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_wp029

Request ID: cder_iqp_wp029

Request Description: In this report we aimed to characterize patients with evidence of cannabis-derived product use.

Data Source: We ran this query on October 14, 2022. This query contains data from 76 health care organizations (HCOs), provided through the TriNetX Live™ platform in their USA Network from July 1, 2018 to June 30, 2022.
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: We identified counts of individuals with evidence of cannabis-derived product use or a positive lab test for tetrahydrocannabinol (THC) among a cohort of patients with a history of healthcare utilization. This was done using the Query Builder module in the TriNetX Live™ platform. We additionally summarized the length of individuals' patient record using the Summary Statistics module and each cohort's demographic distribution using the Explore Cohort module. We finally utilized the Analyze Outcomes analytics module to determine the number of patients in the cohort with our baseline characteristics of interest, pregnancy, co-exposures, and subsequent cannabis-derived product exposures.

Exposures of Interest: Our exposures of interest in this request were any cannabis-derived products, excluding Epidiolex, or a positive lab result for THC. We identified Epidiolex for exclusion based on evidence of the brand name or a cannabidiol product with a strength of 100 mg/ml. Please see Appendix A for the list of codes used to define the exposures of interest in this request.

Cohort Eligibility Criteria: We required every patient to have a history of a healthcare visit in order to be included in each cohort. We defined a history of healthcare visits as evidence of any type of visit term in the two years prior to any cannabis-derived product or positive THC lab exposure that occurred during the query period. Patients of all ages were included in the cohorts.

Characteristics: We utilized the Characteristics section of the Analyze Outcomes analytic module to evaluate the following baseline characteristics in the 365 days prior to and including the date of the first qualifying cannabis-derived product or THC lab test exposure (index exposure): alcohol-related disorders, attention-deficit hyperactivity disorders (ADHD), anxiety disorders, autism, cancer, cannabis-related disorders, cerebrovascular diseases, chronic kidney disease, dorsalgia (back and spine pain), fibromyalgia, pain (including chronic pain syndrome and chronic pain not elsewhere classified), pain (unspecified), chronic respiratory conditions, dementia (unspecified), dementia (vascular), diabetes, Dravet syndrome, dystonia, eating disorders, glaucoma, human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), Huntington's disease, hypertension, intracranial injury, irritable bowel syndrome, ischemic heart diseases, Lennox-Gastaut syndrome, liver disease, mood disorders, multiple sclerosis, nicotine dependence, nicotine use, obesity, opioid-related disorders, other epilepsies, Parkinson's disease, personality disorders, post-traumatic stress disorder, psychologic developmental conditions, psychotic disorders, rheumatologic and inflammatory conditions, sleep disorders, spinal cord injury, Tourette syndrome, tuberous sclerosis complex, and vaping-related disorders. We additionally looked for evidence of a diagnosis code for a positive pregnancy test in the 270 days prior to and including the index date. We further assessed co-exposures in the 30 days prior to and including the index date. These co-exposures included: anticonvulsants (overall and specifically: cannabidiol, clobazam, fenfluramine, stiripentol, valproate), antidepressants, antidiabetic agents, antiemetic agents, antihistamines, antipsychotics, anxiolytic and hypnotic drugs, cardiovascular medications, chemotherapeutics, central nervous system (CNS) stimulants, corticosteroids, dronabinol, nabilone, opioids, and other immunosuppressants. In the TriNetX platform, all pre-index characteristics must be defined by a single branch within the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) hierarchy or by a single Veterans Affairs (VA) formulary classification. Please see Appendix B for a list of the codes used to approximate these baseline characteristics.

Overview for Request: cder_iqp_wp029

Characteristics, continued: We utilized the Outcomes section of the Analyze Outcomes analytics module to assess additional post-index characteristics for each cohort. We looked for evidence of the co-exposures and a positive pregnancy test or diagnosis code for a positive test in the 30 days after the index exposure. For the co-exposures we assessed the same medication classes as the pre-index period, with the exception of anticonvulsants. In the post-index period we did not report individual anticonvulsant medications of interest; we reported the overall anticonvulsant category excluding cannabidiol. We finally summarized subsequent cannabis-derived product exposure in the 365 days following the initial index exposure. We evaluated all cannabis-derived products, and then separately assessed cannabidiol and THC labs. For the subsequent cannabis-derived product exposures we report both the number of patients in each cohort with a subsequent exposure, and the mean number of exposures per patient. Please see Appendix C for a list of the codes used to define the post-index characteristics in this request.

Please see Appendices D and E for the specifications of parameters used in this request.

Limitations: Algorithms used to define exposures and characteristics, and mapping of source data to the data model are imperfect and susceptible to misclassification. Additionally, EHR data in the United States (US) lacks longitudinality. The information before or after patients' healthcare encounters could be missing, especially if patient care was administered across different HCOs that 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 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%.

Notes: We ran this query on October 14, 2022. 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).

Sentinel

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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 commonly used laboratory terms, TriNetX aggregates Logical Observation Identifiers Names and Codes (LOINC) laboratory codes at a clinically significant level 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. Values for visit terms include: ambulatory, emergency, field, home health, inpatient encounter, inpatient acute, inpatient non-acute, laboratory, observation, pharmacy, pre-admission, short stay, virtual, and unknown.

