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Real-world treatment escalation from metformin monotherapy in youth-onset Type 2 diabetes mellitus: A retrospective cohort study

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Abstract

Background: Due to high rates of comorbidities and rapid progression, youth with Type 2 diabetes may benefit from early and aggressive treatment. However, until 2019, the only approved medications for this population were metformin and insulin.

Objective: To investigate patterns and predictors of treatment escalation within 5 years of metformin monotherapy initiation for youth with Type 2 diabetes in clinical practice.

Subjects: Commercially-insured patients with incident youth-onset (10–18 years) Type 2 diabetes initially treated with metformin only.

Methods: Retrospective cohort study using a patient-level medical claims database with data from 2000 to 2020. Frequency and order of treatment escalation to insulin and non-insulin antihyperglycemics were determined and categorized by age at diagnosis. Cox proportional hazards regression was used to evaluate potential predictors of treatment escalation, including age, sex, race/ethnicity, comorbidities, complications, and metformin adherence (medication possession ratio ≥ 0.8).

Results: The cohort included 829 (66% female; median age at diagnosis 15 years; 19% Hispanic, 17% Black) patients, with median 2.9 year follow-up after metformin initiation. One-quarter underwent treatment escalation ($n = 207$; 88 to insulin, 164 to non-insulin antihyperglycemic). Younger patients were more likely to have insulin prescribed prior to other antihyperglycemics. Age at diagnosis (HR 1.14, 95% CI 1.07–1.21), medication adherence (HR 4.10, 95% CI 2.96–5.67), Hispanic ethnicity (HR 1.83, 95% CI 1.28–2.61), and diabetes-related complications (HR 1.78, 95% CI 1.15–2.74) were positively associated with treatment escalation.

Conclusions: In clinical practice, treatment escalation for pediatric Type 2 diabetes differs with age. Off-label use of non-insulin antihyperglycemics occurs, most commonly among older adolescents.

KEYWORDS
adolescent, insulin, medication adherence, metformin, type 2 diabetes mellitus

1 | INTRODUCTION

Youth with type 2 diabetes mellitus experience high rates of comorbidities and complications early in the disease course[1] and have more rapid decline in beta cell function than adults with type 2 diabetes.[2-4] In clinical trials, youth with type 2 diabetes also have a higher rate of metformin monotherapy failure (45% over nearly 4 years)[2] than adults (21% at 5 years).[5] Due to their more-rapid disease progression, youth with type 2 diabetes would be expected to benefit from earlier escalation to additional diabetes medication than adults. Unfortunately, limited medication options in youth may impede treatment escalation in practice[6]; until Victoza® (liraglutide) was approved by the United States Food and Drug Administration (FDA) in 2019 for use in pediatric type 2 diabetes,[7] the only option for treatment escalation beyond metformin was insulin. However, due to advantages of non-insulin antihyperglycemics, including promotion of weight loss or avoidance of weight gain,[8] reduced risk of hypoglycemia,[9] and more flexible dosing or oral formulations, non-insulin antihyperglycemics are sometimes used in youth despite the lack of FDA approval.[10,11] To date, patterns and predictors of this off-label use have not been described.

One potential predictor of treatment escalation is age: as adolescents age into adulthood, they may begin to take advantage of a broad array of non-insulin antihyperglycemics. Adherence to metformin may also influence treatment escalation; in clinical practice, better adherence to metformin is associated with higher likelihood of treatment escalation for adults with type 2 diabetes.[12] This seemingly counterintuitive finding, which is likely due to a desire to optimize adherence prior to advancing therapies,[12] may be especially important in a pediatric population with limited approved options for treatment escalation. Ultimately, delay in escalating treatment, whether due to factors including younger patient age or poor adherence, may leave youth with type 2 diabetes at risk for prolonged poor glycemic control.

In this retrospective cohort study using a longitudinal patient-level commercial insurance claims database, we evaluated patterns of treatment escalation beyond metformin monotherapy among individuals with youth-onset type 2 diabetes. We used survival analysis to account for not only age but also diabetes duration, a risk factor for inadequate durable glycemic control in youth on metformin monotherapy.[13,14] Due to the conflicting realities of generally more-severe disease in youth with type 2 diabetes and limited treatment options, we hypothesized that age would be directly associated with treatment escalation to non-insulin antihyperglycemics. If present, an age-related disparity would underscore the potential harm facing younger adolescents with type 2 diabetes, who are at relatively higher risk for poor glycemic control and long-term morbidity. In addition, we hypothesized that, similar to findings in adult patients with type 2 diabetes, metformin adherence would be positively associated with treatment escalation.

2 | METHODS

2.1 | Data source

Our data source was Optum's de-identified Clinformatics® Data Mart Database, a patient-level medical claims database consisting of the inpatient, outpatient, pharmacy, procedure, and laboratory claims of more than 88 million unique patients enrolled in large United States commercial and Medicare Advantage health plans from April 1, 2000 to March 31, 2020. Laboratory results are available for a subset of enrollees. Body size and vital sign measurements are unavailable. Data from Optum have previously been used to study diabetes in youth.[15-17] This study was determined to be Not Human Subjects Research by the Children's Hospital of Philadelphia Institutional Review Board.

2.2 | Cohort inclusion and exclusion criteria

Our retrospective cohort consisted of individuals with active enrollment October 2000–March 2020 who were diagnosed with incident type 2 diabetes while 10–18 years of age. Individuals were classified as having type 2 diabetes if they had at least 2 individual diabetes-specific International Classification of Diseases (ICD) -9 and − 10 codes (Supplemental Table 1) during follow up and if the ratio of type 2-specific codes to type 1 + type 2 diabetes codes was ≥0.6, which has previously been shown to have sensitivity, specificity and positive predictive values exceeding 80% for type 2 diabetes in youth.[18]

The cohort was restricted to individuals with only metformin and no other diabetes-related medications dispensed within the first 90 days after the first diabetes diagnosis code. A time period of 90 days was chosen in order to minimize misclassification of delayed filling of a medication co-prescribed with metformin as treatment escalation. Patients were not included in the cohort if they never filled a prescription for metformin, or if they filled prescriptions for metformin, insulin, or other diabetes medications within 180 days of enrollment or prior to diabetes diagnosis. Only individuals with at least 180 days of continuous enrollment in Optum prior to the first ICD-9/10 medical claim for any form of diabetes mellitus were included in order to minimize misclassification of prevalent diabetes as incident.[19] For individuals with multiple discontinuous enrollments in Optum, only the first enrollment was included in order to avoid misclassification of diabetes diagnosis, outcomes and covariates that may have occurred during the gap in enrollment. All individuals in the cohort had at least 180 days of continuous follow-up after first metformin fill to allow for sufficient time for outcome ascertainment.

