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Glucagon remains underutilized overall and among groups at high risk of severe hypoglycemia in the U.S.

Context:
- There is minimal contemporary literature on glucagon utilization and cost
- The impact of easier-to-use glucagon formulations, which have come to market in the last 5 years, has not been explored.

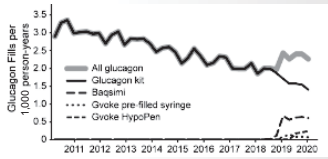
Objective:
- Characterize trends in the glucagon fill rates and expenditures among adults with diabetes overall and by key demographic and clinical characteristics

Setting:
- Retrospective analysis of medical and pharmacy claims data from the OptumLabs Data Warehouse (OLDW)

Participants:
- Commercial and Medicare Advantage beneficiaries aged ≥ 18 in OLDW between 1 January 2011 and 31 March 2021.

Outcomes:
- Glucagon fills were identified from pharmacy claims during each calendar quarter that the individual had medical and pharmacy insurance coverage
- Costs (total, patient out-of-pocket, health plan)

Results:
- The study population comprised 2,814,464 U.S. adults
- Glucagon fill rates were low overall and among high-risk groups such as those with a history of severe hypoglycemia
- Cost steadily increased over time



Conclusion:
- Glucagon remains underutilized and cost may be a significant barrier

Diabetes Care

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ARTICLE HIGHLIGHTS

- There is minimal contemporary literature on glucagon utilization and cost, particularly since new formulations have come to market.
- We characterized glucagon fill rates and expenditures for adults with diabetes overall and by key subgroups from 2011 to 2021.
- Glucagon fill rates were concerningly low among high-risk groups, such as those with type 1 diabetes or a history of severe hypoglycemia, with glucagon costs steadily increasing through the study period.
- Glucagon remains underutilized in high-risk groups, and cost may be a significant barrier in the U.S.; legislative and insurer efforts are critical to increase utilization and control costs.

Glucagon Prescribing and Costs Among U.S. Adults With Diabetes, 2011–2021

Joseph R. Herges,[1] Rodolfo J. Galindo,[2] Joshua J. Neumiller,[3] Herbert C. Heien,[4] Guillermo E. Umpierrez,[2] and Rozalina G. McCoy[4–6]

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ORIGINAL ARTICLE

OBJECTIVE

To characterize contemporary trends in glucagon fill rates and expenditures in a nationwide cohort of adults with diabetes overall and by key demographic and clinical characteristics.

RESEARCH DESIGN AND METHODS

In this retrospective cohort study, we examined *1*) glucagon fill rates per 1,000 person-years and *2*) patient out-of-pocket and health plan costs per filled glucagon dose among adults with diabetes included in OptumLabs Data Warehouse between 1 January 2011 and 31 March 2021.

RESULTS

The study population comprised 2,814,464 adults with diabetes with a mean age of 62.8 (SD 13.2) years. The overall glucagon fill rate decreased from 2.91 to 2.28 per 1,000 person-years (−22%) over the study period. In groups at high risk for severe hypoglycemia, glucagon fill rates increased from 22.46 to 36.76 per 1,000 person-years (64%) among patients with type 1 diabetes, 11.64 to 16.63 per 1,000 person-years (43%) among those treated with short-acting insulin, and 16.08 to 20.12 per 1,000 person-years (25%) among those with a history of severe hypoglycemia. White patients, women, individuals with high income, and commercially insured patients had higher glucagon fill rates compared with minority patients, males, individuals with low income, and Medicare Advantage patients, respectively. Total cost per dosing unit increased from $157.97 to $275.32 (74%) among commercial insurance beneficiaries and from $150.37 to $293.57 (95%) among Medicare Advantage beneficiaries.

CONCLUSIONS

Glucagon fill rates are concerningly low and declined between 2011 and 2021 but increased in appropriate subgroups with type 1 diabetes, using short-acting insulin, or with a history of severe hypoglycemia. Fill rates were disproportionately low among minority patients and individuals with low income.

Severe hypoglycemia in people with insulin-treated diabetes is common (1,2) and dangerous (3–6). The clinical and economic implications of severe hypoglycemia are considerable and include reduced quality of life (7,8), increased cost of care (8–10), and a higher risk of hospital admissions (11,12), readmissions (13), and mortality (4). Patients with type 1 diabetes (14), insulin-treated type 2 diabetes (15), multiple/advanced comorbidities; who are Black; and with low income are at highest risk (16). Because not all episodes of hypoglycemia can be prevented, it is

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imperative that all at-risk patients have access to glucagon to reverse severe hypoglycemia and prevent hospitalization or death. Therefore, guidelines recommend glucagon be prescribed to all patients treated with insulin for type 1 and type 2 diabetes at high risk of hypoglycemia (17).