*all terms may not be used in this report

Table 1. Baseline Characteristics Among Patients with Cannabis-Derived Product Exposures or a Positive Tetrahydrocannabinol (THC) Lab Test from July 1, 2018 through June 30, 2022

	Cannabis-Derived Product, Excluding Known Epidiolex		Positive THC Lab Test	
	Number	Percent	Number	Percent
Total Number of Patients	**34,130**		**45,490**	
Baseline Clinical Characteristics [-365, 0 days][1]	32,070		45,280	
Alcohol-related disorders	1,690	5%	6,290	14%
Anxiety disorders	8,560	27%	13,250	29%
Attention-deficit hyperactivity disorders (ADHD)	1,370	4%	3,560	8%
Autism	1,060	3%	130	<1%
Cancer[2]	10,680	33%	4,160	9%
Cannabis-related disorders	1,450	5%	10,570	23%
Cerebrovascular diseases	3,540	11%	1,950	4%
Chronic kidney disease (CKD)	2,840	9%	1,410	3%
Chronic liver disease	4,090	13%	2,920	6%
Chronic Pain				
Back and spine pain (dorsalgia)	9,830	31%	9,300	21%
Fibromyalgia	1,600	5%	1,110	2%
Pain, not elsewhere classified (includes Chronic Pain Syndrome and Chronic Pain not elsewhere classified)	6,880	21%	8,620	19%
Pain, unspecified	11,770	37%	2,910	6%
Chronic respiratory conditions	5,600	17%	7,260	16%
Dementia (unspecified)	460	1%	160	<1%
Dementia (vascular)	80	<1%	70	<1%
Diabetes	5,560	17%	3,920	9%
Dravet syndrome	110	<1%	10	<1%
Dystonia	560	2%	160	<1%
Eating disorders	550	2%	450	1%
Glaucoma	890	3%	370	1%
HIV/AIDS	690	2%	1,230	3%
Huntington's disease	80	<1%	30	<1%
Hypertension	9,950	31%	9,240	20%
Irritable bowel syndrome	1,070	3%	590	1%
Ischemic heart diseases	3,680	11%	2,860	6%
Lennox-Gastaut syndrome	1,370	4%	10	<1%
Mood disorders	9,370	29%	16,640	37%
Multiple sclerosis	570	2%	250	1%
Nicotine use	4,370	14%	14,550	32%
Obesity	4,870	15%	4,190	9%
Opioid-related disorders	650	2%	6,680	15%
Other epilepsies	3,660	11%	1,530	3%
Other neurological or developmental conditions	3,210	10%	430	1%
Parkinson's disease	550	2%	70	<1%
Personality disorders	390	1%	890	2%
Post-traumatic stress disorder (PTSD)	1,060	3%	3,250	7%
Psychotic disorders	1,300	4%	4,010	9%
Rheumatologic and inflammatory conditions	3,090	10%	1,320	3%
Sleep disorders	7,640	24%	5,840	13%
Spinal cord injury	10	<1%	40	<1%
Tourette syndrome	70	<1%	40	<1%

Table 1. Baseline Characteristics Among Patients with Cannabis-Derived Product Exposures or a Positive Tetrahydrocannabinol (THC) Lab Test from July 1, 2018 through June 30, 2022

	Cannabis-Derived Product, Excluding Known Epidiolex		Positive THC Lab Test	
	Number	Percent	Number	Percent
Traumatic brain injury or intracranial hemorrhage	1,100	3%	1,150	3%
Tuberous sclerosis complex	160	<1%	10	<1%
Vaping-related disorder	20	<1%	40	<1%
Baseline Clinical Characteristics [-270, 0 days]	32,750		44,580	
Encounter for pregnancy test, result positive	80	<1%	960	2%
Pre-Index Co-Exposures [-30, 0 days]	33,160		44,880	
Anticonvulsants	31,060	94%	6,630	15%
Cannabidiol	30,570	92%	100	<1%
Clobazam	1,650	5%	30	<1%
Fenfluramine	30	<1%	0	<1%
Stiripentol	20	<1%	0	<1%
Valproate	1,800	5%	550	1%
Antidepressants	12,150	37%	8,160	18%
Antidiabetic agents	6,250	19%	5,050	11%
Antiemetics	9,770	29%	13,800	31%
Antihistamines	9,420	28%	9,710	22%
Antipsychotics	3,310	10%	7,240	16%
Anxiolytic and hypnotic drugs	11,950	36%	12,060	27%
Cardiovascular medications	17,660	53%	13,780	31%
Chemotherapeutics	4,710	14%	740	2%
CNS stimulants	4,400	13%	2,170	5%
Corticosteroids	9,730	29%	5,130	11%
Dronabinol[3]	2,010	6%	380	1%
Nabilone	10	<1%	0	<1%
Opioids	13,250	40%	15,290	34%
Other immunosuppressants	1,430	4%	240	1%
Post-Index Co-Exposures [1, 30 days]	34,130		45,490	
Anticonvulsants (excluding Cannabidiol)	6,450	19%	5,310	12%
Antidepressants	6,520	19%	7,250	16%
Antidiabetic agents	4,520	13%	3,390	7%
Antiemetics	7,240	21%	6,720	15%
Antihistamines	5,830	17%	6,790	15%
Antipsychotics	2,330	7%	5,290	12%
Anxiolytic and hypnotic drugs	7,670	22%	7,340	16%
Cardiovascular medications	10,870	32%	10,150	22%
Chemotherapeutics	3,330	10%	690	2%
CNS stimulants	2,550	7%	1,890	4%
Corticosteroids	6,830	20%	3,980	9%
Dronabinol[3]	610	2%	370	1%
Nabilone	10	<1%	0	<1%
Opioids	9,300	27%	11,000	24%
Other immunosuppressants	780	2%	220	<1%
Post-index Clinical Characteristics [1, 30 days]	34,130		45,490	
Pregnancy (positive test or diagnosis)	20	<1%	140	<1%
Post-index Subsequent Cannabis-Derived Product Exposures [1, 365 days]	34,130		45,490	
Any cannabis-derived product	14,710	43%	260	1%