2.3 | Outcome

The outcome of interest was treatment escalation that occurred between 90 days and 5 years after initiation of metformin

monotherapy. Follow-up was restricted to within 5 years of metformin initiation to constrain the focus on the transition period from pediatric to adult medical care. Treatment escalation was divided into insulin and non-insulin antihyperglycemics, including glucagon-like peptide-1 receptor agonists (GLP1 RA), sulfonylureas (SU), dipeptidyl peptidase 4 inhibitors (DPP4), sodium-glucose co-transporter 2 inhibitors (SGLT2), thiazolidinediones (TZD), amylin analogues, alpha-glucosidase inhibitors, meglitinides, bile acid sequestrants,[20,21] and combination medications, including those containing metformin. For the primary analysis, treatment escalation included escalation to either insulin or non-insulin antihyperglycemics, with the date of escalation the earliest date of insulin or non-insulin antihyperglycemic prescription fill.

2.4 | Covariates

Covariates included sex, race/ethnicity (white, Black, Hispanic, Asian, unknown), geographic region (9 census divisions: East North Central, East South Central, Middle Atlantic, Mountain, New England, Pacific, South Atlantic, West North Central, West South Central), calendar year of diabetes diagnosis, and time from diabetes diagnosis to metformin initiation (measure of diabetes duration). Adherence was approximated using medication possession ratio (MPR) of metformin. MPR was calculated as the proportion of days of metformin supplied until treatment escalation (or end of follow-up if no treatment escalation). "Adherence" was defined as an MPR of ≥0.8, based on a target of at least 80% adherence in the Treatment Options for Type 2 diabetes in Adolescents and Youth (TODAY) study.[2,22]

Comorbidities were defined by the presence or absence of at least one ICD 9/10 code associated with each condition (Supplemental Table 2) and included hypertension, hyperlipidemia, microalbuminuria, obstructive sleep apnea or snoring, non-alcoholic fatty liver disease, and polycystic ovary syndrome (PCOS). In addition, a combined outcome of either ICD-based diagnosis or claim for medication to treat the comorbid condition was created for both hypertension (*antihypertensive medications*: angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, diuretics, beta blockers, and calcium channel blockers) and dyslipidemia (*lipid-lowering medications*: statins, fibrates, ezetimibe, PCSK9 inhibitors, bile acid sequestrants, niacin). Diabetes-related complications were assessed based on presence or absence of at least one ICD 9/10 code specific to each complication (*diabetes with renal manifestations*: 250.4X, E10.2x; *ophthalmic manifestations*: 250.5X,

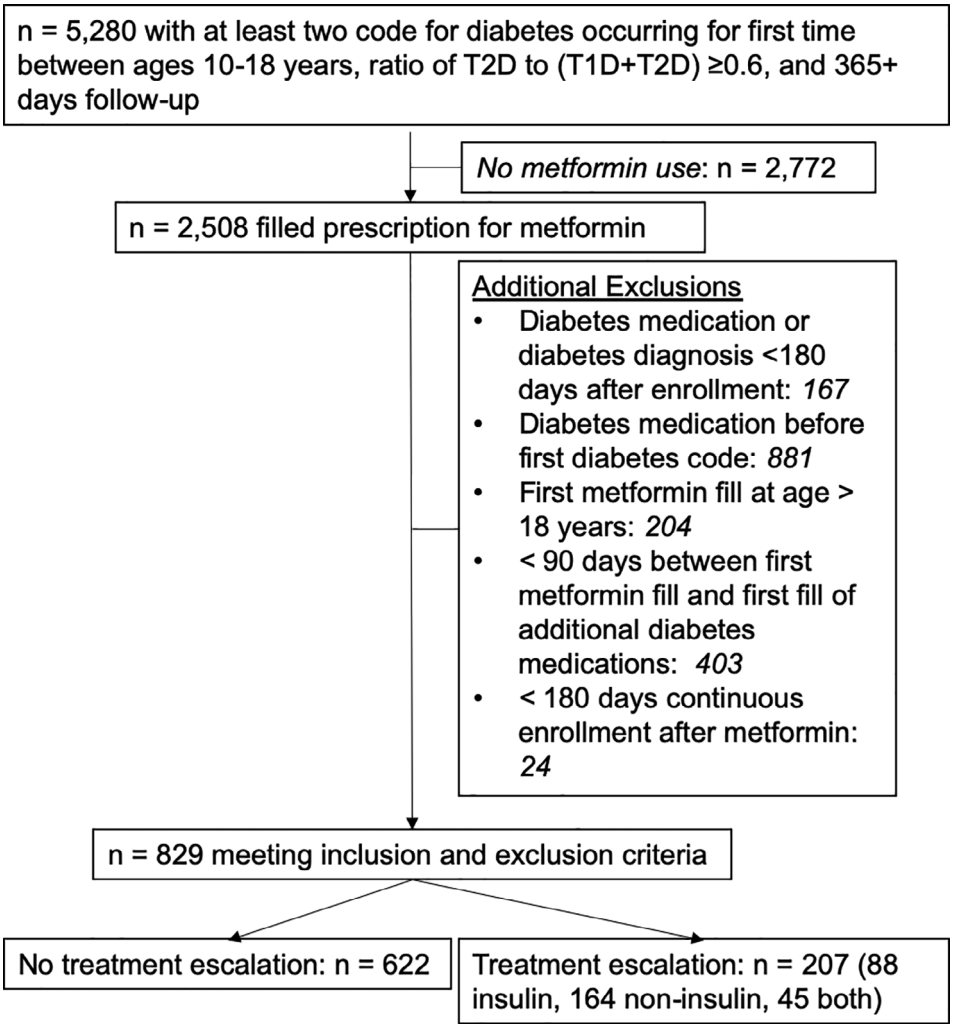

FIGURE 1 Patient flow diagram, depicting number of, and reasons for, patients excluded from the cohort

