Disclaimer

The following report(s) provides findings from an FDA-initiated query using Sentinel. While Sentinel queries may be undertaken to assess potential medical product safety risks, they may also be initiated for various other reasons. Some examples include determining a rate or count of an identified health outcome of interest, examining medical product use, exploring the feasibility of future, more detailed analyses within Sentinel, and seeking to better understand Sentinel capabilities.

Data obtained through Sentinel are intended to complement other types of evidence such as preclinical studies, clinical trials, postmarket studies, and adverse event reports, all of which are used by FDA to inform regulatory decisions regarding medical product safety. The information contained in this report is provided as part of FDA's commitment to place knowledge acquired from Sentinel in the public domain as soon as possible. Any public health actions taken by FDA regarding products involved in Sentinel queries will continue to be communicated through existing channels.

FDA wants to emphasize that the fact that FDA has initiated a query involving a medical product and is reporting findings related to that query does not mean that FDA is suggesting health care practitioners should change their prescribing practices for the medical product or that patients taking the medical product should stop using it. Patients who have questions about the use of an identified medical product should contact their health care practitioners.

The following report contains a description of the request, request specifications, and results from the modular program run(s).

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Overview for Request: cder_iqp_wp037

Request ID: cder_iqp_wp037

Request Description: In this report we aimed to characterize patients with an incident medication fact record for select non-insulin antidiabetics between October 1, 2017 to September 30, 2023 in the TriNetX Live™ platform.

Data Source: We ran this query on February 12, 2024. This query was distributed to 81 health care organizations (HCOs) provided through the TriNetX Live™ platform in their USA Network. This query contains data from the 80 HCOs that responded.

TriNetX aggregates electronic health record (EHR) systems data from its partner HCOs to create queryable datasets. TriNetX datasets primarily comprise clinical patient data such as demographics, diagnoses, procedures, labs, and medications. For more information on the TriNetX Live™ platform and the TriNetX data visit their website here: https://trinetx.com/

Study Design: In this retrospective cohort study, we identified counts of individuals with an incident medication fact record for select non-insulin antidiabetics. We built 12 distinct cohorts using the Query Builder module in the TriNetX Live™ platform.

Exposures of Interest: We examined five categories of select non-insulin antidibetics of interest including glucagon-like peptide-1 receptor agonists (GLP-1 RAs), sodium-glucose co-transporter 2 (SGLT2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, 2nd Generation Sulfonylurea, and Metformin. Seven GLP-1 RAs were also examined including albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide, and tirzepatide.

We used RxNorm medication terms in the Query Builder module. In order to be included in a cohort, we required evidence of a prescription, administration, or dispensing with the relevant non-insulin antidiabetic of interest (with or without additional filters) between October 1, 2017 and September 30, 2023.

Please see Appendix A for the list of RxNorm medication terms with information on filters used to define the exposures of interest in this request.

Cohort Eligibility Criteria: Individuals of all ages were included. They were eligible to be an incident user in a given cohort if they had:

1) Evidence of a visit 10/1/17 - 9/30/23, and
2) No evidence of the exposure of interest prior to the window of interest*, and
3) Evidence of the exposure of interest in the window of interest from 10/1/17-9/30/23

Please see Appendix B for the list of terms used to define inclusion criteria in this request. **Please see Appendix C for the specifications of the cohort parameters for each of the 12 cohorts as included in the Query Builder.**

Overview for Request: cder_iqp_wp037

Limitations: Algorithms used to define exposures, characteristics, and pregnancy, and mapping of source data to the data model are imperfect and susceptible to misclassification. Additionally, EHR data in the United States lacks longitudinality. The information before or after patients' healthcare encounters could be missing, especially if patient care was administered across different HCOs that may or might not participate in the TriNetX USA network. We are unable to determine if absence of evidence of a condition implies a true absence of a condition or if the condition was not observed in the data. Furthermore, not all HCOs provide brand name or route information for RxNorm terms or laboratory data. Therefore, data should be interpreted with these limitations in mind.

All counts provided through the TriNetX Live™ platform are rounded up to the nearest 10 to protect patient privacy. This rounding affects error, especially as sample sizes decrease. Error due to rounding can range from <0.09% when sample sizes are >10,000 to nearly 20% as sample sizes drop. Thus, all estimates should be interpreted as ranges, and small sample sizes should be interpreted with caution. Additionally, percentages are calculated based on these rounded numerators and denominators. Thus, due to rounding, the sum of each value in a category may not total to 100%.

The TriNetX Live™ platform uses RxNorm terms to identify medications, specifically the primary ingredient RxNorm terms. In the case of fixed dose combinations/co-packaged medications, the drugs are identified in the platform as the presence of primary ingredient RxNorm terms for all the individual medications on the same day (even if a multiple ingredient RxNorm term is made available by the National Library of Medicine), under the assumption that this refers only to the combined drugs and not two individual drugs prescribed concomitantly.

A subset of HCOs that contribute to the TriNetX USA Network may implement date shifting in either direction. Each HCO chooses the number of days shifted, at the level of the patient record, prior to data ingestion at TriNetX as a method to preserve patient privacy. It is difficult to characterize the full impact of date shifting on a specific set of results. When interpreting the results of an analysis, the impact of date shifting should be considered and readers should exercise caution when extrapolating information related to time.

