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Incidence of Pancreatic Malignancy and Thyroid Neoplasm in Type 2 Diabetes Mellitus Patients who Initiate Exenatide Compared to Other Antihyperglycemic Drugs—Phase 2 (Extended Accrual and Follow-up)

Approved by:

Principal Investigator	Date

Author	[redacted]

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1. ABSTRACT

Title

Incidence of Pancreatic Malignancy and Thyroid Neoplasm in Type 2 Diabetes Mellitus Patients who Initiate Exenatide Compared to Other Antihyperglycemic Drugs—Phase 2 (Extended Accrual and Follow-up). Revised Final Report Submitted 17 April 2018 by Optum Epidemiology.

Keywords

Exenatide, glucagon-like peptide-1 receptor agonist, pancreatic cancer, thyroid neoplasm

Rationale and background

Exenatide is a glucagon-like peptide-1 [GLP-1] receptor agonist used to treat type 2 diabetes mellitus. There is uncertainty about the use of exenatide and potential risk of pancreatic cancer but limited data exists from studies with robust design, large sample sizes, and long-term follow-up. The effects of GLP-1 receptor agonists on thyroid cancer in humans is also uncertain, with some rodent carcinogenicity studies showing changes in thyroid C-cells with exenatide use. This study adds to the limited literature on exenatide use among humans and risk of pancreatic cancer and thyroid neoplasms.

Research question and objectives

The primary objectives of this study were to estimate the incidence of pancreatic and thyroid cancer in exenatide users compared to users of other antidiabetic drugs [OAD]. The secondary objectives were to estimate the incidence of all thyroid neoplasms, including medullary thyroid cancer [MTC], non-MTC, and benign thyroid neoplasm.

Study design

This was a retrospective cohort study and a complementary nested case-control study.

Setting

Adult patients with type 2 diabetes mellitus who were new initiators of exenatide or another antihyperglycemic drug were accrued from 01 June 2005 through 30 June 2015. Exenatide initiators were matched to OAD initiators using propensity scores and patients were followed for a new occurrence of pancreatic cancer or thyroid neoplasms.

Subjects and study size, including dropouts

The matched cohorts included a total of 47,946 exenatide initiators and 84,443 OAD initiators. The nested case-control study included 86 medical record-confirmed pancreatic cancer cases, 83 confirmed thyroid cancer cases, and 296 controls without either of the two cancers.

Variables and data sources

The data were derived from health insurance claims from the Optum Research Database [ORD] and the Impact National Benchmark Database™ [Impact]. Medical records were retrieved for a subset of patients to validate claims-based outcome algorithms as well as to collect covariate information for nested case-control study patients that is typically captured poorly in claims data.

Results

In the matched, intention-to-treat cohort analysis, exenatide use was not associated with an increased risk of pancreatic cancer (adjusted hazard ratio [HR] 0.76, 95% confidence interval [CI] 0.47 to 1.21) or risk of thyroid cancer (adjusted HR 1.46, 95% CI 0.98 to 2.19). Looking within each database separately, the adjusted HR of thyroid cancer was 1.78 (95% CI 1.06 to 2.99) among ORD patients and 1.05 (95% CI 0.54 to 2.04) among Impact patients.

In a nested case-control study that additionally adjusted for medical record-derived confounders, including body mass index [BMI], smoking, alcohol, systolic blood pressure, hemoglobin A1c, and race, exenatide use was associated with a statistically significant lower risk of pancreatic cancer: adjusted relative risk [RR] 0.48 (95% CI 0.25 to 0.91). A similar nested case-control study of thyroid cancer found no association with exenatide use: adjusted RR 0.87 (95% CI 0.59 to 1.29).

Conclusions

The results of the cohort study suggest that exenatide use was not associated with an increased risk of pancreatic or thyroid cancer. A nested case-control study within the ORD that adjusted for additional chart-derived covariates found no elevation in risk of pancreatic or thyroid cancer with exenatide use. Given the long latency period of pancreatic and thyroid cancer, and the relatively short follow-up for many patients, these results should be interpreted with caution.