TABLE 1 Cohort characteristics overall and by age at T2D diagnosis

Characteristic	Overall N = 829		10–12 years n = 145		13–15 years n = 306		16–18 years n = 378		
	n	%	n	%	n	%	n	%	p
Female	543	65.5	96	66.2	199	65.0	248	65.6	1.0
Male	286	34.5	49	33.8	107	35.0	130	34.4	
Race/Ethnicity									
Asian	45	5.4	6	4.1	19	6.2	20	5.3	0.7
Black	140	16.9	31	21.4	52	17.0	57	15.1	
Hispanic	159	19.2	32	22.1	54	17.6	73	19.3	
White	366	44.1	58	40.0	135	44.1	173	45.8	
Unknown	119	14.4	18	12.4	46	15.0	55	14.6	
Comorbidities at baseline									
Hypertensive	132	15.4	21	14.5	42	13.7	69	18.3	0.2
Hypertensive[a]	158	18.5	25	17.2	50	16.3	83	22.0	0.1
Dyslipidemia	176	20.6	29	20.0	61	19.9	86	22.8	0.6
Dyslipidemia[b]	178	20.7	29	20.0	61	19.9	88	23.3	0.5
Microalbuminuria	24	2.9	5	3.4	11	3.6	8	2.1	0.5
OSA/snoring	92	10.3	30	20.7	31	10.1	31	8.2	<0.001
Fatty liver	47	4.8	6	4.1	18	5.9	23	6.1	0.7
PCOS (F)	100	18.4	7	7.3	37	18.6	56	22.6	0.005
Diabetes-related complications at baseline									
Renal	3	0.4	0	0.0	2	0.7	1	0.3	0.5
Ophthalmic	5	0.6	1	0.7	3	1.0	1	0.3	0.5
Neurological	4	0.5	0	0.0	1	0.3	3	0.8	0.4
Peripheral circulatory	3	0.4	0	0.0	1	0.3	2	0.5	0.7
Other specified	74	8.9	15	10.3	18	5.9	4	1.1	0.06
Unspecified	18	2.2	5	3.4	6	2.0	7	1.9	0.5
	Median IQR		Median IQR		Median IQR		Median IQR		*p*
MPR	24	10–55	33	10–69	25	11–57	23	9–50	0.04
Baseline HbA1c, % (n = 123)	6.9	6.2–9.5	6.4	5.8–7.1	7.3	6.4–10.0	7.1	6.1–10.5	0.05
Days to metformin	0	1–143	48	2–544	31	1–260	6	0–62	<0.001
Years follow-up after metformin	2.9	1.7–5.0	2.8	1.9–5.0	3.1	1.7–5.0	2.7	1.6–5.0	0.5

Abbreviations: PCOS, polycystic ovary syndrome; MPR, Medication possession ratio; HbA1c, hemoglobin A1c.
[a]ICD-based or prescribed antihypertensive medication.
[b]ICD-based or prescribed lipid-lowering medication.

E10.3X; *neurological manifestations*: 250.6X, E10.4X; *peripheral circulatory disorders*: 250.7X, E10.5X; *other specified or unspecified complication*: 250.8X, E10.6X; 250.9X, E10.8X). Comorbidities and diabetes-related complications were considered present at baseline if the first documentation or associated prescription occurred on or before the day of metformin initiation.

Specific diabetes medication types were summarized by proportion of patients prescribed, time from metformin to first prescription fill, and age at first prescription fill. Baseline (within 90 days of metformin initiation) laboratory-based hemoglobin A1c (HbA1c) results were obtained when available; point-of-care measurements were unavailable in the dataset. Serum glucose values were not obtained due to the inability to determine fasting status or to identify glucose tolerance tests reliably.

2.5 | Analysis

Cox proportional hazards regression was used to assess factors associated with treatment escalation. The first metformin claim date was used as the index date. Patients were censored at the first of: additional antihyperglycemic medication claim, insurance plan termination date, or pregnancy-related ICD code to minimize the impact of medication changes due primarily to pregnancy (Supplemental Table 2).

TABLE 2 Diabetes medication utilization during follow-up

Medication	Any escalation	Insulin	Non-insulin	GLP1 RA	DPP4i	SU	TZD	SGLT2i	Combination
n, % of total, % of escalated	207, 24.9%, N/A	88, 10.6%, 42.5%	164, 19.8%, 79.2%	49, 5.9%, 23.7%	24, 2.9%, 11.6%	69, 8.3%, 33.3%	31, 3.7%, 15.0%	12, 1.4%, 5.8%	37, 4.5%, 17.9%
Months from metformin, median (IQR)	13 (7–25)	18 (10–26)	14 (9–28)	26 (12–40)	17 (9–28)	15 (8–26)	26 (12–41)	21 (14–51)	19 (11–32)
Age at first prescription fill, median (IQR)	18 (16–19)	17 (15–19)	18 (16–19)	18 (17–19)	18 (17–19)	18 (16–19)	18 (16–20)	19 (18–20)	19 (17–19)
Age at first prescription fill, range	11–22	11–22	11–22	11–22	12–22	13–22	13–23	12–21	13–22
Age at diagnosis (years); *n*, % of total, % of escalated									
10–12	29, 20%, N/A	19, 13%, 66%	16, 11%, 55%	6, 4%, 21%	2, 1%, 7%	2, 1%, 7%	4, 3%, 14%	1, 0.7%, 3%	4, 3%, 14%
13–15	65, 21%, N/A	27, 9%, 42%	50, 16%, 77%	13, 4%, 20%	5, 2%, 8%	24, 8%, 37%	12, 4%, 18%	4, 1%, 6%	10, 3%, 15%
16–18	113, 30%, N/A	42, 11%, 37%	98, 26%, 87%	30, 8%, 27%	17, 4%, 15%	43, 11%, 38%	15, 4%, 13%	7, 2%, 6%	23, 6%, 20%
p (overall)	0.011	0.4	<0.0001	0.08	0.04	0.001	0.8	0.6	0.10
p (escalated)	(N/A)	0.02	0.001	0.6	0.2	0.005	0.6	0.8	0.7

Diabetes diagnosis date was the date of first diabetes-related ICD code. Duration of diabetes prior to metformin initiation was calculated as the date of first metformin claim minus date of diabetes diagnosis.

Separate Cox proportional hazards models were created for the outcomes of treatment escalation to insulin or to non-insulin antihyperglycemics. Univariable models were assessed, and covariates significant at $p < 0.2$ were included in multivariable models. Covariates significant at $p < 0.05$ in multivariable models were retained. Interactions between age at diabetes diagnosis and presence of comorbidities, age at diagnosis and adherence, and adherence and comorbidities were assessed in multivariable models and were retained if significant at $p < 0.05$. If normally distributed, continuous data were summarized using mean and standard deviation (SD), and unpaired *t*-tests were used to compare group means; otherwise, data were summarized using median and interquartile range (IQR), and Wilcoxon rank-sum test was used to compare groups. Categorical variables were summarized using proportions, and distributions compared using the chi-squared test. To compare characteristics and visualize time to treatment escalation across groups, age at type 2 diabetes diagnosis was divided into 3-year groups (10–12, 13–15, 16–18 years).