Notes: We ran this query on February 12, 2024. A re-run of this query for the same query period in the future may not yield the same results owing to the dynamic nature of the TriNetX Live™ network.

Please contact the Sentinel Operations Center (info@sentinelsystem.org) for questions and to provide comments/suggestions for future enhancements to this document. For more information on Sentinel's querying in the TriNetX platform, please refer to the Sentinel Website (https://www.sentinelinitiative.org/methods-data-tools/methods/trinetx-rapid-querying).

*Due to the visit term being looked for anytime in the window of interest, there may be some patients that indexed into the cohort with their visit term following their drug exposure.

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Glossary of Terms for Analyses Using TriNetX Live™ Platform*

Characteristic - A medical fact (e.g., diagnosis, procedure, lab result) that occurred on or before the cohort-defining index event.

Explore Cohort - A description module on the TriNetX platform that presents a clinical profile of patients in a given cohort. Patient counts are rounded up to the nearest 10 before percentages are calculated, so the sum each of the values in one category may not total to 100%.

Date Shifting - A data obfuscation technique that some HCOs use to preserve patient privacy. Date shifting entails assigning each patient a random number of days (e.g., -365 to +365 days) and consistently adjusting each of their dates by that number of days, thus maintaining temporal relationships between records within a single patient.

Fact - (Medical Fact) A unit of utilization that represents a medical observation on a patient (e.g., diagnosis, procedure, clinical observation).

Filter - A method of limiting terms included in queries to a specific subset of data. Filters include age at time of event, data source (electronic health record or natural language processing); brand name, route, and strength for medication terms; occurrence (first or most recent) for lab terms; and priority for diagnosis and procedure terms.

Group - A series of codes and terms defined with Boolean logic that are used to create a query cohort. For each group, users have the ability to specified time periods of interest, and the number of instances that the group must occur for cohort entry.

> **Subgroup -** Within a group, additional subgroups can be specified to define temporal relationships between the terms in the subgroup (e.g., terms in subgroup B must occur within 5 days after terms in subgroup A). Users can require that these temporal constraints be applied to the 1) first, 2) last, or 3) any instance of each subgroup.

Health Care Organization (HCO) - Organizations that contribute electronic healthcare record data to the TriNetX data networks. HCOs include academic institutions and community health provider systems and a single HCO may contain one or more individual sites or facilities.

Index - The first date when a patient meets all of the cohort-defining criteria. In Analytics modules, the index can be defined as the date when a patient meets all of the cohort criteria, or only one specific group's criteria.

Module - A subsection of the TriNetX platform that performs a distinct functionality. Cohorts are created using the Query Builder module. Descriptive modules include Healthcare Organizations, Explore Cohorts, Rate of Arrival, Summary Statistics, and Analyze Criteria. Advanced analytic modules include Analyze Outcomes, Compare Outcomes, Compare Cohorts, Treatment Pathways, and Incidence and Prevalence.

Network - An aggregation of HCOs contributing data to the platform. Multiple networks are available for querying on the platform; the different networks represent subsets of HCOs organized by date-shifting practices or availability of downloadable datasets.

Outcome - A medical fact (e.g., diagnosis, procedure, lab result) that occurred on or after the cohort-defining index event.

Query - In the TriNetX platform, a query is a distinct cohort with a unique set of terms and logic. Query cohorts are created using the Query Builder platform module.

Risk - In Advanced Analytics modules, risk refers to the percentage of patients in each cohort with the specified outcome of interest.

Priority - An indication whether the code was the condition that the provider spent the most time evaluating or treating during a visit. Possible values include primary, secondary, or unknown.

Term - The codes used to specify patient cohort criteria in a query. Code options include diagnoses, procedures, medications, labs, demographics, genomics, and visits. Terms can be linked together using and/or Boolean logic. TriNetX also creates terms that group together multiple medical codes into single clinical concepts.

Cannot Have Term - A category of terms within a query group that patients must not have evidence of to be included in the cohort.

Must Have Term - A category of terms within a query group that patients must have evidence of to be included in the cohort.

Time Constraint - used to define time periods of interest for each group within a query. Time constraints can be defined relative to the date the query was run (e.g., any time before today), or defined based on specific dates (e.g., January 1, 2015 to September 30, 2020).

Treatment Pathway - In Advanced Analytics modules, the Treatment Pathways module returns the order in which patients received treatment and the prevalence of treatments, including combination of medications, following an index event.

TriNetX Codes - For certain laboratory terms, TriNetX aggregates Logical Observation Identifiers Names and Codes (LOINC) laboratory codes to new queryable TNX:LAB terms.

Visit - A type of term used to specify the type of medical encounter or facility where the encounter was recorded. Visit terms are derived by TriNetX from the source data. Visits are recorded separately from the codes or labs that occurred during the encounter; care settings are not attached to individual codes.