Contemporary data on glucagon prescribing and fill patterns are limited. Analysis of national data among commercially insured and Medicare Advantage beneficiaries in 2014 revealed that filling of glucagon prescriptions was rare (1.21%), even among patients at high risk, such as those with type 1 diabetes (14.5%) and previous hospitalizations for hypoglycemia (4.8%) (18). Another study examining glucagon prescribing patterns in patients receiving new insulin prescriptions between 2009 and 2011 found similar gaps (19). The reasons for low glucagon prescription fill rates are not well understood, though a study from Japan identified the complex preparation and administration procedure for glucagon kits as the most significant barrier (20). However, over the past 5 years, new, convenient glucagon formulations have become available in clinical practice that do not require reconstitution and can be administered subcutaneously, intramuscularly, or intranasally. With time to peak blood concentration of just 20 min (21), easier administration procedures, and longer shelf-lives (22,23), these glucagon formulations may have addressed the preparation and administration complexity barriers of traditional lyophilized preparations.

In the context of a changing landscape of glucagon availability and consistent guideline recommendations to prescribe glucagon to patients with type 1 diabetes and insulin-treated type 2 diabetes who have history of or are at risk for severe hypoglycemia, there is a paucity of data on *1*) contemporary glucagon prescription fill patterns; *2*) trends in the use of different glucagon formulations; *3*) costs of glucagon over time, particularly among Medicare beneficiaries who are ineligible for copay savings cards that reduce the patient's out-of-pocket cost-sharing responsibility; and *4*) socioeconomic disparities in glucagon fill rates. Accordingly, we examined glucagon fill patterns and costs per unit of glucagon filled over a 10-year span in a large and diverse population of commercially insured and Medicare Advantage beneficiaries with diabetes across the U.S.

RESEARCH DESIGN AND METHODS

Study Design

Retrospective analysis of medical and pharmacy claims data from OptumLabs Data Warehouse (OLDW), a deidentified claims database of enrollees in multiple private (employee-sponsored) commercial and Medicare Advantage health plans offered by a single large nationwide health plan (24), was performed. The OLDW contains longitudinal health information on enrollees, representing a diverse mixture of ages, races/ethnicities, and geographic regions across the U.S. All study data were deidentified consistent with Health Insurance Portability and Accountability Act expert deidentification determination (25), and the study was exempt from Mayo Clinic institutional review board review. Results are reported in accordance with Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines (26).

Participants

We identified adults (≥18 years old) with diabetes included in OLDW between 1 January 2010 and 31 March 2020 ascertained using validated Healthcare Effectiveness Data and Information Set (HEDIS) criteria (27). Individuals were subsequently required to have 12 months of uninterrupted medical and pharmacy coverage (defined by absence of gaps in coverage ≥45 days) after the date that HEDIS criteria for diabetes were met; this period was used to categorize diabetes as type 1 or type 2 (described below) and to ascertain baseline covariates. The index date was therefore set to 12 months after the HEDIS date and spanned 1 January 2011 through 31 March 2021.

Outcomes

Glucagon formulations were approved by the U.S. Food and Drug Administration for glucagon kit in 1998, Baqsimi intranasal in 2019, Gvoke HypoPen in 2019, and Gvoke prefilled syringe in 2019. Glucagon fills (overall and individually) were identified from pharmacy claims during each calendar quarter that the individual had medical and pharmacy insurance coverage.

Independent Variables

Age, sex, race/ethnicity, geographic region, and annual household income were identified from OLDW enrollment files at the index date. Comorbidities were ascertained from all claims during the 12 months preceding the index date (Supplementary Table 1). Diabetes was categorized as type 1 or type 2 as previously described (5) based on diagnosis codes and medication fills during the baseline period. Glucose-lowering therapy was characterized based on prescriptions filled during the 120-day period prior to the index date (Supplementary Table 2).

Statistical Analysis

We calculated overall frequencies (percentages) and means (SDs) for baseline characteristics overall and by baseline insulin regimen categorized as no insulin, long-acting insulin only (with or without noninsulin medications), and any short-acting insulin (with or without long-acting insulin, noninsulin medications). Glucagon fills were captured for each calendar quarter with medical and pharmacy insurance coverage and reported per 1,000 person-years overall and by glucagon product, baseline category of insulin regimen, history of hypoglycemia requiring emergency department (ED) or hospital care, diabetes type, race/ethnicity, sex, annual household income, and insurance type (commercial vs. Medicare Advantage). The glucagon fill rate could include multiple fills for a single patient if they occurred in the same calendar quarter. Reported relative percent changes were calculated from the first quarter of 2011 and first quarter of 2021.