Two-sided p-values <0.05 were considered statistically significant. All analyses were performed with Stata version 16.1 (StataCorp LP, College Station, TX).

3 | RESULTS

The cohort consisted of 829 (543, 66% female) patients (patient flow diagram, Figure 1) with a median (IQR; range) follow-up after metformin initiation of 2.9 (1.7–5.0; 0.5–5.0) years. Median (IQR) age at diabetes diagnosis was 15 (13–17) years, and median year of diagnosis was 2009 (2006–2014). Race/ethnicity data was missing for 14% of patients. Of those with documented race/ethnicity, white individuals made up the largest proportion of the cohort (52% of the cohort), followed by Hispanic (22%), Black (20%), and Asian (6%) (Table 1). Of the 9 geographic regions, most patients were from the South Atlantic (24%), West South Central (20%), and East North Central (17%) regions, with the remaining regions each accounting for <10% of the cohort. Compared to patients included in the cohort, patients who were excluded (no metformin: $n = 2772$; too-early treatment escalation: $n = 403$) had a more equal sex balance (no metformin: 53% female; too-early treatment escalation: 59% female). In addition, the group excluded due to no metformin use had a lower proportion of Black (13%) and Hispanic patients (17%) while the group excluded due to too-early treatment escalation had a larger proportion of Black patients (27%). The group excluded due to no metformin use was slightly older at diagnosis (median 16, IQR 13–17 years) but the group with too-early treatment escalation did not differ in age from the main cohort. Eligible follow-up time in the database did not differ between the main cohort and excluded patients (Supplemental Table 3).

Metformin was initiated at a median of 21 (IQR 1–169) days after diabetes diagnosis. The maximum metformin dose was a median (IQR) of 1500 (1000–2000) mg/day (n = 828 with dose available).

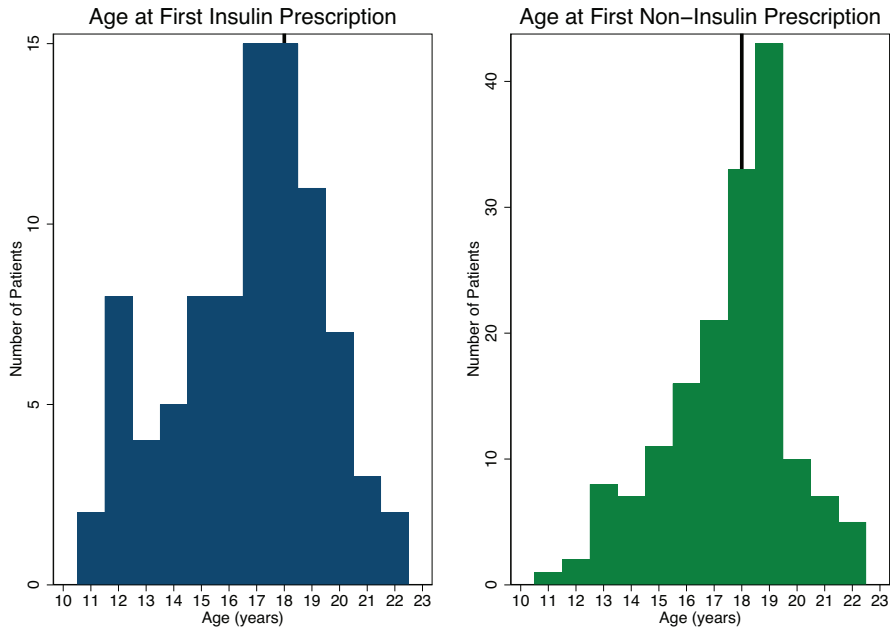

FIGURE 2 Distribution of age at first prescription for insulin or non-insulin antihyperglycemic medication. The age distribution is narrowed and right-shifted for non-insulin anithyperglycemics as compared to insulin, demonstrating the tendency to prescribe non-insulin antihyperglycemics more frequently as patients age into young adulthood

Eleven percent of patients had at least one mail order delivery of metformin. The median (IQR) metformin MPR prior to treatment escalation was 0.25 (0.10–0.56). The percent of patients with MPR ≥0.8 ("adherent") prior to treatment escalation was 14%. A higher proportion of adherent than non-adherent patients had at least one mail order delivery of metformin (20% vs. 10%, p = 0.001).

Comorbidities associated with type 2 diabetes were commonly documented at baseline (Table 1). Baseline hypertension and dyslipidemia occurred in approximately one-fifth of patients and did not differ with age at type 2 diabetes diagnosis. Microalbuminuria and fatty liver were infrequently documented at baseline and did not differ with age at type 2 diabetes diagnosis. OSA or snoring was documented in 10% of patients at baseline and was more commonly documented in younger patients (p < 0.001). PCOS was documented in 18% of females at baseline, more commonly in patients older at type 2 diabetes diagnosis (p = 0.005). Diabetes-related complications were rare at baseline, with renal, ophthalmic, neurologic, or peripheral circulatory complications each occurring in less than 1% of patients, while "other specified" or "other unspecified" manifestations were documented more frequently (Table 1). Baseline HbA1c (within 90 days of metformin initiation) was available for 123 patients; for this subset, median baseline HbA1c was 6.9% (52 mmol/mol) (IQR 6.2–9.5%; 44–80 mmol/mol) and did not differ significantly with age (p = 0.05).