Table 1. Baseline Characteristics Among Patients with Cannabis-Derived Product Exposures or a Positive Tetrahydrocannabinol (THC) Lab Test from July 1, 2018 through June 30, 2022

	Cannabis-Derived Product, Excluding Known Epidiolex		Positive THC Lab Test	
	Number	Percent	Number	Percent
Cannabidiol	13,640	40%	260	1%
Positive THC lab test	160	<1%	8,590	19%
Post-index Subsequent Cannabis-Derived Product Exposures [1, 365 days]	**Mean**	**Standard Deviation**	**Mean**	**Standard Deviation**
Mean number of cannabis-derived product exposures	4	5.82	3	5.44
Mean number of cannabidiol exposures	4	5.81	3	5.48
Mean number of positive THC lab tests	1	0.73	2	2.84

[1]Characteristics assessed in the pre-index period are taken from a convenience sample of the full cohort. Values in header rows represent the sample size for each look back period. Percentages for each section are calculated using these values as the denominator.

[2]Cancer baseline characteristic definition includes malignant, benign, and in situ neoplasms.

[3]Dronabinol is a subset of the overall antiemetics category. Counts for dronabinol will be counted in both co-exposures.

NOTE: All counts provided through the TriNetX Live™ platform are rounded up to the nearest 10 to protect patient privacy. Thus, all estimates should be interpreted as ranges, with the lower value of the range ≤ 0.09% less than the presented value unless otherwise noted.

Figure 1. Distribution of Length of Patient Record for Patients with Cannabis-Derived Product Exposures from July 1, 2018 through June 30, 2022

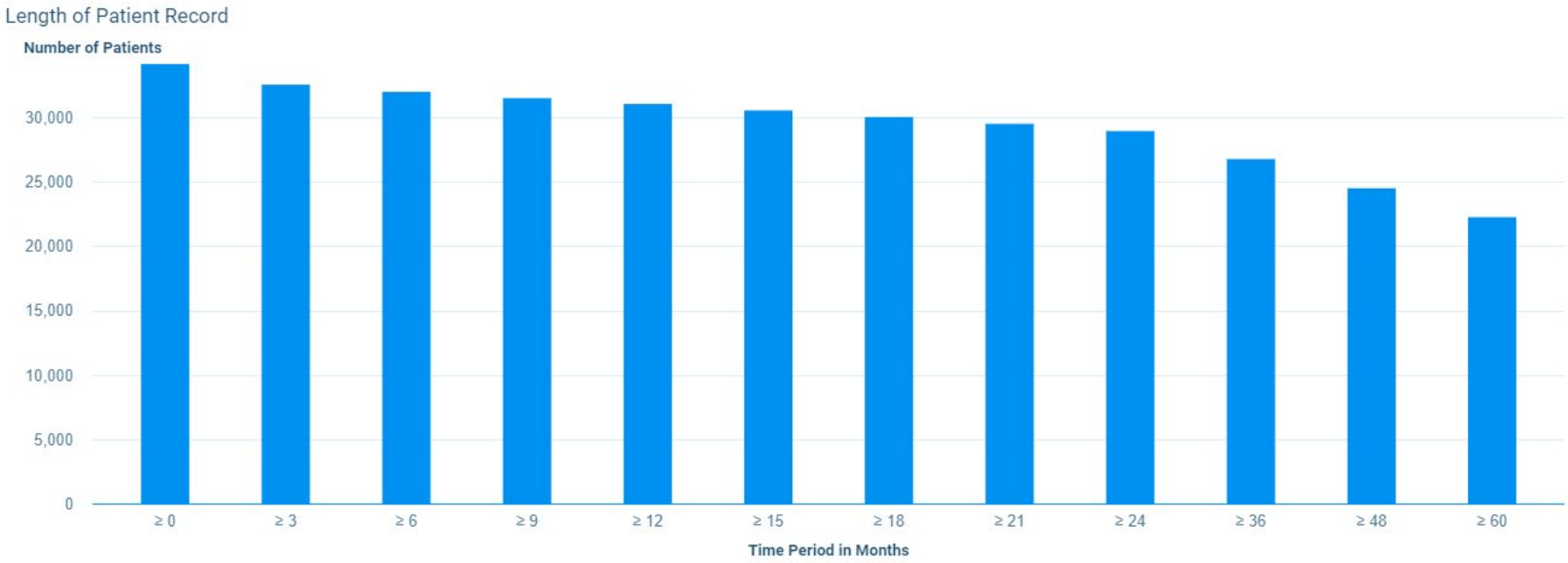


Figure 2. Distribution of Length of Patient Record for Patients with a Positive Lab Test for Tetrayhydrocannabinol (THC) from July 1, 2018 through June 30, 2022