Costs were standardized to the first quarter of 2021 and calculated separately for commercial and Medicare Advantage beneficiaries using pharmacy claims. Total costs included out-of-pocket expenses paid by the patient and costs to the health plan. Medicare Advantage plans also have other costs, which reflect the portion of cost paid by Medicare to cover various subsidies to offset cost burden to enrollees (e.g., the Low-Income Subsidy program [28]). Analyses were conducted using SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC).

Data and Resource Availability

The data sets generated and/or analyzed during the study are available from the corresponding author upon reasonable request.

RESULTS

Study Population

The study population comprised 2,814,464 Medicare Advantage and commercially insured adults across the U.S. Overall, 41,514 (1.5%) had at least one glucagon fill during the study period. Included patients were 62.8 (SD, 13.2) years old, 50.1% were women, 61.5% were non-Hispanic White, and 3.2% had type 1 diabetes. Of the 308,281 patients treated with short-acting insulin, 26,838 (8.7%) had at least one glucagon fill during the study period. Glucagon fill rates were lower among patients treated with long-acting insulin only (5,439 of 235,939 [2.3%]) and were minimal among patients without any insulin fills at baseline (9,237 of 2,270,244 [0.4%]). Baseline characteristics of patients included in each of these groups are summarized in Table 1. Percentages of patients with at least one glucagon fill in the study period by subgroup are shown in Supplementary Table 3.

Trends in Glucagon Fills

Temporal trends in glucagon fill rates per 1,000 person-years are depicted in Fig. 1. Overall, glucagon fill rates decreased from 2.91 per 1,000 person-years in the first quarter of 2011 to 2.28 per 1,000 person-years in the first quarter of 2021 (−22% relative change). Glucagon fill rates decreased from 3.22 to 1.96 per 1,000 person-years (−39%) for individuals with Medicare Advantage health plans, while increasing from 2.63 to 3.14 per 1,000 person-years (19%) among patients with commercial insurance. The rate of glucagon kit fills decreased gradually during the study period, while fills for newer glucagon formulations, primarily intranasal glucagon, steadily increased beginning in the first quarter of 2020. The majority of glucagon fills, however, remained for the original lyophilized glucagon kit.

Among patients with a history of severe hypoglycemia requiring ED or hospital care, glucagon fills increased from 16.08 to 20.12 per 1,000 person-years (25%). Fill rates also increased over time among patients with type 1 diabetes from 22.46 to 36.76 per 1,000 person-years (64%) but decreased among patients with type 2 diabetes from 1.85 to 1.46 per 1,000 person-years (−21%). Glucagon fills increased from 11.64 to 16.63 per 1,000 person-years (43%) among patients with baseline short-acting insulin fills, from 1.84 to 3.60 per 1,000 person-years (96%) among those with baseline long-acting insulin fills only, and from 0.45 to 0.60 per 1,000 person-years (34%) among those without baseline insulin fills. Thus, while all three of these treatment groups had increased glucagon fills over time, we saw an overall reduction in glucagon fills due to increasing numbers of patients not treated with insulin whose glucagon fill rates were lowest, which highlighted the need to examine individual subgroups rather than the entire population together.

Consistently higher glucagon fill rates were seen in White patients (3.32–2.60 per 1,000 person-years), while Asian patients had lower rates (2.23 to 1.09 per 1,000 person-years) among the racial/ethnic groups. Glucagon fill rates were progressively lower among individuals with lower annual household incomes compared with those with higher income. From the first quarter of 2011 to the first quarter of 2021, fill rates per 1,000 person-years were 5.21 and 4.63, respectively, in the highest income category (>$200,000) and 1.88 and 2.02 in the lowest income category (<$40,000). Likewise, glucagon fill rates per 1,000 person-years for women (3.25 and 2.43) were higher than for men (2.54 and 2.12), although the gap between them narrowed over time. Within each demographic subgroup, glucagon fill rates decreased over time and mirrored that of the general population.