3.1 | Frequency and patterns of treatment escalation

207 (25.0%) patients had treatment escalation within 5 years of metformin monotherapy initiation; 88 (10.6%) escalated to insulin, 164 (19.8%) to non-insulin antihyperglycemic, and 45 (5.4%) to both insulin and non-insulin antihyperglycemics. Time to treatment escalation was a median of 13 months (IQR 7–25). Among patients with treatment escalation, insulin was used in 43% of patients; however, this pattern differed significantly with age at type 2 diabetes diagnosis, with older patients more likely to be prescribed non-insulin

TABLE 3 Multivariable Cox proportional hazards regression for treatment escalation

Multivariable (n = 829)	HR	95% CI
Age at diabetes (per 1-year increase)	1.14	1.07,1.21
≥80% of days metformin supplied (ref: <80%)	4.1	2.96,5.67
Race/ethnicity (ref: White)		
Asian	0.96	0.51,1.80
Black	1.46	0.97,2.18
Hispanic	1.83	1.28,2.61
Unknown	1.2	0.77,1.86
Other specified diabetes-related complications at baseline (ref: not documented)	1.78	1.15,2.74
Multivariable: females only (*n* = 543)	HR	95% CI
Age at diabetes (per 1-year increase)	1.19	1.10,1.30
≥80% of days metformin supplied (ref: <80%)	5.08	3.30,7.82
Race/ethnicity (ref: White)		
Asian	1.21	0.55,2.68
Black	1.62	0.98,2.66
Hispanic	1.72	1.08,2.76
Unknown	1.07	0.60,1.88
Other specified diabetes-related complications at baseline (ref: not documented)	1.82	1.04,3.16
Polycystic ovary syndrome (females only) (ref: not documented)	0.57	0.33,0.97

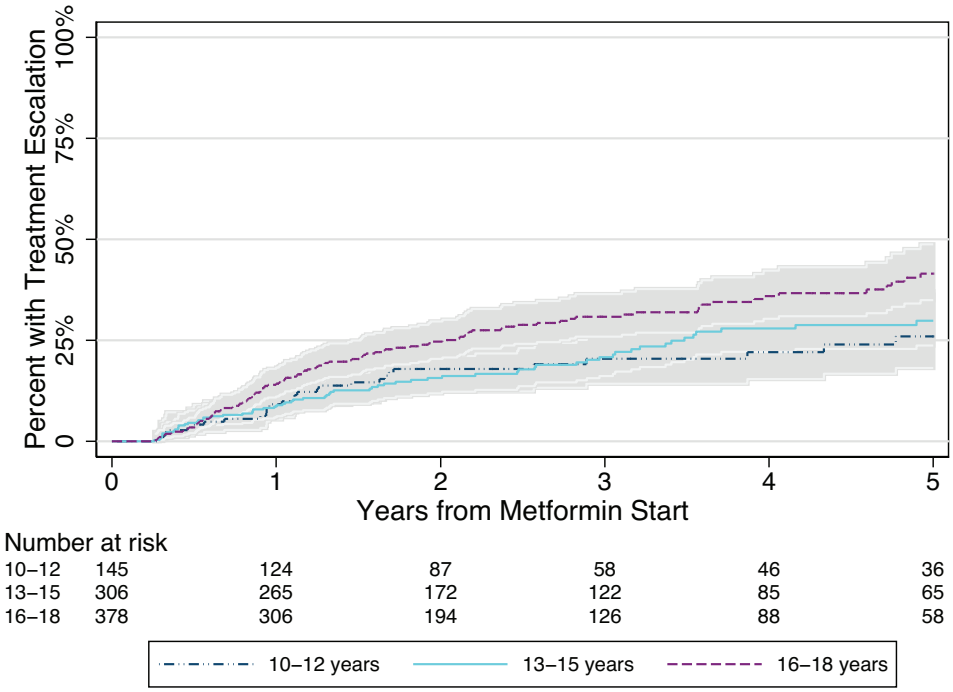

FIGURE 3 Cumulative incidence curve depicting the proportion of patients with treatment escalation from metformin monotherapy within 5 years. Grey shaded areas represent 95% confidence intervals

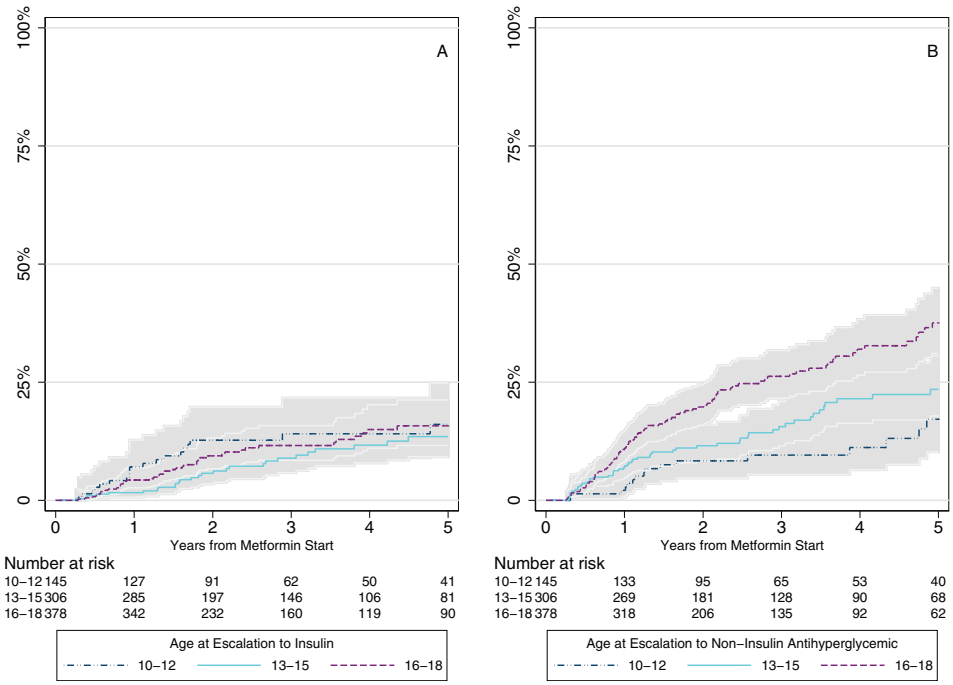

FIGURE 4 Cumulative incidence curve depicting the proportion of patients with treatment escalation to (A) insulin, or (B) non-insulin antihyperglycemic within 5 years. Grey shaded areas represent 95% confidence intervals

antihyperglycemics alone or before insulin (Table 2, $p < 0.0001$; Supplemental Figure).

The most commonly used non-insulin antihyperglycemic class was sulfonylurea (8.3% of patients), followed by GLP-1RA (5.9%) (Table 2). Of the 49 prescriptions for GLP-1RA, 5 (10%) occurred in the 10 months from Victoza® approval to the end of the study period (June 2019–March 2020). Metformin combination antihyperglycemics, thiazolidinediones, DPP4 inhibitors, and SGLT2 inhibitors were each used in fewer than 5% of patients overall, or fewer than 20% of patients who had treatment escalation. Only 11 total patients were prescribed alpha glucosidase inhibitors, amylin analogs, bile acid sequestrants, or meglitinide medications. Of the 164 patients who underwent treatment escalation to non-insulin antihyperglycemic, 40% ($n = 66$) were younger than 18 years at treatment escalation (Figure 2). The minimum age of first use was as low as 11–13 years for all medications.