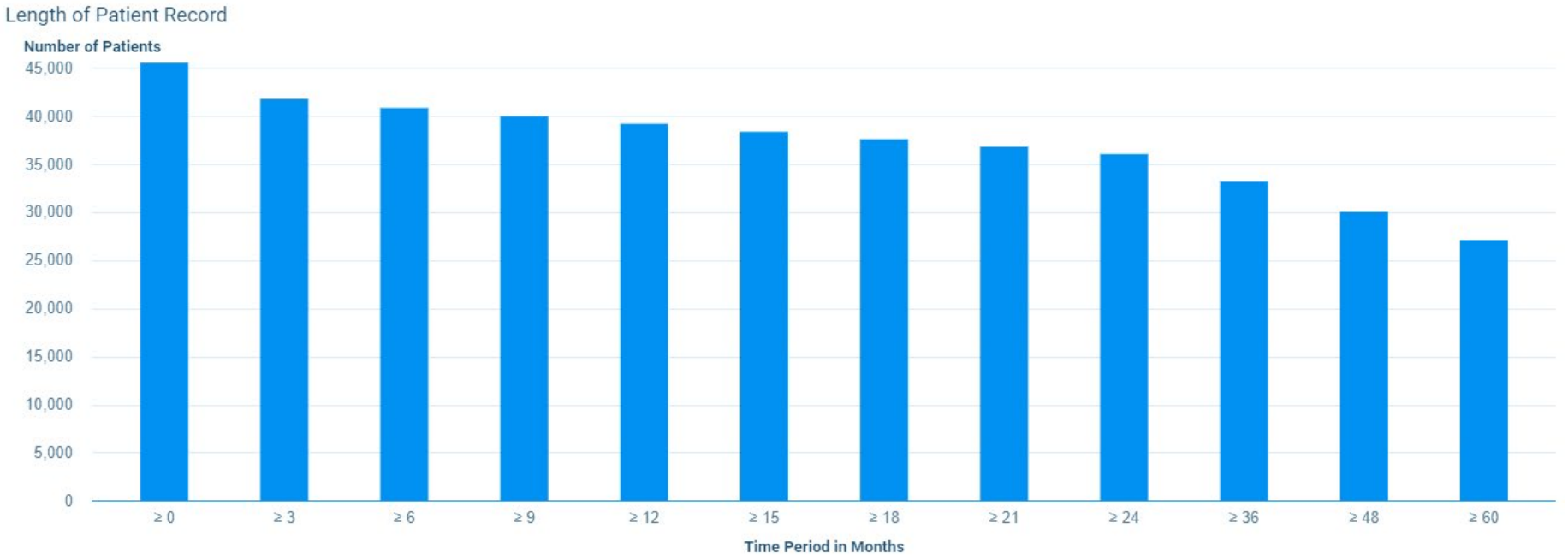
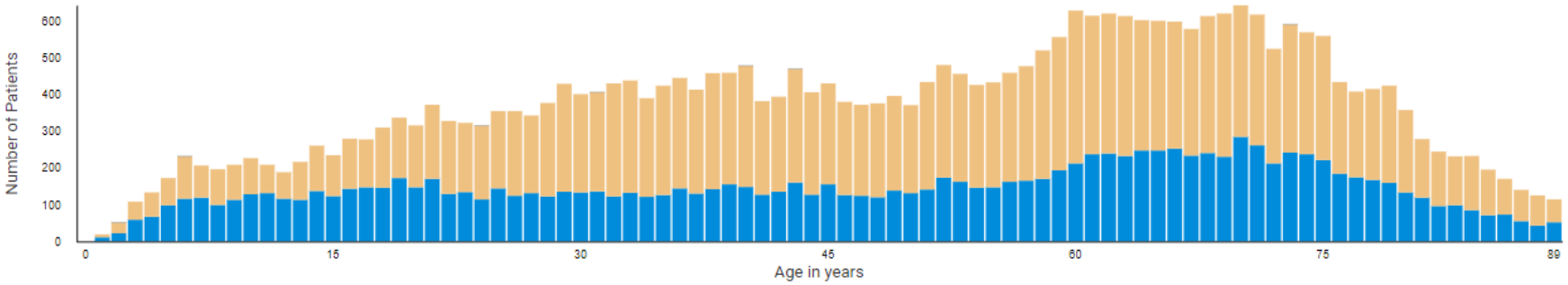


Figure 3. Demographic Characteristics for Patients with Cannabis-Derived Product Exposures from July 1, 2018 through June 30, 2022