*all terms may not be used in this report

Table 1a. Characteristics of Incident Users of Selected Non-Insulin Antidiabetic Medications in the TriNetX Live™ USA Network[1] from October 1, 2017 to September 30, 2023

	GLP-1 RA[2] Incident Users[7]		SGLT-2 Inhibitor[4] Incident Users[7]		DPP-4 Inhibitor[5] Incident Users[7]		2nd Gen. Sulfonylurea[6] Incident Users[7]		Metformin Incident Users[7]	
	Number/ Mean	Percent/ Standard Deviation[3]	Number/ Mean	Percent/ Standard Deviation[3]	Number/ Mean	Percent/ Standard Deviation[3]	Number/ Mean	Percent/ Standard Deviation[3]	Number/ Mean	Percent/ Standard Deviation[3]
Total Patients	971,750	100.0%	793,840	100.0%	523,610	100.0%	845,310	100.0%	2,690,490	100.0%
Age at Index, Years	54.7	14.2	61.6	12.9	63.6	13.2	62.7	13.6	56.7	16.2
Sex										
Female	577,620	59.4%	332,350	41.9%	256,320	49.0%	384,230	45.5%	1,379,470	51.3%
Male	363,550	37.4%	438,610	55.3%	255,220	48.7%	442,440	52.3%	1,248,880	46.4%
Other	30,590	3.1%	22,900	2.9%	12,070	2.3%	18,650	2.2%	62,150	2.3%
Race										
Asian	25,800	2.7%	35,190	4.4%	29,310	5.6%	36,160	4.3%	121,460	4.5%
American Indian or Alaska Native	4,430	0.5%	3,630	0.5%	2,570	0.5%	3,970	0.5%	14,460	0.5%
Black or African American	170,380	17.5%	138,500	17.4%	98,770	18.9%	147,290	17.4%	465,060	17.3%
Native Hawaiian or Other Pacific Islander	3,530	0.4%	3,470	0.4%	2,540	0.5%	3,270	0.4%	10,070	0.4%
Other	45,360	4.7%	39,280	4.9%	31,150	5.9%	44,480	5.3%	161,370	6.0%
Unknown	115,540	11.9%	94,970	12.0%	65,190	12.5%	105,410	12.5%	360,910	13.4%
White	606,740	62.4%	478,830	60.3%	294,100	56.2%	504,780	59.7%	1,557,180	57.9%

NOTE: All counts provided through the TriNetX Live™ platform are rounded up to the nearest 10 to protect patient privacy. For this reason, number of incident users in each time period may not sum to the number in the overall query period. Percentages were calculated based on the rounded estimates, and are presented here rounded to the tenths position to avoid mischaracterizing the precision of the measurement. Due to rounding, all estimates should be interpreted as ranges, with the presented value equivalent to the high end of the range and the lower value of the range ≤ 0.05% less than the presented value (unless otherwise noted).

[1] A subset of HCOs that contribute to the TriNetX USA network may implement date shifting - between 0 and 365 days shifted in either direction - at the level of the patient record prior to data ingestion at TriNetX as a method to preserve patient privacy. When interpreting the results of an analysis, the impact of date shifting should be considered and readers should exercise caution when extrapolating information related to time.

[2] GLP-1 Receptor Agonists include medication products with the following ingredients: albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide, or tirzepatide.

[3] Percentages in this column are calculated using the count of total incident users of the drug class described in the column header as the denominator.

[4] SGLT-2 Inhibitors include medication products with the following ingredients: bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, or ertugliflozin.

[5] DPP-4 Inhibitors include medication products with the following ingredients: alogliptin, linagliptin, saxagliptin, or sitagliptin.

[6] 2nd Generation Sulfonylureas include medication products with the following ingredients: glimepiride, glipizide, or glyburide.

[7] Cohorts for this query had an inclusion criteria that looked for a visit term anytime in the window of interest. Because of this, there may be a small percentage of patients who indexed into a cohort with their visit term following their drug exposure.

Table 1b. Characteristics of Incident Glucagon-Like Peptide-1 Receptor Agonist (GLP-1 RA) Users, by Drug, in the TriNetX Live™ USA Network[1] from October 1, 2017 to September 30, 2023

	Albiglutide[3] Incident Users[5]		Dulaglutide Incident Users[5]		Exenatide Incident Users[5]		Liraglutide Incident Users[5]		Lixisenatide[4] Incident Users[5]		Semaglutide Incident Users[5]		Tirzepatide Incident Users[5]	
	Number/ Mean	Percent/ Standard Deviation[2]	Number/ Mean	Percent/ Standard Deviation[2]	Number/ Mean	Percent/ Standard Deviation[2]	Number/ Mean	Percent/ Standard Deviation[2]	Number/ Mean	Percent/ Standard Deviation[2]	Number/ Mean	Percent/ Standard Deviation[2]	Number/ Mean	Percent/ Standard Deviation[2]
Total Patients	1,190	100.0%	472,390	100.0%	48,380	100.0%	253,020	100.0%	12,970	100.0%	677,430	100.0%	95,930	100.0%
Age at Index, Years	58.7	11.8	57.3	13.2	56.4	13.3	51.3	14.9	60.5	12.4	53.3	13.9	51.8	12.7
Sex														
Female	620	52.1%	256,980	54.4%	27,390	56.6%	167,930	66.4%	6,520	50.3%	422,970	62.4%	62,360	65.0%
Male	560	47.1%	204,050	43.2%	20,540	42.5%	76,630	30.3%	6,230	48.0%	225,440	33.3%	28,950	30.2%
Other	20	1.7%	11,380	2.4%	460	1.0%	8,470	3.3%	230	1.8%	29,040	4.3%	4,620	4.8%
Race														
Asian	30	2.5%	13,030	2.8%	1,300	2.7%	4,610	1.8%	440	3.4%	18,400	2.7%	1,880	2.0%
American Indian or Alaska Native	10	0.8%	2,400	0.5%	230	0.5%	1,470	0.6%	50	0.4%	2,440	0.4%	340	0.4%
Black or African American	230	19.3%	94,110	19.9%	8,660	17.9%	45,320	17.9%	2,540	19.6%	109,400	16.1%	13,830	14.4%
Native Hawaiian or Other Pacific Islar	10	0.8%	1,730	0.4%	190	0.4%	680	0.3%	90	0.7%	2,850	0.4%	290	0.3%
Other	50	4.2%	23,490	5.0%	2,250	4.7%	10,420	4.1%	390	3.0%	30,160	4.5%	3,250	3.4%
Unknown	110	9.2%	58,210	12.3%	4,200	8.7%	31,640	12.5%	1,220	9.4%	73,400	10.8%	8,990	9.4%
White	770	64.7%	279,450	59.2%	31,570	65.3%	158,910	62.8%	8,280	63.8%	440,810	65.1%	67,370	70.2%