3.2 | Predictors of treatment escalation

In multivariable regression (Table 3), older age at type 2 diabetes diagnosis was associated with increased hazard of treatment escalation (HR 1.14, 95% CI 1.07–1.21) (Figure 3). Ethnicity was the only demographic factor associated with treatment escalation: patients of Hispanic ethnicity were nearly twice as likely to undergo treatment escalation, as compared with white patients (HR 1.83, 95% CI 1.28–2.61). Metformin adherence (MPR≥0.8) was associated with an approximately 4-fold greater likelihood of treatment escalation (HR 4.10, 95% CI 2.96–5.67). Documentation of "other specified" diabetes-related complications at baseline was positively associated with treatment escalation (HR 1.78, 95% CI 1.15–2.74). Among female patients, baseline PCOS was associated with a lower likelihood of treatment escalation (HR 0.57, 95% CI 0.33–0.97), and the significant associations with age and adherence persisted. In the subset of patients with available data (n = 123), higher baseline HbA1c was associated with greater likelihood of treatment escalation in univariable regression (HR 1.38, 95% CI 1.22–1.56 per 1% NGSP; HR 1.03, 95% CI 1.02–1.04 per 1 mmol/mol).

Predictors of treatment escalation to insulin and non-insulin antihyperglycemics differed. In multivariable regression, older age at diagnosis was a significant predictor of treatment escalation to non-insulin antihyperglycemics (HR 1.20, 95% CI 1.12–1.30) but not to insulin (Figure 4; Supplemental Table 4). Metformin adherence was associated with an approximately 3-4-fold higher likelihood of treatment escalation to either insulin (HR 3.03, 95% CI 1.75–5.22) or non-insulin antihyperglycemic (HR 4.11, 95% CI 2.90–5.83). Additional predictors of escalation to insulin included Hispanic ethnicity (HR 2.27, 95% CI 1.31–3.94) and Black race (HR 2.29, 95% CI 1.27–4.14), diabetes-related neurological manifestations at baseline (HR 9.8, 95% CI 2.34–41.1), and calendar year of type 2 diabetes diagnosis (*per year from 2000*, HR 1.08, 95% CI 1.03–1.13). Among female patients, baseline PCOS was associated with lower likelihood of treatment escalation to insulin (HR 0.20, 95% CI 0.06–0.70) but not to non-insulin antihyperglycemics.

4 | DISCUSSION

In a large, longitudinal cohort of commercially-insured patients with youth-onset type 2 diabetes followed in clinical practice, treatment escalation within the first 5 years of metformin monotherapy initiation differed by age, and use of non-insulin antihyperglycemic medications was increasingly common in older youth. In addition, treatment escalation occurred more often among patients with greater adherence to metformin. The off-label use of antihyperglycemic medications for adolescents with type 2 diabetes highlights the critical need for additional therapeutic options in this high-risk population.

Our results demonstrate the more-frequent use of non-insulin antihyperglycemics in older youth than in younger adolescents. The lack of approved medications for pediatric type 2 diabetes is worrisome given evidence of improved glycemic control and reduction in treatment failure for early combination therapy versus metformin monotherapy.[23,24] Due to the potential risk of adverse outcomes with off-label use of medications,[25,26] as well as potential insurance authorization denials, pediatric physicians may be reluctant to prescribe medications that lack regulatory approval; hence the deferral to insulin as the primary treatment in children with type 2 diabetes, particularly younger adolescents. Insufficient treatment options for younger patients with type 2 diabetes along with noncompliance with insulin may translate to early and prolonged poor glycemic control and result in a lifetime of downstream effects. Indeed, an inverse association between age of type 2 diabetes onset and complications exists: younger (15–30 years) versus older (40–50 years) age at type 2 diabetes is associated with greater morbidity and mortality.[27,28] In addition, although insulin therapy may help to stabilize worsening dyslipidemia in youth with type 2 diabetes, its uncertain compliance and potential weight additive effects may limit its benefits if glycemic control is not achieved.[29]

In addition to limited medication options, another factor that may contribute to delayed treatment escalation is poor adherence. We found that adherence, as measured by a medication possession ratio of ≥0.8, was associated with an approximately 4-fold greater likelihood of treatment escalation. Notably, greater adherence has been associated with higher rates of treatment intensification in adults with type 2 diabetes,[30] perhaps due to provider preference to optimize metformin therapy prior to escalation. However, the utility of high levels of adherence prior to treatment escalation may be modest in pediatric type 2 diabetes, as no metformin adherence threshold predicted loss of glycemic control in the TODAY.[2,22] Notably, gastrointestinal symptoms are frequent after initiation of metformin in both children and adults[31] and may contribute to poor adherence and treatment discontinuation. Unlike in adults, however, no alternate oral antihyperglycemic medications are approved for pediatric type 2 diabetes. Thus, in youth with type 2 diabetes, discontinuation of metformin may result in inadequately treated chronic hyperglycemia unless insulin is used.

Our finding that patients of Hispanic ethnicity were more likely to undergo treatment escalation is curious, as the TODAY study demonstrated that Non-Hispanic Black participants experienced the highest rate of metformin monotherapy failure.[2] Black and Hispanic youth both tend to have a higher degree of insulin resistance than non-Hispanic white youth, independent of adiposity.[32] However, among youth with obesity, insulin resistance is greater among Black than Hispanic youth.[33] Despite more severe insulin resistance and higher rates of glycemic failure in a clinical trial setting,[2] Black patients in our study were not more likely to undergo treatment escalation. However, when separated by type of medication used for treatment escalation, both Black and Hispanic patients were more likely than white patients to undergo treatment escalation to insulin. This discrepancy in treatment escalation by type of antihyperglycemic medication (insulin versus non-insulin) should be further explored.

The lower likelihood of treatment escalation among females with PCOS at baseline was due to a significantly lower likelihood of escalation to insulin. Although this finding may reflect a lower threshold for

diagnosis of type 2 diabetes in patients with PCOS, leading to a greater proportion with good glycemic control, female patients with PCOS were equally likely to undergo treatment escalation to non-insulin antihyperglycemics as compared to females without PCOS. The cause of this differential rate of treatment escalation to insulin is unclear.