Names and affiliations of principal investigators

[redacted] Optum Epidemiology

[redacted] Optum Epidemiology

[redacted] Optum Epidemiology

[redacted] Optum Epidemiology and the Department of Medicine at Brigham and Women's Hospital and Harvard Medical School

[redacted] Medical Evidence and Observational Research, AstraZeneca

2. LIST OF ABBREVIATIONS

Table A List of Abbreviations

Abbreviation or special term	Explanation
ARR	apparent relative risk
BID	bis in die (Latin for twice daily)
BMI	body mass index
CI	confidence interval
CPT	Current Procedural Terminology
DDP-4	dipeptidyl peptidase-4
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
GLP-1	glucagon-like peptide-1
HCPCS	Healthcare Common Procedure Coding System
HIPAA	Health Insurance Portability and Accountability
HR	hazard ratio
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
IR	incidence rate
IRB	institutional review board
MAR	missing at random
MCG	micrograms
MTC	medullary thyroid cancer
OAD	other antidiabetic drug
OR	odds ratio
ORD	Optum Research Database
PPV	positive predictive value
QC	quality control
RR	relative risk
SOP	standard operating procedure
SU	sulfonylurea
T2D	type 2 diabetes
TZD	thiazolidinedione
US	United States

3. INVESTIGATORS

[redacted] Optum Epidemiology

[redacted] Optum Epidemiology

[redacted] Optum Epidemiology

[redacted] Optum Epidemiology and the Department of Medicine at Brigham and Women's Hospital and Harvard Medical School

[redacted] Medical Evidence and Observational Research, AstraZeneca

4. OTHER RESPONSIBLE PARTIES

There are no additional responsible parties.

5. MILESTONES

Table B Milestones

Milestone	Planned date	Actual date	Comments
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]

Milestone	Planned date	Actual date	Comments
[redacted]	[redacted]	[redacted]	[redacted]

6. RATIONALE AND BACKGROUND

Diabetes is a leading cause of blindness, end-stage renal disease and non-traumatic lower limb amputation, and is a risk factor for coronary artery disease and stroke (1). Interventions to improve glycemic control among patients with diabetes are important to reduce microvascular complications involving the eyes, kidneys, and nerves, and to reduce macrovascular complications such as myocardial infarction (2). Exenatide is one of several newer treatments that improve long-term glycemic control among individuals with type 2 diabetes [T2D].

Exenatide is a GLP-1 receptor agonist, approved by the United States [US] Food and Drug Administration [FDA] for the treatment of T2D. BYETTA® (exenatide BID) was approved on 28 April 2005 and is self-administered via subcutaneous injection twice daily [BID]. BYDUREON™ (exenatide once weekly) is administered through subcutaneous injection once weekly and was approved on 27 January 2012 in the US. Exenatide facilitates glucose control through enhancement of glucose-dependent insulin secretion by pancreatic beta cells, reduction of gluconeogenesis via suppression of excess glucagon secretion, and slowing of gastric emptying (3, 4).

In rodent carcinogenicity studies, a statistically significant increase in thyroid C-cell tumor incidence (adenomas and/or carcinomas) was observed with exenatide once weekly, raising concern about the effects of GLP-1 receptor agonists on thyroid C-cells in humans, potentially leading to MTC (5, 6). The available data on GLP-1 receptor expression suggests strong expression in the thyroid C-cells of rats and mice but little to no expression in humans or monkeys (5, 7, 8). Similarly, in contrast to the rat model, monkey studies with GLP-1 receptor agonists have not identified changes in thyroid C-cells (7). These data are consistent with those reported for liraglutide, in which no effects on thyroid C-cells were noted in monkey studies of up to 87 weeks (5, 9).

MTC is a C-cell cancer that produces excessive calcitonin (6), a marker of C-cell proliferation; however, calcitonin concentrations were unaffected in humans after up to 2 years of clinical exposure to exenatide once weekly or liraglutide in the phase 3 Liraglutide Effect and Action in Diabetes (LEAD) studies (5, 10, 11). Data from clinical studies showed no increased risk of thyroid malignancy with liraglutide or exenatide use (12-14), however cases of MTC have been reported during post-approval use of liraglutide (15).

Little epidemiologic information exists on the potential association between incretin-modulating therapies (GLP-1 receptor agonists and dipeptidyl peptidase-4 [DPP-4] inhibitors) and pancreatic cancer. A study using Medicare claims data observed no increased pancreatic

cancer risk for patients with sitagliptin relative to thiazolidinediones [TZD] and sulfonylureas [SU] (16). Romley et al. found no association between exenatide use and pancreatic cancer (17) and Funch et al. reported no excess risk of pancreatic cancer among users of liraglutide relative to users of other antihyperglycemic therapies (18).