NOTE: All counts provided through the TriNetX Live™ platform are rounded up to the nearest 10 to protect patient privacy. For this reason, number of incident users in each time period may not sum to the number in the overall query period. Percentages were calculated based on the rounded estimates, and are presented here rounded to the tenths position to avoid mischaracterizing the precision of the measurement. Due to rounding, all estimates should be interpreted as ranges, with the presented value equivalent to the high end of the range and the lower value of the range ≤ 0.05% less than the presented value (unless otherwise noted).

[1] A subset of HCOs that contribute to the TriNetX USA network may implement date shifting - between 0 and 365 days shifted in either direction - at the level of the patient record prior to data ingestion at TriNetX as a method to preserve patient privacy. When interpreting the results of an analysis, the impact of date shifting should be considered and readers should exercise caution when extrapolating information related to time.

[2] Percentages in this column are calculated using the count of total incident users of the drug described in the column header as the denominator.

[3] Albiglutide: Due to rounding, all estimates should be interpreted as ranges, with the presented value equivalent to the high end of the range. Due to a small denominator in this row, and the lower value of the range is 0.76% less than the presented value.

[4] Lixisenatide: Due to rounding, all estimates should be interpreted as ranges, with the presented value equivalent to the high end of the range. Due to a small denominator in this row, and the lower value of the range is 0.07% less than the presented value.

[5]Cohorts for this query had an inclusion criteria that looked for a visit term anytime in the window of interest. Because of this, there may be a small percentage of patients who indexed into a cohort with their visit term following their drug exposure.

Appendix A. List of RxNorm Medication Terms Used to Define Exposures in this Request

Code	Description	Code Category	Code Type	Filter
Non-Insulin Antidiabetics of Interest				
1534763	albiglutide	Medication	RxNorm	Not applicable
1368001	alogliptin	Medication	RxNorm	Not applicable
2627044	bexagliflozin	Medication	RxNorm	Not applicable
OMOP5174738	BEXAGLIFLOZIN	Medication	RxNorm	Not applicable
1373458	canagliflozin	Medication	RxNorm	Not applicable
1488564	dapagliflozin	Medication	RxNorm	Not applicable
1551291	dulaglutide	Medication	RxNorm	Not applicable
1545653	empagliflozin	Medication	RxNorm	Not applicable
1992672	ertugliflozin	Medication	RxNorm	Not applicable
60548	exenatide	Medication	RxNorm	Not applicable
25789	glimepiride	Medication	RxNorm	Not applicable
4821	glipizide	Medication	RxNorm	Not applicable
4815	glyburide	Medication	RxNorm	Not applicable
1100699	linagliptin	Medication	RxNorm	Not applicable
475968	liraglutide	Medication	RxNorm	Not applicable
1440051	lixisenatide	Medication	RxNorm	Not applicable
6809	metformin	Medication	RxNorm	Not applicable
857974	saxagliptin	Medication	RxNorm	Not applicable
1991302	semaglutide	Medication	RxNorm	Not applicable
593411	sitagliptin	Medication	RxNorm	Not applicable
2601723	tirzepatide	Medication	RxNorm	Not applicable
2nd Generation Sulfonylurea				
25789	glimepiride	Medication	RxNorm	Not applicable
4821	glipizide	Medication	RxNorm	Not applicable
4815	glyburide	Medication	RxNorm	Not applicable
Dipeptidyl Peptidase-4 (DPP-4) Inhibitor				
1368001	alogliptin	Medication	RxNorm	Not applicable
1100699	linagliptin	Medication	RxNorm	Not applicable
857974	saxagliptin	Medication	RxNorm	Not applicable
593411	sitagliptin	Medication	RxNorm	Not applicable
Glucagon-Like Peptide-1 Receptor Agonist (GLP-1 RA)				
1534763	albiglutide	Medication	RxNorm	Not applicable
1551291	dulaglutide	Medication	RxNorm	Not applicable
60548	exenatide	Medication	RxNorm	Not applicable
475968	liraglutide	Medication	RxNorm	Not applicable
1440051	lixisenatide	Medication	RxNorm	Not applicable
1991302	semaglutide	Medication	RxNorm	Not applicable
2601723	tirzepatide	Medication	RxNorm	Not applicable
Metformin				
6809	metformin	Medication	RxNorm	Not applicable