Our study's strengths include the large cohort of patients with youth-onset type 2 diabetes, use of a stringent and validated algorithm for identification of type 2 diabetes in a medical claims database, and prescription data to identify timing of medication use as well as a proxy for adherence. Importantly, our long duration of follow-up after metformin initiation with patients aging into adulthood allowed for a comparison of treatment options available for both pediatric and adult type 2 diabetes.

As with any study based on medical claims, several limitations should be considered. First, we were unable to fully evaluate the impact of glycemic control on treatment escalation. However, among the subset with HbA1c available, higher baseline HbA1c was associated with greater frequency of treatment escalation, in line with findings from the TODAY study, which demonstrated that HbA1c soon after metformin monotherapy initiation is predictive of durable glycemic control.[34] Second, our commercially-insured cohort with relatively low proportion of non-white patients may represent a different, lower-risk population, as patients with pediatric type 2 diabetes are more often from racial/ethnic minority groups[1,13] and tend to have government/non-commercial insurance.[13,35] Thus, the absolute rates of treatment escalation may not be generalizable to populations with higher proportions of individuals of racial and ethnic minority, as metformin treatment failure occurred more rapidly in Black and Hispanic patients than Non-Hispanic white patients in the TODAY study.[2] There may also be differences in diabetes care and outcomes related to unmeasured differences in social determinants of health between our cohort and patients with government-sponsored insurance. However, rates of documented hypertension and dyslipidemia in our cohort at baseline were very similar to those in the TODAY study, suggesting a similar baseline risk profile.[2]

Despite the use of a validated algorithm, misclassification of diabetes type (type 1 incorrectly classified as type 2) or monogenic diabetes is still possible. However, by limiting our cohort to new-onset diabetes that was treated with only metformin for at least 90 days, this likelihood is reduced. Notably, algorithms to identify type 2 diabetes using medications alone or in combination with laboratory results did not perform better than ICD-9 codes alone,[18,36] and in adults, adding medications to ICD9 codes did not improve classification.[37] While true adherence to metformin was unmeasurable, our finding of a positive association between treatment escalation and metformin medication possession ratio is in line with previous findings in adults.[12] Additional potential risk factors for glycemic failure such as diabetic ketoacidosis at diagnosis,[38] family history of type 2 diabetes, body mass index, or social determinants of health were unavailable. The time period of our study included only 10 months after Victoza® was FDA-approved for children; due to this approval, we anticipate that GLP1RA use will increase significantly among younger patients. Our findings reflect medication claims that were filled, and did not capture prescriptions by providers that were not covered by insurance. Finally, our study did not evaluate treatment escalation patterns of patients who were prescribed insulin or non-insulin antihyperglycemic medications within 90 days of starting metformin.

Overall, our findings highlight the important role of age in real-world treatment escalation from metformin monotherapy in youth-onset type 2 diabetes. Although the need for additional therapeutic options in adolescents with type 2 diabetes is high, there are many logistical barriers to completion of clinical trials to generate adequate evidence of safety and efficacy in the pediatric population; these barriers include narrow eligibility requirements, the relatively small population of youth with type 2 diabetes, and inadequate reimbursement to promote participation in multicenter studies.[6] Ultimately, expanded eligibility requirements and new organizational approaches to drug development and evaluation for pediatric type 2 diabetes may be required to expand the therapeutic options for this high-risk population.[6] As new therapies are eventually made available for pediatric type 2 diabetes, trends in treatment escalation should be reassessed. In addition, healthcare provider familiarity with use of new medications should be proactively addressed to counteract potential therapeutic inertia in the pediatric population. Ongoing evaluation of trends in medication use in real-world clinical practice may help to identify opportunities to optimize therapies and to ultimately address the poor outcomes of youth-onset type 2 diabetes.

CONFLICT OF INTEREST

Dr. Lee serves as a consultant to T1D Exchange, has received grant funding from Lenovo, and is on the medical advisory board for GoodRx. All other authors have no relevant conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

Mary Ellen Vajravelu was responsible for conception and design of the study, analysis and interpretation of data, and drafting and critical revision of the article. Talia A. Hitt, Sandra Amaral, Lorraine E. Levitt Katz, Joyce M. Lee and Joyce M. Lee assisted with study conception and design, analysis and interpretation, and critical revision of the article for important intellectual content. All authors have read and approved the final manuscript. Mary Ellen Vajravelu is the guarantor of this work, had full access to all the data in the study, and takes responsibility for the integrity of the data and accuracy of the data analysis.

ETHICS STATEMENT

This study was determined to be Not Human Subjects Research by the Children's Hospital of Philadelphia Institutional Review Board.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/pedi.13232.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Optum Clinformatics. Restrictions apply to the availability of these data, which were used under license for this study.