Patients 90 and Older: 500

Total Patients	Minimum Age	Maximum Age	Mean Age	Standard Deviation
34,130	1	90	50	22

Sex

Female	61%
Male	39%
Unknown	0%

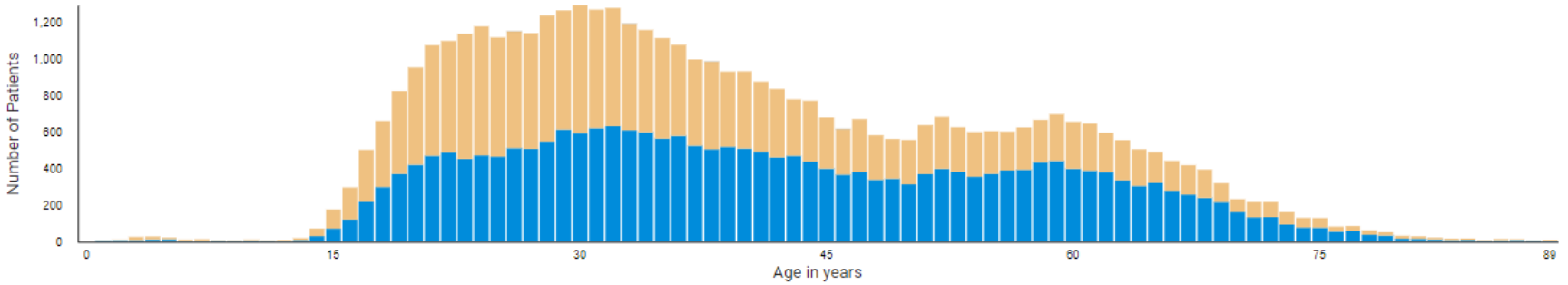
Ethnicity

Not Hispanic or Latino	84%
Unknown Ethnicity	10%
Hispanic or Latino	6%

Race

White	83%
Unknown Race	10%
Black or African American	5%
American Indian or Alaska N...	1%
Asian	1%
Native Hawaiian or Other Pa...	0%

Figure 4. Demographic Characteristics for Patients with a Positive Lab Test for Tetrahydrocannabinol (THC) from July 1, 2018 through June 30, 2022



Patients 90 and Older: 28

Total Patients	Minimum Age	Maximum Age	Mean Age	Standard Deviation
45,490	1	90	40	16

Sex

Male	53%
Female	47%
Unknown	0%

Ethnicity

Not Hispanic or Latino	69%
Unknown Ethnicity	24%
Hispanic or Latino	7%

Race

White	64%
Black or African American	22%
Unknown Race	13%
Asian	1%
American Indian or Alaska N...	0%
Native Hawaiian or Other Pa...	0%

Appendix A. List of RxNorm Medication Terms and Logical Observation Identifiers, Names and Codes (LOINC) Laboratory Codes Used to Define Exposures in this Request

Code	Description	Code Category	Code Type	Filter
Cannabis and Cannabis-Derived Products				
2045371	Cannabidiol	Medication	RxNorm	n/a
1976	Cannabinol	Medication	RxNorm	n/a
1788846	Hemp	Medication	RxNorm	n/a
1305550	Cannabis sativa seed oil	Medication	RxNorm	n/a
2177094	Cannabis Sativa subsp. Sativa whole extract	Medication	RxNorm	n/a
2464938	Cannabigerol	Medication	RxNorm	n/a
2279519	Cannabigerolate (*note: this term has 0 patients)	Medication	RxNorm	n/a
2585216	Cannabichromene (*note: this term has 0 patients)	Medication	RxNorm	n/a
2168435	Cannabis sativa susp. indica top extract (*note: this term has 0 patients)	Medication	RxNorm	n/a
1484855	Cannabis Sativa subsp. Flowering top extract (*note: this term has 0 patients)	Medication	RxNorm	n/a
2002575	Cannabis sativa pollen extract (*note: this term has 0 patients)	Medication	RxNorm	n/a
2048033	Cannabis sativa whole extract (*note: this term has 0 patients)	Medication	RxNorm	n/a
1429926	Cannabis sativa seed extract (*note: this term has 0 patients)	Medication	RxNorm	n/a
Epidiolex				
2045371	Cannabidiol	Medication	RxNorm	Brand Name, or 100 mg/ml strength
Tetrahydrocannabinol (THC) Lab Tests				
19415-9	Tetrahydrocannabinol [presence] in urine by screen method	Laboratory Test	LOINC	Positive result
14312-3	Tetrahydrocannabinol [presence] in urine by screen method >50 ng/ml	Laboratory Test	LOINC	Positive result
3426-4	Tetrahydrocannabinol [presence] in urine	Laboratory Test	LOINC	Positive result
21556-6	Tetrahydrocannabinol [presence] in urine by screen method >20 ng/ml	Laboratory Test	LOINC	Positive result
19416-7	Tetrahydrocannabinol [presence] in urine by confirmatory method	Laboratory Test	LOINC	Positive result
8175-2	Tetrahydrocannabinol [presence] in urine by samhsa screen method	Laboratory Test	LOINC	Positive result
21557-4	Tetrahydrocannabinol [presence] in urine by screen method >100 ng/ml	Laboratory Test	LOINC	Positive result
43834-1	Tetrahydrocannabinol [presence] in specimen	Laboratory Test	LOINC	Positive result
58047-2	Tetrahydrocannabinol [presence] in blood by confirmatory method (*note: 0 positive patients)	Laboratory Test	LOINC	Positive result
3435-5	Carboxy tetrahydrocannabinol [presence] in urine	Laboratory Test	LOINC	Positive result
19381-3	Carboxy tetrahydrocannabinol [presence] in urine by screen method	Laboratory Test	LOINC	Positive result
19382-1	Carboxy tetrahydrocannabinol [presence] in urine by confirmatory method	Laboratory Test	LOINC	Positive result
42492-9	Carboxy tetrahydrocannabinol [presence] in blood	Laboratory Test	LOINC	Positive result