Trends in Glucagon Costs

Quarterly per-unit costs for each glucagon fill are depicted in Fig. 2 for Medicare Advantage beneficiaries and Fig. 3 for patients with commercial health plans. Total cost increased from $150.37 to $293.57 per unit of glucagon (95%) among Medicare Advantage beneficiaries and from $157.97 to $275.32 per unit of glucagon (74%) among commercially insured beneficiaries. A large proportion of the costs were borne by the health plan. In Medicare Advantage plans, health plan costs increased from $91.21 to $181.17 (99%) and in commercial plans, from $119.54 to $215.43 (80%). Patient out-of-pocket costs increased from $11.32 to $19.97 (76%) among Medicare Advantage beneficiaries and from $38.43 to $59.89 (56%) among commercially insured beneficiaries. Other Medicare Advantage costs increased from $47.83 to $92.43 (93%). In the first quarter of 2021, the total cost per unit of the various glucagon formulations for Medicare Advantage beneficiaries and commercial health plans, respectively, were $293.81 and $268.21 for glucagon kit, $283.93 and $203.52 for Baqsimi intranasal, $302.19 and $281.80 for Gvoke HypoPen, and $320.56 and $288.10 for Gvoke prefilled syringe.

CONCLUSIONS

Despite high rates of ED visits and hospitalizations for hypoglycemia (1,12–14), the frequency of glucagon fills remained low in a large national sample of Medicare Advantage beneficiaries and commercially insured patients from 2011 to 2021. The low overall rates of glucagon use are consistent with prior studies examining glucagon fill rates between 2009 and 2011 (19) and in 2014 (18). Reassuringly, glucagon fill rates have increased slowly in high-risk groups, such as patients with type 1 diabetes, patients treated with short-acting insulin, and patients with a history of severe hypoglycemia. Yet, there is significant opportunity to increase glucagon use in high-risk groups, which is highlighted by a sixfold increased risk of recurrent severe hypoglycemia following an ED visit or hospital admission in the preceding year (13). Concerningly, we saw pervasive disparities in glucagon fill rates among racial/ethnic minoritized groups and individuals with low income. Between 2011 and 2021, the total cost of glucagon per unit increased by 95% and 75% for Medicare Advantage and commercial health plan beneficiaries, respectively, though most of the cost increase was borne by health plans with a smaller increase in patient out-of-pocket expenditures.

Given the recency of newly available glucagon formulations to market, our study is the first to examine whether and how these products affected glucagon fill rates and costs of care. These formulations, including intranasal (23) and premixed (22) glucagons, remove the need for reconstitution, which has been a barrier to prescribing and procurement. The longer shelf-life of contemporary glucagon formulations may also help to alleviate the hesitancy of filling an expensive medication that may be rarely or never required. We found that intranasal glucagon, which was approved by the U.S. Food and Drug Administration in July 2019, saw a steep increase in fill rate in the first quarter of