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REFERENCES

1. Copeland KC, Zeitler P, Geffner M, et al. Characteristics of adolescents and youth with recent-onset type 2 diabetes: the TODAY cohort at baseline. *J Clin Endocrinol Metab*. 2011;96(1):159-167.
2. Today Study Group. A clinical trial to maintain glycemic control in youth with type 2 diabetes. *N Engl J Med*. 2012;366(24):2247-2256.
3. Today Study Group. Effects of metformin, metformin plus rosiglitazone, and metformin plus lifestyle on insulin sensitivity and beta-cell function in TODAY. *Diabetes Care*. 2013;36(6):1749-1757.
4. Kahn SE, Lachin JM, Zinman B, et al. Effects of rosiglitazone, glyburide, and metformin on beta-cell function and insulin sensitivity in ADOPT. *Diabetes*. 2011;60(5):1552-1560.
5. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med*. 2006;355(23):2427-2443.
6. Tamborlane WV, Haymond MW, Dunger D, et al. Expanding Treatment Options for Youth With Type 2 Diabetes: Current Problems and Proposed Solutions: A White Paper From the NICHD Diabetes Working Group. *Diabetes Care*. 2016;39(3):323-329.
7. FDA approves new treatment for pediatric patients with type 2 diabetes [press release]. 2019.
8. Brown A, Guess N, Dornhorst A, Taheri S, Frost G. Insulin-associated weight gain in obese type 2 diabetes mellitus patients: What can be done? *Diabetes Obes Metab*. 2017;19(12):1655-1668.
9. Iqbal A, Heller S. Managing hypoglycaemia. *Best Pract Res Clin Endocrinol Metab*. 2016;30(3):413-430.
10. Akhlaghi F, Matson KL, Mohammadpour AH, Kelly M, Karimani A. Clinical Pharmacokinetics and Pharmacodynamics of Antihyperglycemic Medications in Children and Adolescents with Type 2 Diabetes Mellitus. *Clin Pharmacokinet*. 2017;56(6):561-571.
11. Micale SJ, Kane MP, Hogan E. Off-label use of liraglutide in the management of a pediatric patient with type 2 diabetes mellitus. *Case Rep Pediatr*. 2013;2013:703925.
12. Brown JB, Conner C, Nichols GA. Secondary failure of metformin monotherapy in clinical practice. *Diabetes Care*. 2010;33(3):501-506.
13. Bacha F, Cheng P, Gal RL, et al. Initial Presentation of Type 2 Diabetes in Adolescents Predicts Durability of Successful Treatment with Metformin Monotherapy: Insights from the Pediatric Diabetes Consortium T2D Registry. *Horm Res Paediatr*. 2018;89(1):47-55.
14. Badaru A, Klingensmith GJ, Dabelea D, et al. Correlates of treatment patterns among youth with type 2 diabetes. *Diabetes Care*. 2014;37(1):64-72.
15. O'Brien SH, Koch T, Vesely SK, Schwarz EB. Hormonal contraception and risk of thromboembolism in women with diabetes. *Diabetes Care*. 2017;40(2):233-238.
16. Rogers MAM, Kim C, Banerjee T, Lee JM. Fluctuations in the incidence of type 1 diabetes in the United States from 2001 to 2015: a longitudinal study. *BMC Med*. 2017;15(1):199.
17. Wang SY, Andrews CA, Herman WH, Gardner TW, Stein JD. Incidence and risk factors for developing diabetic retinopathy among youths with type 1 or type 2 diabetes throughout the United States. *Ophthalmology*. 2017;124(4):424-430.
18. Zhong VW, Obeid JS, Craig JB, et al. An efficient approach for surveillance of childhood diabetes by type derived from electronic health record data: the SEARCH for Diabetes in Youth Study. *J Am Med Inform Assoc*. 2016;23(6):1060-1067.
19. Lewis JD, Bilker WB, Weinstein RB, Strom BL. The relationship between time since registration and measured incidence rates in the General Practice Research Database. *Pharmacoepidemiol Drug Saf*. 2005;14(7):443-451.
20. Handelsman Y. Role of bile acid sequestrants in the treatment of type 2 diabetes. *Diabetes Care*. 2011;34(Suppl 2):S244-S250.
21. Ooi CP, Loke SC. Colesevelam for Type 2 diabetes mellitus: an abridged Cochrane review. *Diabet Med*. 2014;31(1):2-14.
22. Katz LL, Anderson BJ, McKay SV, et al. Correlates of medication adherence in the TODAY cohort of youth with type 2 Diabetes. *Diabetes Care*. 2016;39(11):1956-1962.
23. Cai X, Gao X, Yang W, Han X, Ji L. Efficacy and safety of initial combination therapy in treatment-naive type 2 diabetes patients: a systematic review and meta-analysis. *Diabetes Ther*. 2018;9(5):1995-2014.
24. Matthews DR, Paldánius PM, Proot P, Chiang Y, Stumvoll M, Del Prato S. Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial. *Lancet*. 2019;394(10208):1519-1529.
25. Yackey K, Stukus K, Cohen D, Kline D, Zhao S, Stanley R. Off-label medication prescribing patterns in pediatrics: An update. *Hosp Pediatr*. 2019;9(3):186-193.
26. Turner S, Nunn AJ, Fielding K, Choonara I. Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. *Acta Paediatr*. 1999;88(9):965-968.
27. Al-Saeed AH, Constantino MI, Molyneaux L, et al. an inverse relationship between age of type 2 diabetes onset and complication risk and mortality: the impact of youth-onset type 2 diabetes. *Diabetes Care*. 2016;39(5):823-829.
28. Koye DN, Ling J, Dibato J, Khunti K, Montvida O, Paul SK. Temporal trend in young-onset type 2 diabetes-macrovascular and mortality risk: study of UK primary care electronic medical records. *Diabetes Care*. 2020;43(9):2208-2216.
29. Levitt Katz LE, Bacha F, Gidding SS, et al. Lipid profiles, inflammatory markers, and insulin therapy in youth with type 2 diabetes. *J Pediatr*. 2018;196:208-216.
30. Grant R, Adams AS, Trinacty CM, et al. Relationship between patient medication adherence and subsequent clinical inertia in type 2 diabetes glycemic management. *Diabetes Care*. 2007;30(4):807-812.
31. Jones KL, Arslanian S, Peterokova VA, Park JS, Tomlinson MJ. Effect of metformin in pediatric patients with type 2 diabetes: a randomized controlled trial. *Diabetes Care*. 2002;25(1):89-94.
32. Goran MI, Bergman RN, Cruz ML, Watanabe R. Insulin resistance and associated compensatory responses in african-american and Hispanic children. *Diabetes Care*. 2002;25(12):2184-2190.
33. Hasson RE, Adam TC, Davis JN, et al. Ethnic differences in insulin action in obese African-American and Latino adolescents. *J Clin Endocrinol Metab*. 2010;95(8):4048-4051.
34. Zeitler P, Hirst K, Copeland KC, et al. HbA1c after a short period of monotherapy with metformin identifies durable glycemic control among adolescents with type 2 diabetes. *Diabetes Care*. 2015;38(12):2285-2292.
35. Gregg B, Connor CG, Cheng P, et al. C-peptide levels in pediatric type 2 diabetes in the Pediatric Diabetes Consortium T2D Clinic Registry. *Pediatr Diabetes*. 2016;17(4):274-280.
36. Zhong VW, Pfaff ER, Beavers DP, et al. Use of administrative and electronic health record data for development of automated algorithms for childhood diabetes case ascertainment and type classification: the SEARCH for Diabetes in Youth Study. *Pediatr Diabetes*. 2014;15(8):573-584.
37. Schroeder EB, Donahoo WT, Goodrich GK, Raebel MA. Validation of an algorithm for identifying type 1 diabetes in adults based on electronic health record data. *Pharmacoepidemiol Drug Saf*. 2018;27(10):1053-1059.

38. Levitt Katz LE, Magge SN, Hernandez ML, Murphy KM, McKnight HM, Lipman T. Glycemic control in youth with type 2 diabetes declines as early as two years after diagnosis. *J Pediatr*. 2011;158(1):106-111.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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