Appendix A. List of RxNorm Medication Terms and Logical Observation Identifiers, Names and Codes (LOINC) Laboratory Codes Used to Define Exposures in this Request

Code	Description	Code Category	Code Type	Filter
26743-5	Carboxy tetrahydrocannabinol [presence] in serum or plasma	Laboratory Test	LOINC	Positive result
61063-4	Carboxy tetrahydrocannabinol [presence] in specimen	Laboratory Test	LOINC	Positive result
74678-4	Carboxy tetrahydrocannabinol [presence] in saliva (oral fluid) by confirmatory method	Laboratory Test	LOINC	Positive result
78754-9	11-hydroxy delta-9 tetrahydrocannabinol [presence] in urine by screen method (*note: 0 positive patients)	Laboratory Test	LOINC	Positive result
14313-1	Tetrahydrocannabinol [Mass/volume] in Urine by Confirmatory method	Laboratory Test	LOINC	15 ng/ml - 800 ng/ml
3530-3	Tetrahydrocannabinol [Mass/volume] in Urine	Laboratory Test	LOINC	50 ng/ml - 800 ng/ml
3528-7	Tetrahydrocannabinol [Mass/volume] in Serum or Plasma	Laboratory Test	LOINC	2 ng/ml - 125 ng/ml
44049-5	Tetrahydrocannabinol [Mass/volume] in Serum or Plasma by Confirmatory method	Laboratory Test	LOINC	2 ng/ml - 125 ng/ml
73935-9	Tetrahydrocannabinol [Mass/volume] in Serum, Plasma, or Blood by Confirmatory method	Laboratory Test	LOINC	2 ng/ml - 125 ng/ml

Appendix B. List of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Hierarchy Codes and Veterans Affairs (VA) Formulary Classifications used to Define Baseline Characteristics in this Request

Characteristic	ICD-10 Hierarchy Term/VA Code and Description
Alcohol-Related disorders	F10 (alcohol-related disorders)
ADHD	F90 (Attention-deficit hyperactivity disorders)
Anxiety Disorders	F41 (Other anxiety disorders)
Autism	F84.0 (Autistic disorder)
Cancer	C00-D49 (Neoplasms)
Cannabis-Related Disorders	F12 (Cannabis related disorders)
Cerebrovascular diseases	I60-I69 (Cerebrovascular diseases)
Chronic Kidney Disease	N18 (Chronic kidney disease)
Chronic Liver Disease	K70-K77 (Diseases of liver)
Chronic Pain	
Back and Spine pain	M54 (Dorsalgia)
Fibromyalgia	M79.7 (Fibromyalgia)
Pain, not elsewhere classified (includes Chronic Pain Syndrome and Chronic Pain not elsewhere classified)	G89 (pain, not elsewhere classified)
Pain, unspecified	R52 (Pain, unspecified)
Chronic Respiratory Conditions	J40-J47 (Chronic lower respiratory diseases)
Dementia (vascular)	F01 (Vascular dementia)
Dementia (unspecified)	F03 (Unspecified dementia)
Diabetes	E08-E13 (Diabetes mellitus)
Dravet Syndrome	G40.83 (Dravet syndrome)
Dystonia	G24 (Dystonia)
Eating Disorders	F50 (Eating disorders)
Glaucoma	H40-H42 (Glaucoma)
HIV/AIDS	B20 (Human immunodeficiency virus [HIV] disease)
Huntington's Disease	G10 (Huntington's disease)
Hypertension	I10 (Essential (primary) hypertension)
Irritable Bowel Syndrome	K58 (Irritable bowel syndrome)
Ischemic Heart Diseases	I20-I25 (Ischemic heart diseases)
Lennox-Gastaut Syndrome	G40.81 (Lennox-Gastaut syndrome)
Mood Disorders	F30-F39 (Mood [affective] disorders)
Multiple Sclerosis	G35 (Multiple sclerosis)
Nicotine Use	F17 (Nicotine dependence)
Obesity	E66 (Overweight and obesity)
Opioid-related disorders	F11 (opioid-related disorders)
Other Epilepsies	G40.9 (Epilepsy, unspecified)
Other Neurological Or Developmental Conditions	F80-F89 (Pervasive and specific developmental disorders)
Parkinson's Disease	G20 (Parkinson's disease)
Personality Disorders	F60 (Specific personality disorders)
Post-Traumatic Stress Disorder	F43.1 (Post-traumatic stress disorder (PTSD))
Psychotic Disorders	F20-F29 (Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders)
Rheumatologic And Inflammatory Conditions	M05-M14 (Inflammatory polyarthropathies)
Sleep Disorders	G47 (Sleep disorders)
Spinal Cord Injury	S34 (Injury of lumbar and sacral spinal cord and nerves at abdomen, lower back and pelvis level)
Tourette Syndrome	F95.2 (Tourette's disorder)
Traumatic Brain Injury Or Intracranial Hemorrhage	S06 (Intracranial injury)
Tuberous Sclerosis Complex	Q85.1 (Tuberous sclerosis)
Vaping-Related Disorders	U07.0 (Vaping-related disorder)