Table 1—Baseline characteristics

	No insulin (n = 2,270,244 [80.7%])	Long-acting insulin only (n = 235,939 [8.4%])	Short-acting insulin (n = 308,281 [11.0%])	Total (N = 2,814,464)
Age, years, mean (SD)	63.2 (12.9)	63.8 (12.1)	59.3 (15.6)	62.8 (13.2)
Age category, years				
18–39	116,955 (5.2)	9,245 (3.9)	39,891 (12.9)	166,091 (5.9)
40–64	975,749 (43.0)	100,305 (42.5)	133,876 (43.4)	1,209,930 (43.0)
≥65	1,177,540 (51.9)	126,389 (53.6)	134,514 (43.6)	1,438,443 (51.1)
Sex				
Female	1,133,171 (49.9)	118,258 (50.1)	159,340 (51.7)	1,410,769 (50.1)
Male	1,137,073 (50.1)	117,681 (49.9)	148,941 (48.3)	1,403,695 (49.9)
Race/ethnicity				
Asian	101,883 (4.5)	5,965 (2.5)	6,943 (2.3)	114,791 (4.1)
Black	389,379 (17.2)	44,447 (18.8)	57,153 (18.5)	490,979 (17.4)
Hispanic	311,200 (13.7)	32,475 (13.8)	34,506 (11.2)	378,181 (13.4)
White	1,390,533 (61.3)	143,523 (60.8)	197,773 (64.2)	1,731,829 (61.5)
Other/unknown	77,249 (3.4)	9,529 (4.0)	11,906 (3.9)	98,684 (3.5)
Income, $				
<40,000	719,128 (31.7)	85,033 (36.0)	102,342 (33.2)	906,503 (32.2)
40,000–74,999	657,488 (29.0)	66,178 (28.0)	81,615 (26.5)	805,281 (28.6)
75,000–124,999	505,143 (22.3)	46,692 (19.8)	62,991 (20.4)	614,826 (21.8)
125,000–199,999	188,909 (8.3)	16,249 (6.9)	24,838 (8.1)	229,996 (8.2)
≥200,000	89,207 (3.9)	6,892 (2.9)	13,802 (4.5)	109,901 (3.9)
Other/unknown	110,369 (4.9)	14,895 (6.3)	22,693 (7.4)	147,957 (5.3)
Region				
Midwest	519,407 (22.9)	54,774 (23.2)	77,692 (25.2)	651,873 (23.2)
Northeast	309,505 (13.6)	31,791 (13.5)	40,684 (13.2)	381,980 (13.6)
South	1,185,188 (52.2)	122,049 (51.7)	154,295 (50.1)	1,461,532 (51.9)
West	252,831 (11.1)	27,056 (11.5)	35,211 (11.4)	315,098 (11.2)
Other/unknown	3,313 (0.1)	269 (0.1)	399 (0.1)	3,981 (0.1)
Insurance				
Commercial	975,345 (43.0)	84,160 (35.7)	133,334 (43.3)	1,192,839 (42.4)
Medicare Advantage	1,294,899 (57.0)	151,779 (64.3)	174,947 (56.7)	1,621,625 (57.6)
Diabetes type				
Type 1	12,454 (0.5)	4,760 (2.0)	71,986 (23.4)	89,200 (3.2)
Type 2	2,257,790 (99.5)	231,179 (98.0)	236,295 (76.6)	2,725,264 (96.8)
Noninsulin glycemic medication*				
DPP-4 inhibitor	204,534 (9.0)	33,199 (14.1)	18,364 (6.0)	256,097 (9.1)
GLP-1RAs	97,465 (4.3)	30,313 (12.8)	20,859 (6.8)	148,637 (5.3)
Metformin	1,302,576 (57.4)	140,444 (59.5)	105,950 (34.4)	1,548,970 (55.0)
SGLT2 inhibitor	75,293 (3.3)	15,759 (6.7)	10,908 (3.5)	101,960 (3.6)
Sulfonylureas	492,215 (21.7)	68,379 (29.0)	30,163 (9.8)	590,757 (21.0)
Thiazolidinediones	116,720 (5.1)	15,380 (6.5)	8,460 (2.7)	140,560 (5.0)
Comorbidities†‡				
Cancer	198,904 (8.8)	20,881 (8.9)	25,263 (8.2)	245,048 (8.7)
Cardiovascular	696,013 (30.7)	89,602 (38.0)	118,347 (38.4)	903,962 (32.1)
Cerebrovascular	269,164 (11.9)	36,421 (15.4)	50,323 (16.3)	355,908 (12.6)
Cirrhosis	22,775 (1.0)	4,057 (1.7)	6,016 (2.0)	32,848 (1.2)
Chronic kidney disease stage 3–4	198,286 (8.7)	38,553 (16.3)	54,595 (17.7)	291,434 (10.4)
Chronic kidney disease stage 5	28,327 (1.2)	6,434 (2.7)	11,251 (3.6)	46,012 (1.6)
Dementia	81,912 (3.6)	11,070 (4.7)	19,563 (6.3)	112,545 (4.0)
Depression	351,649 (15.5)	44,666 (18.9)	67,653 (21.9)	463,968 (16.5)
Heart failure	231,292 (10.2)	37,618 (15.9)	57,641 (18.7)	326,551 (11.6)
Baseline neuropathy	479,757 (21.1)	87,665 (37.2)	127,939 (41.5)	695,361 (24.7)
Peripheral vascular disease	314,470 (13.9)	53,065 (22.5)	78,561 (25.5)	446,096 (15.9)
Retinopathy	250,882 (11.1)	55,581 (23.6)	91,916 (29.8)	398,379 (14.2)

Data are n (%) unless otherwise indicated. DPP-4, dipeptidyl peptidase 4; GLP-1RA, glucagon-like peptide 1 receptor agonist; SGLT2, sodium–glucose cotransporter 2. *Supplementary Table 1. †Comorbidities were ascertained from all claims during the 12 months preceding the index date. Glucose-lowering therapy was characterized based on prescriptions filled during the 120 days preceding the index date. ‡Supplementary Table 2.