Appendix A. List of RxNorm Medication Terms Used to Define Exposures in this Request

Code	Description	Code Category	Code Type	Filter
Sodium-Glucose Co-transporter 2 (SGLT2) Inhibitor				
2627044	bexagliflozin	Medication	RxNorm	Not applicable
OMOP5174738	BEXAGLIFLOZIN	Medication	RxNorm	Not applicable
1373458	canagliflozin	Medication	RxNorm	Not applicable
1488564	dapagliflozin	Medication	RxNorm	Not applicable
1545653	empagliflozin	Medication	RxNorm	Not applicable
1992672	ertugliflozin	Medication	RxNorm	Not applicable

Appendix B. List of Terms Used to Define Inclusion Criteria in this Request

Code	Code Type	Description	Filter
		Visit	
AMB	HL7 V3 VisiT Type	Visit: Ambulatory	Not Applicable
EMER	HL7 V3 VisiT Type	Visit: Emergency	Not Applicable
HH	HL7 V3 VisiT Type	Visit: Home Health	Not Applicable
IMP	HL7 V3 VisiT Type	Visit: Inpatient Encounter	Not Applicable
NONAC	HL7 V3 VisiT Type	Visit: Inpatient Non-acute	Not Applicable
LAB	HL7 V3 VisiT Type	Visit: Laboratory	Not Applicable
OBSENC	HL7 V3 VisiT Type	Visit: Observation Encounter	Not Applicable
PHARM	HL7 V3 VisiT Type	Visit: Pharmacy	Not Applicable
PRENC	HL7 V3 VisiT Type	Visit: Pre-admission	Not Applicable
SS	HL7 V3 VisiT Type	Visit: Short Stay	Not Applicable
UNKNOWN	HL7 V3 VisiT Type	Visit: Unknown	Not Applicable
VR	HL7 V3 VisiT Type	Visit: Virtual	Not Applicable

Appendix C. Specifications Defining Query Builder Modules in this Request

Network:
TriNetX Live™ USA Network

Cohort 1A (query name: Incident 2nd Generation Sulfonylurea 10/1/17 - 9/30/23)

This query was run on the USA network with 81 HCO(s) queried and 80 HCO(s) responded.

Group 1	*date constraint:*	*The terms in this group occurred between Oct 1, 2017 and Sep 30, 2023*	
Any Visit 10/1/17 - 9/30/23			
must have any of	visit	UMLS:HL7V3.0:VisitType:AMB	Visit: Ambulatory
	visit	UMLS:HL7V3.0:VisitType:EMER	Visit: Emergency
	visit	UMLS:HL7V3.0:VisitType:HH	Visit: Home Health
	visit	UMLS:HL7V3.0:VisitType:IMP	Visit: Inpatient Encounter
	visit	UMLS:HL7V3.0:VisitType:NONAC	Visit: Inpatient Non-acute
	visit	UMLS:HL7V3.0:VisitType:LAB	Visit: Laboratory
	visit	UMLS:HL7V3.0:VisitType:OBSENC	Visit: Observation Encounter
	visit	UMLS:HL7V3.0:VisitType:PHARM	Visit: Pharmacy
	visit	UMLS:HL7V3.0:VisitType:PRENC	Visit: Pre-admission
	visit	UMLS:HL7V3.0:VisitType:SS	Visit: Short Stay
	visit	UMLS:HL7V3.0:VisitType:UNKNOWN	Visit: Unknown
	visit	UMLS:HL7V3.0:VisitType:VR	Visit: Virtual
Group 2			
Group 2A First 2nd Generation Sulfonylurea			
must have any of	medication	…* SEE CODE LIST FOR ADDITIONAL MEDICATION CODES *…	
	medication	NLM:RXNORM:25789	glimepiride
	medication	NLM:RXNORM:4821	glipizide
	medication	NLM:RXNORM:4815	glyburide
event relationship	Any instance of Group 2B (No 2nd Generation Sulfonylurea) occurred at least 1 day before the first instance of Group 2A (First 2nd Generation Sulfonylurea)		
Group 2B No 2nd Generation Sulfonylurea			
cannot have any of	medication	…* SEE CODE LIST FOR ADDITIONAL MEDICATION CODES *…	
	medication	NLM:RXNORM:25789	glimepiride
	medication	NLM:RXNORM:4821	glipizide
	medication	NLM:RXNORM:4815	glyburide
Group 3	*date constraint:*	*The terms in this group occurred between Jan 1, 1900 and Sep 30, 2017*	
No 2nd Generation Sulfonylurea before 10/1/17			
cannot have any of	medication	…* SEE CODE LIST FOR ADDITIONAL MEDICATION CODES *…	
	medication	NLM:RXNORM:25789	glimepiride
	medication	NLM:RXNORM:4821	glipizide
	medication	NLM:RXNORM:4815	glyburide
Group 4	*date constraint:*	*The terms in this group occurred between Oct 1, 2017 and Sep 30, 2023*	
2nd Generation Sulfonylurea 10/1/17 - 9/30/23			
must have any of	medication	…* SEE CODE LIST FOR ADDITIONAL MEDICATION CODES *…	
	medication	NLM:RXNORM:25789	glimepiride, filter: no age restrictions[1]
	medication	NLM:RXNORM:4821	glipizide, filter: no age restrictions[1]
	medication	NLM:RXNORM:4815	glyburide, filter: no age restrictions[1]

Cohort 2A (query name: Incident Dipeptidyl Peptidase-4 [DPP-4] Inhibitors 10/1/17 - 9/30/23)

This query was run on the USA network with 81 HCO(s) queried and 80 HCO(s) responded.