Optum recently completed a cohort study with patients accrued from 01 June 2005 to 31 July 2010 to estimate the association between use of exenatide BID and the occurrence of pancreatic cancer or thyroid neoplasms (19). There were few outcomes, and the resulting lack of statistical power prevented conclusive interpretation of the results. This extension study includes several key changes as compared to the previous study: extended follow-up through 30 June 2015, the addition of exenatide once weekly (BYDUREON), combination of the Optum Research Database [ORD] and Impact National Benchmark Database™ [Impact] for increased statistical power, matching on propensity scores within 6-month calendar blocks, adjudication of outcomes in the extension period (in a subset of the study population), validation of pancreatic and thyroid cancer algorithms in the extension period (in a subset of the study population), and a nested case-control study with covariates abstracted from medical records.

7. RESEARCH QUESTION AND OBJECTIVES

7.1 Primary Objectives

The primary objectives were to estimate the absolute and relative incidence of pancreatic cancer and thyroid cancer that occurred at least one year after initiation of exenatide BID or once weekly (hereafter exenatide) or initiation of other antidiabetic drugs [OADs]—overall and by duration of follow-up and duration of exposure.

7.2 Secondary Objectives

The secondary objectives were to estimate incidence rates [IRs] of thyroid neoplasms, including benign thyroid neoplasm and MTC and non-MTC cancers that occurred at least one year after initiation of exenatide or OADs.

8. AMENDMENTS AND UPDATES

No amendments or updates were made after finalization of the study protocol of 18 December 2015.

9. RESEARCH METHODS

This analysis follows the approach described in the study protocol of 18 December 2015 (20) (Appendix 1).

9.1 Study design

This was a retrospective cohort study that compared IRs of pancreatic cancer and thyroid neoplasms between initiators of exenatide and initiators of OADs. Exenatide initiators (exenatide cohort) were matched to OAD initiators (OAD cohort) 1:1 or 1:2 (exenatide:OAD) on propensity scores within 6-month calendar blocks. The aggregated, matched cohorts formed the analytic population. Both time-fixed and time-dependent, cumulative exenatide exposure classifications were used.

Pancreatic cancer and thyroid neoplasms were identified via patterns of claims using the "restricted" algorithms applied in the previous study (19) (Appendix 2). Subtypes of thyroid neoplasms including MTC, non-MTC, and benign thyroid neoplasm were included as part of the secondary objectives. A second validation of the restricted algorithms was conducted within a sample of medical records of patients identified in the ORD during the extension period.

A nested case-control analysis was performed to account for potential confounders that are captured poorly in the claims data. These clinical characteristics were abstracted from a subset of patients in the ORD with medical records.

9.2 Setting

9.2.1 Location and relevant dates

This study used 2 administrative databases from commercial health plans in the US: the ORD and Impact. In this extension study, Optum recreated the exenatide and OAD study cohorts to include patients accrued from 01 June 2005 through 30 June 2015. The protocol dated 18 December 2015 originally stated patients would be accrued through 31 December 2015, but the most recent data available at the time of cohort creation was 30 June 2015 for the ORD and 31 March 2015 for Impact.

Table C Study Time Period

Previous study period	01 June 2005 to 31 July 2010
Extension period	01 August 2010 to 30 June 2015 (or 31 March 2015 for Impact)
Study period for this report	01 June 2005 to 30 June 2015 (or 31 March 2015 for Impact)

9.2.2 Follow-up period

Each cohort member was followed from study drug initiation until the first occurrence of a study outcome, disenrollment from the health plan (a > 32-day gap in membership), or the end of the study period (30 June 2015 for ORD and 31 March 2015 for Impact). Person-time and

events observed in the first year post study drug initiation were not included in the primary analyses.

9.3 Subjects

The study population consisted of patients with T2D who had at least 9 months of continuous enrollment in their health plan between 01 September 2004 and 30 June 2015 for ORD (and 31 March 2015 for Impact). The initial date of cohort eligibility was 01 June 2005, the launch date of exenatide BID in the US.

9.3.1 Inclusion criteria

Eligible patients had:

- Complete medical and pharmacy benefits and at least 9 months of continuous enrollment in the health plan prior to the cohort entry date;
- A diagnosis of T2D (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] diagnosis codes 250.x0, 250.x2) during the 9-month baseline period, including the cohort entry date; and
- A dispensing of at least one antidiabetic drug other than the initiating drug during the 9-month baseline period, including the cohort entry date

A list of OADs included in this study is included in Appendix 3.