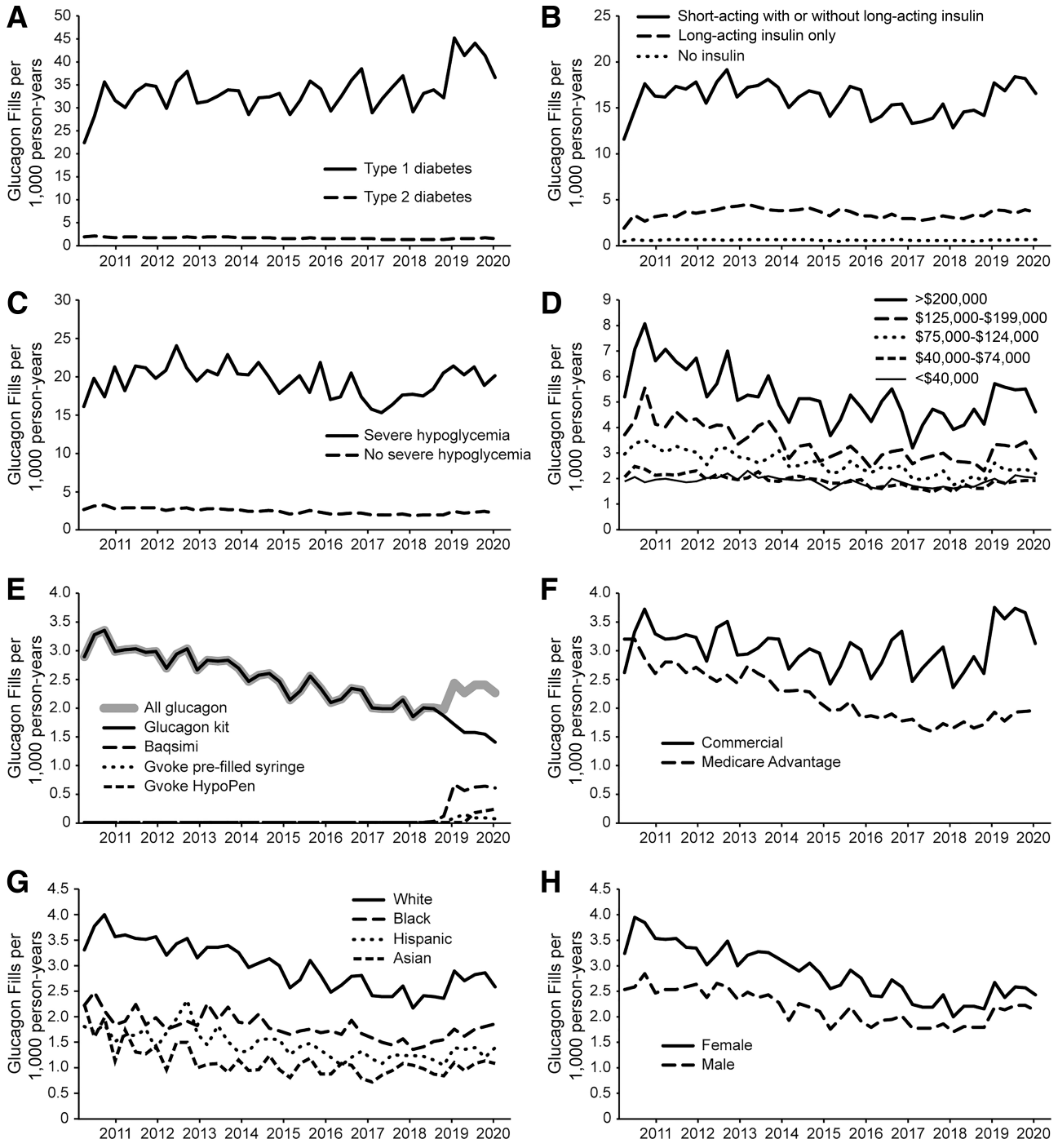

Figure 1—Observed rates of glucagon fills per 1,000 person-years, first quarter of 2011 through first quarter of 2021 by diabetes type (*A*), insulin regimen (*B*), history of severe hypoglycemia (*C*), income (*D*), glucagon type (*E*), insurance type (*F*), race/ethnicity (*G*), and sex (*H*).

2020, then plateaued through the end of the study period, while negligible fill rates were observed for premixed injectables, which entered the market in September 2019. Overall glucagon fills increased from 1.98 per 1,000 person-years to 2.28 per 1,000 person-years from the fourth quarter of 2019 to the first quarter of 2021, which may indicate some progress. In the same period, the cost per glucagon dosage unit decreased from $284.75 to $267.37 among commercially insured beneficiaries, which could be due to market competition, though similar reductions were not seen among Medicare Advantage beneficiaries. Nevertheless, traditional glucagon kits that require reconstitution still accounted for 61% of glucagon fills by the first quarter of 2021. This finding is unexpected given the added ease of use with newer glucagon formulations and similar cost compared with traditional glucagon kits and may indicate a lack of familiarity of clinicians with contemporary glucagon options and/or that patients are apprehensive to switch products. An automated prescription renewal system may also circumvent the regular assessment of available options.