Group 1	*date constraint:*	*The terms in this group occurred between Oct 1, 2017 and Sep 30, 2023*	
Any Visit 10/1/17 - 9/30/23			

Appendix C. Specifications Defining Query Builder Modules in this Request

must have any of	visit	UMLS:HL7V3.0:VisitType:AMB	Visit: Ambulatory
	visit	UMLS:HL7V3.0:VisitType:EMER	Visit: Emergency
	visit	UMLS:HL7V3.0:VisitType:HH	Visit: Home Health
	visit	UMLS:HL7V3.0:VisitType:IMP	Visit: Inpatient Encounter
	visit	UMLS:HL7V3.0:VisitType:NONAC	Visit: Inpatient Non-acute
	visit	UMLS:HL7V3.0:VisitType:LAB	Visit: Laboratory
	visit	UMLS:HL7V3.0:VisitType:OBSENC	Visit: Observation Encounter
	visit	UMLS:HL7V3.0:VisitType:PHARM	Visit: Pharmacy
	visit	UMLS:HL7V3.0:VisitType:PRENC	Visit: Pre-admission
	visit	UMLS:HL7V3.0:VisitType:SS	Visit: Short Stay
	visit	UMLS:HL7V3.0:VisitType:UNKNOWN	Visit: Unknown
	visit	UMLS:HL7V3.0:VisitType:VR	Visit: Virtual
Group 2			
Group 2A First DPP-4i			
must have any of	medication	…* SEE CODE LIST FOR ADDITIONAL MEDICATION CODES *…	
	medication	NLM:RXNORM:1368001	alogliptin
	medication	NLM:RXNORM:1100699	linagliptin
	medication	NLM:RXNORM:857974	saxagliptin
	medication	NLM:RXNORM:593411	sitagliptin
event relationship	Any instance of Group 2B (No DPP-4i) occurred at least 1 day before the first instance of Group 2A (First DPP-4i)		
Group 2B No DPP-4i			
cannot have any of	medication	…* SEE CODE LIST FOR ADDITIONAL MEDICATION CODES *…	
	medication	NLM:RXNORM:1368001	alogliptin
	medication	NLM:RXNORM:1100699	linagliptin
	medication	NLM:RXNORM:857974	saxagliptin
	medication	NLM:RXNORM:593411	sitagliptin
Group 3	*date constraint:*	*The terms in this group occurred between Jan 1, 1900 and Sep 30, 2017*	
No DPP-4i before 10/1/17			
cannot have any of	medication	…* SEE CODE LIST FOR ADDITIONAL MEDICATION CODES *…	
	medication	NLM:RXNORM:1368001	alogliptin
	medication	NLM:RXNORM:1100699	linagliptin
	medication	NLM:RXNORM:857974	saxagliptin
	medication	NLM:RXNORM:593411	sitagliptin
Group 4	*date constraint:*	*The terms in this group occurred between Oct 1, 2017 and Sep 30, 2023*	
DPP-4i 10/1/17 - 9/30/23			
must have any of	medication	…* SEE CODE LIST FOR ADDITIONAL MEDICATION CODES *…	
	medication	NLM:RXNORM:1368001	alogliptin, filter: no age restrictions[1]
	medication	NLM:RXNORM:1100699	linagliptin, filter: no age restrictions[1]
	medication	NLM:RXNORM:857974	saxagliptin, filter: no age restrictions[1]
	medication	NLM:RXNORM:593411	sitagliptin, filter: no age restrictions[1]

Cohort 3A (query name: Incident Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs) 10/1/17 - 9/30/23)

This query was run on the USA network with 81 HCO(s) queried and 80 HCO(s) responded.

Group 1	*date constraint:*	*The terms in this group occurred between Oct 1, 2017 and Sep 30, 2023*	
Any Visit 10/1/17 - 9/30/23			
must have any of	visit	UMLS:HL7V3.0:VisitType:AMB	Visit: Ambulatory