9.3.2 Exclusion criteria

Patients were excluded if they had:

- A dispensing of the same class of drugs as the initiating drug during the 9-month baseline period (excluding cohort entry date), or
- Claims associated with pancreatic or thyroid neoplasms (including benign and malignant neoplasms) during the 9-month baseline period (including cohort entry date)
    - Malignant neoplasm of pancreas (ICD-9-CM 157.xx)
    - Benign neoplasm of pancreas (ICD-9-CM 211.6, 211.7)
    - Malignant neoplasm of thyroid (ICD-9-CM 193.xx)
    - Benign neoplasm of thyroid (ICD-9-CM 226), or
- A dispensing of DPP-4 inhibitors or GLP-1 receptor agonists (including exenatide) during the 9-month baseline period (including cohort entry date)

OAD patients were censored at the time of DPP-4 inhibitor or GLP-1 receptor agonist initiation in the follow-up period.

9.3.3 Study cohorts

9.3.3.1 Exenatide initiators (exposure cohort)

Between 01 June 2005 and 30 June 2015 for ORD (and 31 March 2015 for Impact), pharmacy claims were searched for exenatide dispensings. The date of cohort eligibility was the date of

the first dispensing of exenatide without an exenatide dispensing in the previous 9 months, excluding the cohort entry date, but with at least one OAD dispensing in the previous 9-month period, including the cohort entry date, (with the exception of DPP-4 inhibitors/GLP-1 receptor agonists on the cohort entry date as noted above in the exclusion criteria). The rationale for requiring that patients were taking at least one other OAD was to limit cohort membership to patients initiating exenatide (or an OAD in the OAD cohort) as add-on therapy in order to improve the comparability of patient characteristics across the exposure cohorts.

9.3.3.2 OAD initiators (comparison cohort)

A contemporaneous comparison cohort of new users of OADs was identified in the same manner as the exenatide cohort. The date of cohort entry was the date of the first dispensing of an OAD with no dispensing of the same drug, or another drug from the same class, in the previous 9 months (excluding cohort entry date). OAD initiators must have had at least one dispensing of a different OAD in the previous 9 months (including cohort entry date). See Appendix 3 for a list of OAD drugs. DPP-4 inhibitors and GLP-1 receptor agonists were not included in the list of eligible initiating OAD drugs because they have a similar mechanism of action as exenatide.

For patients initiating multiple antidiabetic medications during the study period, we preferentially chose initiators of exenatide first, such that a patient who initiated exenatide and an SU during the study period was assigned to the exenatide cohort even if she or he initiated exenatide later than SU. This hierarchical cohort selection allowed for the attribution of exenatide-exposed person-time to the exenatide cohort in the primary analysis, because that analysis is time-fixed. Although this hierarchical cohort selection can result in immortal time bias (21), this approach did not introduce appreciable immortal time bias in our previous work on exenatide (22).

9.3.3.3 Matching of the comparison cohort to the exenatide cohort

Within each database, each exenatide initiator was matched within 6-month calendar blocks to up to 2 OAD initiators on estimated propensity score. Matching within blocks of calendar time accounts for potential changes in exenatide prescribing behavior over time and six-month blocks were used based on experience from the previous exenatide study which demonstrated that a shorter time block (6 months instead of one year) would better capture this variability. Patients were assigned to calendar blocks based on their index date (cohort entry date). There was a total of 20 calendar blocks: calendar blocks one through 19 were 6-months long starting 01 June 2005 and ending 30 November 2014. The 20th calendar block was 7 months long in the ORD (01 December 2014 to 30 June 2015) and 4 months long in Impact (01 December 2014 to 31 March 2015).

A patient's propensity score is her or his probability of being a member of the exenatide cohort, given membership in the study population and her or his particular covariate pattern. In expectation, matching on propensity score creates exposed (exenatide initiator) and unexposed (OAD initiator) cohorts with balanced distributions of all covariates modeled to estimate the propensity score (23).

Within each calendar block, separately within each database, propensity scores were estimated from baseline covariates described in Section 9.4 (Variables) using logistic regression modeling. To fit the propensity score model efficiently within each calendar block, initial estimation and covariate balance checking were automated.

A common set of variables was used to begin development of the propensity score model, including clinically important *a priori* variables as well as the 200 most prevalent diagnoses (3-digit ICD-9-CM code), procedures, and drug dispensings in baseline. Before running the propensity score models, correlations between all variables in the common set were checked and variable pairs with a correlation coefficient above 0.8 were examined more closely. For such pairs, the variable of greater clinical importance was retained and the other removed from the analysis. If both variables in the correlated pair had equal clinical relevance, the variable with the highest prevalence was retained and the other removed from the analysis. Finally, variables in the common set with a marginal, intra-block prevalence of < 1% were removed with the exception of variables related to detection bias.

The following steps were applied:

1. *A priori* variables and the 10 variables with the highest univariate c-statistics within a specific calendar block were forced into the propensity score model for each calendar block.