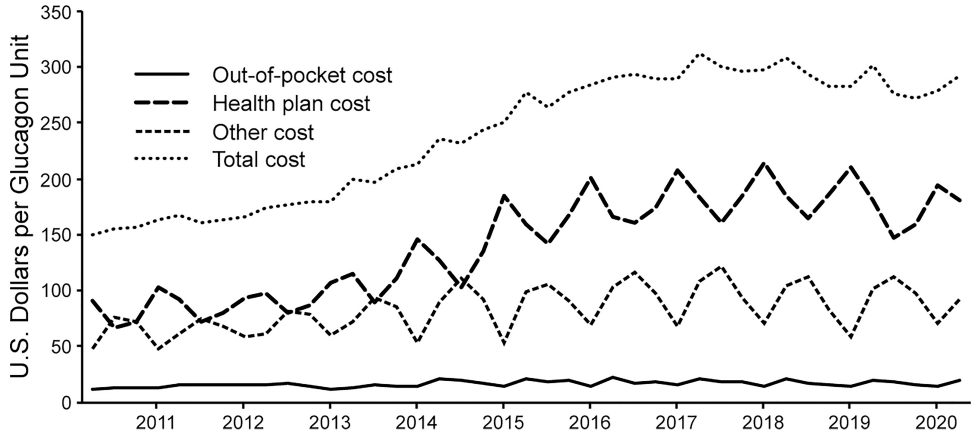

Figure 2—Observed cost in U.S. dollars per unit of glucagon for Medicare Advantage beneficiaries, first quarter of 2011 through first quarter of 2021. Costs were standardized to the first quarter of 2021.

We identified pervasive and persistent disparities in glucagon fill rates among minoritized populations, individuals with low income, and patients with Medicare Advantage (compared with commercial) health plans. These gaps mirror disparities in other evidence-based diabetes treatment practices, specifically use of glucose-lowering medications with cardiorenal benefits among patients with cardiovascular disease, heart failure, and chronic kidney disease (29,30). In the first quarter of 2021, Black, Hispanic, and Asian patients, respectively, filled glucagon at approximate rates of 29% (1.85 per 1,000 person-years), 46% (1.39 per 1,000 person-years), and 58% (1.09 per 1,000 person-years) lower relative to White patients (2.60 per 1,000 person-years). This disparity in glucagon fills by race/ethnicity was present throughout the study period. These gaps in glucagon fill rates are particularly concerning given the higher rate of severe hypoglycemia in Black compared with White patients with diabetes (14), and it will be important to examine, understand, and address the structural factors that hinder optimal prescribing in minoritized populations. Low rates of glucagon fills among patients with low income underscores the impact of medication cost on optimal diabetes management, with such patients more likely to ration or forego recommended medications that they may view as optional in order to afford higher priority medical and nonmedical necessities. Indeed, patients with Medicare Advantage health plans were less likely to fill glucagon prescriptions than patients with commercial health plans, despite their lower out-of-pocket cost-sharing responsibility, potentially because they are ineligible for savings cards that reduce the cost-sharing obligations for eligible patients with commercial health plans. Thus, Medicare Advantage beneficiaries may decline filling glucagon prescriptions until they have met their deductibles, at which time out-of-pocket cost is significantly reduced.

The total cost of glucagon per dosing unit steadily increased to nearly $300 in both the Medicare Advantage and commercially insured populations. From 2018 to the first quarter of 2021, the total cost stayed relatively stable for Medicare Advantage beneficiaries and modestly decreased to $275.32 for commercially insured beneficiaries. The stabilization or reduction in cost could be due to market competition with several available products. Most of the high cost of glucagon was covered by the health plan, with a modest increase in patient out-of-pocket cost over the 10-year, 3-month study period. Affordability of potentially life-saving medications like glucagon, naloxone, and subcutaneous epinephrine for emergency