Appendix C. Specifications Defining Query Builder Modules in this Request

		visit	UMLS:HL7V3.0:VisitType:EMER	Visit: Emergency
		visit	UMLS:HL7V3.0:VisitType:HH	Visit: Home Health
		visit	UMLS:HL7V3.0:VisitType:IMP	Visit: Inpatient Encounter
		visit	UMLS:HL7V3.0:VisitType:NONAC	Visit: Inpatient Non-acute
		visit	UMLS:HL7V3.0:VisitType:LAB	Visit: Laboratory
		visit	UMLS:HL7V3.0:VisitType:OBSENC	Visit: Observation Encounter
		visit	UMLS:HL7V3.0:VisitType:PHARM	Visit: Pharmacy
		visit	UMLS:HL7V3.0:VisitType:PRENC	Visit: Pre-admission
		visit	UMLS:HL7V3.0:VisitType:SS	Visit: Short Stay
		visit	UMLS:HL7V3.0:VisitType:UNKNOWN	Visit: Unknown
		visit	UMLS:HL7V3.0:VisitType:VR	Visit: Virtual
Group 2				
	Group 2A First GLP-1 RA			
	must have any of	medication	…* SEE CODE LIST FOR ADDITIONAL MEDICATION CODES *…	
		medication	NLM:RXNORM:1534763	albiglutide
		medication	NLM:RXNORM:1551291	dulaglutide
		medication	NLM:RXNORM:60548	exenatide
		medication	NLM:RXNORM:475968	liraglutide
		medication	NLM:RXNORM:1440051	lixisenatide
		medication	NLM:RXNORM:1991302	semaglutide
		medication	NLM:RXNORM:2601723	tirzepatide
	event relationship	Any instance of Group 2B (No GLP-1 RA) occurred at least 1 day before the first instance of Group 2A (First GLP-1 RA)		
	Group 2B No GLP-1 RA			
	cannot have any of	medication	…* SEE CODE LIST FOR ADDITIONAL MEDICATION CODES *…	
		medication	NLM:RXNORM:1534763	albiglutide
		medication	NLM:RXNORM:1551291	dulaglutide
		medication	NLM:RXNORM:60548	exenatide
		medication	NLM:RXNORM:475968	liraglutide
		medication	NLM:RXNORM:1440051	lixisenatide
		medication	NLM:RXNORM:1991302	semaglutide
		medication	NLM:RXNORM:2601723	tirzepatide
Group 3	*date constraint:*	*The terms in this group occurred between Jan 1, 1900 and Sep 30, 2017*		
	No GLP-1 RA before 10/1/17			
	cannot have any of	medication	…* SEE CODE LIST FOR ADDITIONAL MEDICATION CODES *…	
		medication	NLM:RXNORM:1534763	albiglutide
		medication	NLM:RXNORM:1551291	dulaglutide
		medication	NLM:RXNORM:60548	exenatide
		medication	NLM:RXNORM:475968	liraglutide
		medication	NLM:RXNORM:1440051	lixisenatide
		medication	NLM:RXNORM:1991302	semaglutide
		medication	NLM:RXNORM:2601723	tirzepatide
Group 4	*date constraint:*	*The terms in this group occurred between Oct 1, 2017 and Sep 30, 2023*		
	GLP-1 RA 10/1/17 - 9/30/23			
	must have any of	medication	…* SEE CODE LIST FOR ADDITIONAL MEDICATION CODES *…	
		medication	NLM:RXNORM:1534763	albiglutide, filter: no age restrictions[1]
		medication	NLM:RXNORM:1551291	dulaglutide, filter: no age restrictions[1]
		medication	NLM:RXNORM:60548	exenatide, filter: no age restrictions[1]
		medication	NLM:RXNORM:475968	liraglutide, filter: no age restrictions[1]
		medication	NLM:RXNORM:1440051	lixisenatide, filter: no age restrictions[1]

Appendix C. Specifications Defining Query Builder Modules in this Request

	medication	NLM:RXNORM:1991302	semaglutide, filter: no age restrictions[1]
	medication	NLM:RXNORM:2601723	tirzepatide, filter: no age restrictions[1]

Replicate Cohort A for each drug name in this drug class

albiglutide
dulaglutide
exenatide
liraglutide
lixisenatide
semaglutide
tirzepatide

Cohort 4A (query name: Incident Metformin 10/1/17 - 9/30/23)

This query was run on the USA network with 81 HCO(s) queried and 80 HCO(s) responded.

Group 1	*date constraint:*		*The terms in this group occurred between Oct 1, 2017 and Sep 30, 2023*	
Any Visit 10/1/17 - 9/30/23				
must have any of	visit	UMLS:HL7V3.0:VisitType:AMB	Visit: Ambulatory	
	visit	UMLS:HL7V3.0:VisitType:EMER	Visit: Emergency	
	visit	UMLS:HL7V3.0:VisitType:HH	Visit: Home Health	
	visit	UMLS:HL7V3.0:VisitType:IMP	Visit: Inpatient Encounter	
	visit	UMLS:HL7V3.0:VisitType:NONAC	Visit: Inpatient Non-acute	
	visit	UMLS:HL7V3.0:VisitType:LAB	Visit: Laboratory	
	visit	UMLS:HL7V3.0:VisitType:OBSENC	Visit: Observation Encounter	
	visit	UMLS:HL7V3.0:VisitType:PHARM	Visit: Pharmacy	
	visit	UMLS:HL7V3.0:VisitType:PRENC	Visit: Pre-admission	
	visit	UMLS:HL7V3.0:VisitType:SS	Visit: Short Stay	
	visit	UMLS:HL7V3.0:VisitType:UNKNOWN	Visit: Unknown	
	visit	UMLS:HL7V3.0:VisitType:VR	Visit: Virtual	
Group 2				
Group 2A First Metformin				
must have any of	medication	…* SEE CODE LIST FOR ADDITIONAL MEDICATION CODES *…		
	medication	NLM:RXNORM:6809	metformin	
event relationship	Any instance of Group 2B (No Metformin) occurred at least 1 day before the first instance of Group 2A (First Metformin)			
Group 2B No Metformin				
cannot have any of	medication	…* SEE CODE LIST FOR ADDITIONAL MEDICATION CODES *…		
	medication	NLM:RXNORM:6809	metformin	
Group 3	*date constraint:*		*The terms in this group occurred between Jan 1, 1900 and Sep 30, 2017*	
No Metformin before 10/1/17				
cannot have any of	medication	…* SEE CODE LIST FOR ADDITIONAL MEDICATION CODES *…		
	medication	NLM:RXNORM:6809	metformin	
Group 4	*date constraint:*		*The terms in this group occurred between Oct 1, 2017 and Sep 30, 2023* [1]	
Metformin 10/1/17 - 9/30/23				
must have any of	medication	…* SEE CODE LIST FOR ADDITIONAL MEDICATION CODES *…		
	medication	NLM:RXNORM:6809	metformin, filter: no age restrictions[1]	