Appendix B. List of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Hierarchy Codes and Veterans Affairs (VA) Formulary Classifications used to Define Baseline Characteristics in this Request

Characteristic	ICD-10 Hierarchy Term/VA Code and Description
Positive Pregnancy Test	Z32.01 (Encounter for pregnancy test, result positive)
Anticonvulsants	CN400 (Anticonvulsants)
Cannabidiol	2045371 (Cannabidiol)
Clobazam	21241 (clobazam)
Fenfluramine	4328 (fenfluramine)
Stiripentol	2054968 (stripentol)
Valproate	40254 (valproate)
Anxiolytic And Hypnotic Drugs	CN300 (Sedatives/hypnotics)
Antidepressants	CN600 (Antidepressants)
Antipsychotics	CN700 (Antipsychotics)
Opioids	CN101 (Opioid analgesics)
Central Nervous System (CNS) Stimulants	CN800 (CNS stimulants)
Cardiovascular Medications	CV000 (Cardiovascular medications)
Antidiabetic Agents	HS500 (Blood glucose regulation agents)
Corticosteroids	HS050 (Adrenal corticosteroids)
Chemotherapeutics	AN000 (Antineoplastics)
Other Immunosuppressants	IM600 (Immune suppressants)
Antiemetic Agents	GA605 (Antiemetics)
Antihistamine	AH000 (Antihistamines)
Dronabinol	10402 (Dronabinol)
Nabilone	31447 (Nabilone)

Appendix C. List of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Diagnosis Codes, RxNorm Medication Terms, and Logical Observation Identifiers, Names and Codes (LOINC) Laboratory Codes Used to Define Post-Index Characteristics in this Request

Code	Description	Code Category	Code Type	Filter
	Pregnancy			
80385-8	Choriogonadotropin (pregnancy test) [Presence] in Serum by Rapid immunoassay	Laboratory Test	LOINC	Positive result
2118-8	Choriogonadotropin (pregnancy test) [Presence] in Serum or Plasma	Laboratory Test	LOINC	Positive result
2106-3	Choriogonadotropin (pregnancy test) [Presence] in Urine	Laboratory Test	LOINC	Positive result
80384-1	Choriogonadotropin (pregnancy test) [Presence] in Urine by Rapid immunoassay	Laboratory Test	LOINC	Positive result
2110-5	Choriogonadotropin.beta subunit (pregnancy test) [Presence] in Serum or Plasma	Laboratory Test	LOINC	Positive result
2112-1	Choriogonadotropin.beta subunit (pregnancy test) [Presence] in Urine	Laboratory Test	LOINC	Positive result
Z32.01	Encounter for pregnancy test, result positive	Diagnosis	ICD-10 DX	
	Cannabis and Cannabis-Derived Products			
2045371	Cannabidiol	Medication	RxNorm	n/a
1976	Cannabinol	Medication	RxNorm	n/a
1788846	Hemp	Medication	RxNorm	n/a
1305550	Cannabis sativa seed oil	Medication	RxNorm	n/a
2177094	Cannabis Sativa subsp. Sativa whole extract	Medication	RxNorm	n/a
2464938	Cannabigerol	Medication	RxNorm	n/a
2279519	Cannabigerolate (*note: this term has 0 patients)	Medication	RxNorm	n/a
2585216	Cannabichromene (*note: this term has 0 patients)	Medication	RxNorm	n/a
2168435	Cannabis sativa susp. indica top extract (*note: this term has 0 patients)	Medication	RxNorm	n/a
1484855	Cannabis Sativa subsp. Flowering top extract (*note: this term has 0 patients)	Medication	RxNorm	n/a
2002575	Cannabis sativa pollen extract (*note: this term has 0 patients)	Medication	RxNorm	n/a
2048033	Cannabis sativa whole extract (*note: this term has 0 patients)	Medication	RxNorm	n/a
1429926	Cannabis sativa seed extract (*note: this term has 0 patients)	Medication	RxNorm	n/a
	Cannabidiol			
2045371	Cannabidiol	Medication	RxNorm	n/a
	Tetrahydrocannabinol (THC) Lab Tests			
19415-9	Tetrahydrocannabinol [presence] in urine by screen method	Laboratory Test	LOINC	Positive result
14312-3	Tetrahydrocannabinol [presence] in urine by screen method >50 ng/ml	Laboratory Test	LOINC	Positive result
3426-4	Tetrahydrocannabinol [presence] in urine	Laboratory Test	LOINC	Positive result
21556-6	Tetrahydrocannabinol [presence] in urine by screen method >20 ng/ml	Laboratory Test	LOINC	Positive result
19416-7	Tetrahydrocannabinol [presence] in urine by confirmatory method	Laboratory Test	LOINC	Positive result
8175-2	Tetrahydrocannabinol [presence] in urine by samhsa screen method	Laboratory Test	LOINC	Positive result
21557-4	Tetrahydrocannabinol [presence] in urine by screen method >100 ng/ml	Laboratory Test	LOINC	Positive result
43834-1	Tetrahydrocannabinol [presence] in specimen	Laboratory Test	LOINC	Positive result
58047-2	Tetrahydrocannabinol [presence] in blood by confirmatory method (*note: 0 positive patients)	Laboratory Test	LOINC	Positive result