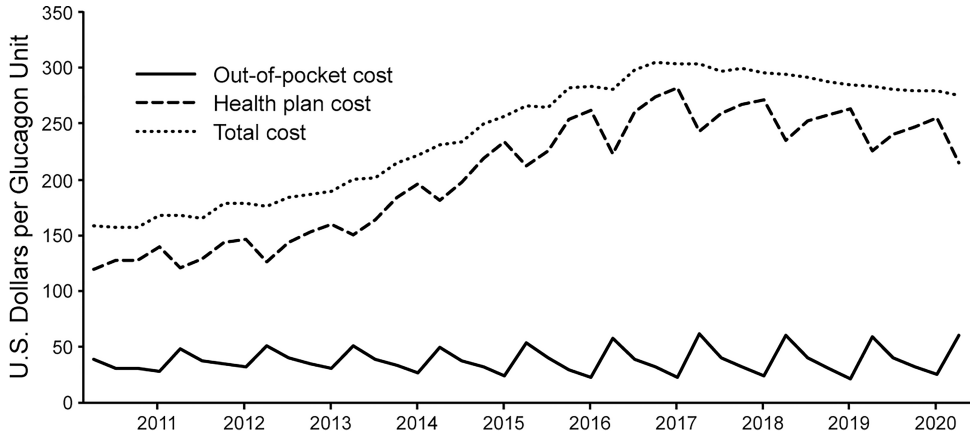

Figure 3—Observed cost in U.S. dollars per unit of glucagon for commercially insured beneficiaries, first quarter of 2011 through first quarter of 2021. Costs were standardized to the first quarter of 2021.

use should be societal priorities and could include legislative action to increase affordability, particularly in low-income and Medicare populations, which has occurred with insulin (31). Health plans can also take action to reduce the cost of these medications. For example, UnitedHealthcare recently announced an elimination of out-of-pocket costs for critical medications, including insulin and glucagon, for eligible plans in 2023 (32).

Our study fills an important gap in the literature by examining contemporary data on glucagon fill patterns, including the impact of easier-to-use formulations introduced to the market, glucagon cost, and socioeconomic factors. It is strengthened by the inclusion of a large and diverse population in terms of age, race/ethnicity, and geographic region. Increasing glucagon prescribing and procurement can reduce the morbidity and mortality associated with severe hypoglycemia, impacting quality of life, cost of care, hospital admissions, and mortality. However, our study also has important limitations. The study population comprised commercial and Medicare Advantage beneficiaries and did not include patients who were uninsured or who had other insurance types. Our pharmacoepidemiologic approach did not allow us to assess for causal relationships between glucagon fills and subsequent hypoglycemia, which is an important area for future study. We examined glucagon fills because prescription data and claims denials were not available in the database, but exploring glucagon prescriptions not subsequently filled would be informative to the barriers of glucagon utilization and availability. Claims data may underrepresent patient conditions present but not billed for during patient encounters; however, to both minimize misclassification and allow for consistency and comparability with other studies, we used validated code sets. Glucagon use was analyzed by baseline insulin regimen, although changes in the insulin regimen over the study period could have affected glucagon fill rates. Finally, because manufacturer copay savings cards are applied after insurance claims are made, we were not able to ascertain how often these were used by commercially insured patients and the actual amounts borne by the patient after these savings cards were applied. In our clinical practice, and likely others, these savings cards are used frequently to improve affordability (31).

In conclusion, glucagon continues to be underutilized, even among patients at high risk for severe hypoglycemia. Interventions to increase glucagon prescribing and address barriers to procurement should be focused on populations most likely to require it, including patients with type 1 diabetes, with a history of severe hypoglycemia, or who are treated with multidose insulin regimens. Among the most important opportunities to increase glucagon prescribing and education is in the hospital setting, particularly when patients are admitted for hypoglycemia or experience it during their stay. Thus, glucagon prescriptions should be issued at hospital discharge, and education on recognizing, preventing, and treating severe hypoglycemia should be delivered and reinforced during the hospital stay. Because cost is likely a significant barrier to glucagon procurement, resources and programs to assist patients with medication affordability are critical and urgently needed. Social workers, community health workers, pharmacists, and other health care professionals can assist patients in finding lower cost options or in using manufacturer patient assistance programs, which can provide free medications to patients meeting eligibility requirements (31).

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Author Contributions. J.R.H. and R.G.M. conceived and designed the study. J.R.H., R.J.G., J.J.N., G.E.U., and R.G.M. interpreted the study results. H.C.H. managed and analyzed the data. J.R.H. wrote the first draft of the manuscript and all authors edited, reviewed, and approved the final manuscript for submission. R.G.M. supervised data analyses and secured funding. All authors edited, reviewed, and approved the final manuscript for submission. J.R.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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