoker (C) **San Diego, CA University of California** (n=280) Michael Gottschalk (PI); Marla Hashiguchi (C) **Tampa, FL University of South Florida Diabetes Center** (n=276) Henry Rodriguez (PI); Craig Bobik (C); Danielle Henson (C) **Nashville, TN Vanderbilt Eskind Diabetes Clinic** (n=276) Jill Simmons (PI); William Russell (I); Brooke Babington (C); Margo Black (C); Faith Brendle (C) **Cleveland, OH Case Western Reserve University** (n=251) Rose Gubitosi-Klug (PI); Beth Kaminski (I); Susan Bergant (C); Wendy Campbell (C); Mary Beth Frohnapfel (C); Jennifer Haky (C); Catherine Tasi (C) **Oklahoma City, OK University of Oklahoma Health Sciences Center Dept. of Pediatric Diabetes and Endocrinology** (n=243) Kenneth Copeland (PI); Joni Beck (I); Jill Schanuel (C); Jennifer Tolbert (C) **San Francisco, CA University of California, San Francisco Medical Center (UCSF)** (n=237) Saleh Adi (PI); Andrea Gerard-Gonzalez (I); Stephen Gitelman (I); Nassim Chettout (C); Christine Torok (C) **Seattle, WA Seattle Children's Hospital** (n=226) Catherine Pihoker (PI); Susan Kearns (C) **Pittsburgh, PA Children's Hospital of Pittsburgh of UPMC** (n=217) Ingrid Libman (PI); Ana Diaz (C) **Minneapolis, MN University of Minnesota** (n=204) Brandon Nathan (PI); Antoinette Moran (I); Melena Bellin (I); Shannon Beasley (C); Anne Kogler (C); Janice Leschyshyn (C); Jennifer Smith (C) **Greenville, SC Greenville Hospital System Pediatric Endocrinology** (n=196) Bryce Nelson (PI); D'Anne Hannah (C) **Houston, TX Baylor College of Medicine / Texas Children's Hospital** (n=187) Morey Haymond (PI); Maria Redondo (I);

Teresa Falk (C); Janette Gonzalez (C); Christina Lopez (C); Mariam Pontifes (C) **Ocean Springs, MS_The Diabetes Center, PLLC** (n=187) Kathleen Arnold (PI); Sharon Sellers (C) **Salt Lake City, UT_University of Utah - Utah Diabetes Center** (n=181) Vandana Raman (PI); Eric Garcia (C) **Worcester, MA_University of Massachusetts Medical School** (n=179) David Harlan (PI); Mary Lee (I); Lisa Hubacz (C) **Durham, NC_University of North Carolina Diabetes Care Center** (n=179) John Buse (PI); Michelle Duclos (C) **Sioux Falls, SD_Sanford Research/USD** (n=178) Verdayne Brandenburg (PI); Julie Blehm (I); Julie Hallanger-Johnson (I); Ryan Bosch (C); Jennifer Weiss (C) **Columbus, OH_The Research Institute at Nationwide Children's Hospital** (n=168) Robert Hoffman (PI); Monika Chaudhari (I); David Repaske (I); Jesse Haines (C) **Billings, MT_St. Vincent Healthcare/Internal Medicine and Diabetes** (n=165) Justen Rudolph (PI); Charles McClave (I); Doris Biersdorf (C) **Bismarck, ND_Medcenter One** (n=156) Anthony Tello (PI); Donna Amundson (C); Rhonda Ward (C) **Philadelphia, PA_University of Pennsylvania School of Medicine/Rodebaugh Diabetes Center** (n=156) Michael Rickels (PI); Stan Schwartz (I); Cornelia Dalton-Bakes (C); Carissa Fuller (C); Nora Rosenfeld (C) **Cincinnati, OH_Cincinnati Children's Hospital Medical Center** (n=148) Lawrence Dolan (PI); Jessica Kichler (I); Holly Baugh (C); Debbie Standiford (C) **Spokane, WA_Rockwood Research Center, P.S.** (n=132) Jeanne Hassing (PI); Jennifer Jones (I); Stephen Willis (I); Carol Wysham (I); Tammy Freels (C); Candice Garcia (C); Deann Rice (C) **Baltimore, MD_Johns Hopkins University Pediatric Endocrinology** (n=120) Scott Blackman (PI); Kimber-Lee Abel (C); Loretta Clark (C); Andrea Jonas (C); Ellie Kagan (C) **Miami, FL_University of Miami, Diabetes Research Institute** (n=119) Jay Sosenko (PI); Ramon Arce (C) **Rapid City, SD_Regional Health Clinical Research** (n=118) Rachel Edelen (PI); Denise Baldwin (C); Christina Conroy (C); Kelly DeGrote (C); Rod Marchiando (C); Michelle Wasson (C) **Jacksonville, FL_Nemours Children's Clinic** (n=116) Larry Fox (PI); Nelly Mauras (I); Katie Black (C); Ligeia Damaso (C) **Cleveland, OH_Cleveland Clinic Department of Endocrinology, Diabetes and Metabolism** (n=111) Laurence Kennedy (PI); Michelle Schweiger (I); Pantelis Konstantinopoulos (C); Carolyn Mawhorter (C); Amy Orasko (C); Denise Rose (C) **Tallahassee, FL_Tallahassee Memorial Diabetes Center** (n=108) Larry Deeb (PI); Kim Rohrbacher (C) **Albany, NY_The Endocrine Group, LLP** (n=107) Jill Abelseth (PI); Carol Duma (C); Sara Duma (C) **Findlay, OH_Blanchard Valley Medical Associates** (n=100) Leroy Schroeder (PI); Amanda Roark (C) **Milwaukee, WI_The Medical College of Wisconsin/ Children's Hospital of WI** (n=99**)** Omar Ali (PI); Joanna Kramer (C); Donna Whitson-Jones (C) **Nashville, TN_Vanderbilt Eskind Diabetes Clinic** (n=98) Amy Potter (PI); Brooke Babington (C); Margo Black (C); Faith Brendle (C) **Vallejo, CA_Kaiser Permanente** (n=74) Heidi Gassner (PI); Sobha Kollipara (I); Vicky Bills (C) **Paterson, NJ_St. Joseph's Children's Hospital** (n=53) Katerina Harwood (PI); Vijaya Prasad (I)