Appendix C. List of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Diagnosis Codes, RxNorm Medication Terms, and Logical Observation Identifiers, Names and Codes (LOINC) Laboratory Codes Used to Define Post-Index Characteristics in this Request

Code	Description	Code Category	Code Type	Filter
3435-5	Carboxy tetrahydrocannabinol [presence] in urine	Laboratory Test	LOINC	Positive result
19381-3	Carboxy tetrahydrocannabinol [presence] in urine by screen method	Laboratory Test	LOINC	Positive result
19382-1	Carboxy tetrahydrocannabinol [presence] in urine by confirmatory method	Laboratory Test	LOINC	Positive result
42492-9	Carboxy tetrahydrocannabinol [presence] in blood	Laboratory Test	LOINC	Positive result
26743-5	Carboxy tetrahydrocannabinol [presence] in serum or plasma	Laboratory Test	LOINC	Positive result
61063-4	Carboxy tetrahydrocannabinol [presence] in specimen	Laboratory Test	LOINC	Positive result
74678-4	Carboxy tetrahydrocannabinol [presence] in saliva (oral fluid) by confirmatory method	Laboratory Test	LOINC	Positive result
78754-9	11-hydroxy delta-9 tetrahydrocannabinol [presence] in urine by screen method (*note: 0 positive patients)	Laboratory Test	LOINC	Positive result
14313-1	Tetrahydrocannabinol [Mass/volume] in Urine by Confirmatory method	Laboratory Test	LOINC	15 ng/ml - 800 ng/ml
3530-3	Tetrahydrocannabinol [Mass/volume] in Urine	Laboratory Test	LOINC	50 ng/ml - 800 ng/ml
3528-7	Tetrahydrocannabinol [Mass/volume] in Serum or Plasma	Laboratory Test	LOINC	2 ng/ml - 125 ng/ml
44049-5	Tetrahydrocannabinol [Mass/volume] in Serum or Plasma by Confirmatory method	Laboratory Test	LOINC	2 ng/ml - 125 ng/ml
73935-9	Tetrahydrocannabinol [Mass/volume] in Serum, Plasma, or Blood by Confirmatory method	Laboratory Test	LOINC	2 ng/ml - 125 ng/ml

Appendix D. Specifications Defining Query Builder Modules in this Request

Cohort 1: Cannabis derived product, excluding Known Epidiolex	
Group 1: Cannabis-derived Product	**Time Restrictions**
Must Have:	
Cannabis-derived product	7/1/2018 - 6/30/2022
Cannot Have:	
Cannabidiol [FILTER: Epidiolex brand] Cannabidiol [FILTER: 100 mg/ml strength]	7/1/2018 - 6/30/2022
Group 2: History of Healthcare Visits	**Time Restrictions**
Must Have:	
Visit	2 year prior to Group 1 (cannabis-derived product) [-720, -1]

Cohort 2: Positive THC Lab Test	
Group 1: THC Lab	**Time Restrictions**
Must Have:	
THC Presence Lab Test [FILTER: Positive Result or meets qualitative cut off. See Appendix C for more details]	7/1/2018 - 6/30/2022
Group 2: History of Healthcare Visits	**Time Restrictions**
Must Have:	
Visit	2 year prior to Group 1 (Positive THC lab) [-720, -1]

Appendix E. Specifications Defining Analytic Modules in this Request

#	Module	Analysis Type	Cohort(s)	Window	Index Event(s)	Characteristics
1	Analyze Outcomes	Characteristics	All Cohorts	[-365, 0]	All cohort-defining criteria	Baseline Characteristics
2	Analyze Outcomes	Characteristics	All Cohorts	[-270, 0]	All cohort-defining criteria	Pregnancy test (diagnosis)
3	Analyze Outcomes	Characteristics	All Cohorts	[-30, 0]	All cohort-defining criteria	Pre-index Co-Exposures
4	Analyze Outcomes	Risk	All Cohorts	[1,30]	All cohort-defining criteria	Pregnancy test (diagnosis or positive lab)
5	Analyze Outcomes	Risk	All Cohorts	[1,30]	All cohort-defining criteria	Pre-index Co-Exposures
6	Analyze Outcomes	Risk/Number of instances	All Cohorts	[1,365]	All cohort-defining criteria	Cannabidiol, positive tetrahydrocannabinol lab test, cannabis, or other cannabis-derived product