Cohort 5A (query name: Incident Sodium-Glucose Co-transporter 2 (SGLT2) Inhibitors 10/1/17 - 9/30/23)

This query was run on the USA network with 81 HCO(s) queried and 79 HCO(s) responded.

Appendix C. Specifications Defining Query Builder Modules in this Request

Group 1	*date constraint:*	*The terms in this group occurred between Oct 1, 2017 and Sep 30, 2023*	
Any Visit 10/1/17 - 9/30/23			
must have any of	visit	UMLS:HL7V3.0:VisitType:AMB	Visit: Ambulatory
	visit	UMLS:HL7V3.0:VisitType:EMER	Visit: Emergency
	visit	UMLS:HL7V3.0:VisitType:HH	Visit: Home Health
	visit	UMLS:HL7V3.0:VisitType:IMP	Visit: Inpatient Encounter
	visit	UMLS:HL7V3.0:VisitType:NONAC	Visit: Inpatient Non-acute
	visit	UMLS:HL7V3.0:VisitType:LAB	Visit: Laboratory
	visit	UMLS:HL7V3.0:VisitType:OBSENC	Visit: Observation Encounter
	visit	UMLS:HL7V3.0:VisitType:PHARM	Visit: Pharmacy
	visit	UMLS:HL7V3.0:VisitType:PRENC	Visit: Pre-admission
	visit	UMLS:HL7V3.0:VisitType:SS	Visit: Short Stay
	visit	UMLS:HL7V3.0:VisitType:UNKNOWN	Visit: Unknown
	visit	UMLS:HL7V3.0:VisitType:VR	Visit: Virtual
Group 2			
Group 2A First SGLT2 inhibitor			
must have any of	medication	…* SEE CODE LIST FOR ADDITIONAL MEDICATION CODES *…	
	medication	NLM:RXNORM:2627044	bexagliflozin
	medication	NLM:RXNORM:OMOP5174738	BEXAGLIFLOZIN
	medication	NLM:RXNORM:1373458	canagliflozin
	medication	NLM:RXNORM:1488564	dapagliflozin
	medication	NLM:RXNORM:1545653	empagliflozin
	medication	NLM:RXNORM:1992672	ertugliflozin
event relationship	Any instance of Group 2B (No SGLT2 inhibitor) occurred at least 1 day before the first instance of Group 2A (First SGLT2 inhibitor)		
Group 2B No SGLT2 inhibitor			
cannot have any of	medication	…* SEE CODE LIST FOR ADDITIONAL MEDICATION CODES *…	
	medication	NLM:RXNORM:2627044	bexagliflozin
	medication	NLM:RXNORM:OMOP5174738	BEXAGLIFLOZIN
	medication	NLM:RXNORM:1373458	canagliflozin
	medication	NLM:RXNORM:1488564	dapagliflozin
	medication	NLM:RXNORM:1545653	empagliflozin
	medication	NLM:RXNORM:1992672	ertugliflozin
Group 3	*date constraint:*	*The terms in this group occurred between Jan 1, 1900 and Sep 30, 2017*	
No SGLT2 inhibitor before 2017			
cannot have any of	medication	…* SEE CODE LIST FOR ADDITIONAL MEDICATION CODES *…	
	medication	NLM:RXNORM:2627044	bexagliflozin
	medication	NLM:RXNORM:OMOP5174738	BEXAGLIFLOZIN
	medication	NLM:RXNORM:1373458	canagliflozin
	medication	NLM:RXNORM:1488564	dapagliflozin
	medication	NLM:RXNORM:1545653	empagliflozin
	medication	NLM:RXNORM:1992672	ertugliflozin
Group 4	*date constraint:*	*The terms in this group occurred between Oct 1, 2017 and Sep 30, 2023* [1]	
SGLT2 inhibitor 10/1/17 - 9/30/23			
must have any of	medication	…* SEE CODE LIST FOR ADDITIONAL MEDICATION CODES *…	
	medication	NLM:RXNORM:2627044	bexagliflozin, filter: no age restrictions[1]
	medication	NLM:RXNORM:OMOP5174738	BEXAGLIFLOZIN, filter: no age restriction

Appendix C. Specifications Defining Query Builder Modules in this Request

medication	NLM:RXNORM:1373458	canagliflozin, filter: no age restrictions[1]
medication	NLM:RXNORM:1488564	dapagliflozin, filter: no age restrictions[1]
medication	NLM:RXNORM:1545653	empagliflozin, filter: no age restrictions[1]
medication	NLM:RXNORM:1992672	ertugliflozin, filter: no age restrictions[1]