2. From the remaining covariates, predictors of exenatide initiation were identified via a stepwise selection process (p-value of 0.2 for model entry and 0.3 for model retention).

3. The propensity score was estimated for each patient via an unconditional logistic regression model.

4. Trimming on extreme values of propensity scores may reduce residual confounding from unmeasured attributes of patients or their context of care (24). Therefore, we excluded patients with the lowest 2% of propensity scores in the exenatide cohort or the top 2% of propensity scores in the OAD cohort from the analytic cohorts.

5. Each exenatide initiator was matched to one or 2 OAD initiators on the estimated propensity score using a “greedy” matching algorithm. Greedy matching is a linear, sequential matching algorithm that identifies patients in the OAD cohort who have propensity scores similar to those in the exenatide cohort. This algorithm identifies matches from the pool of possible matches without replacement. When identifying 2 matches per exposed patient, the greedy algorithm finds the closest match for each exposed patient before returning and identifying the second match. Once an exenatide initiator has been matched with 2 OAD initiators, the triplet is removed from further consideration (25). Specifically, the algorithm matches exposed and unexposed patients iteratively, identifying the closest matches first, where closest is defined as

exenatide-OAD pairs who match on the estimated propensity score at the 8th decimal point. With subsequent iterations, the algorithm identifies matches with less precision, decreasing by one decimal point at each iteration (e.g., 8, 7, 6, etc. decimal points), ending once matches at 0.1 of the propensity score are identified. The matching procedure is "greedy" in the sense that it preserves sample size by accepting matches on calipers as wide as 0.1 of the propensity score but only after identifying all possible matches with greater precision. Thus, greedy matching balances residual bias that could be introduced through inexact matching with preservation of statistical power. The greedy matching algorithm has been used extensively, including within Optum, and its details have been published (26).

6. The balance achieved by propensity score matching was evaluated using the standardized difference of the mean of each covariate comparing exenatide initiators with OAD initiators within database and matching group (1:1 or 1:2). Covariate imbalance was defined as an absolute standardized difference > 0.1 (difference between the 2 mean values of the covariate divided by the pooled standard deviation) (27). We used a weighted standardized difference appropriate for the 1:n matching study design (28). The weighted standardized difference formula is the same as the standardized difference formula, but exenatide initiators are weighted as one patient, OAD initiators matched 1:1 are weighted as one patient, and OAD initiators matched 1:2 are weighted as 1/2 patient.

7. Matched initiators were compiled across all 20 calendar blocks to form the final analytic cohorts.

9.3.4 Nested case-control study

A nested case-control analysis was conducted separately for pancreatic and thyroid malignancies to account for potential confounders that are poorly captured in claims data. This study was conducted in the subset of ORD patients with accessible medical records.

Cases included all medical record-confirmed cases, including cases from the previous study and cases from the new validation in the 2010 to 2015 extension period. Case validation only occurred in a subset of the ORD among identifiable patients with retrieved medical records.

Controls were sampled from those exenatide and OAD cohort patients who were at-risk in follow-up. Controls were frequency matched to cases within 6-month calendar blocks on the number of visits in the baseline period, age, sex, and visit type (in- or out-patient) on index date. Controls were matched to cases on visit type because different types of facilities may record different information about patients. Up to 4 controls were matched to each case. Controls were assigned an index date (similar to the case date of diagnosis) corresponding to the date of first office visit within the 6-month calendar block (or first hospitalization if hospitalized). The set of all controls was used as the same referent group for both the pancreatic and thyroid cancer analyses. No controls had a history of pancreatic or thyroid cancer at the time of the assigned index date.

Both cases and controls were required to meet the following inclusion and exclusion criteria:

Inclusion criteria

Cases: a medical record-confirmed diagnosis of pancreatic or thyroid cancer during the period of 01 June 2005 through 30 June 2015.

Controls: a random sample of the source cohorts and no medical record-confirmed diagnoses of pancreatic or thyroid cancer at the time of case occurrence.

Exclusion criteria

Cases and controls: no medical records available for review or a history of cancer excluding non-melanoma skin cancer.

Controls: a diagnosis of benign neoplasm of the pancreas or thyroid preceding the case-control study index date.

9.4 Variables

9.4.1 Exposure

Exposure to exenatide (and OADs) was defined in both a time-fixed and time-dependent manner. The time-fixed exposure to exenatide and OADs was based on the exposure status at the time of drug initiation, regardless of actual pattern of exposure in follow-up. This analysis allowed for the attribution of remote events (e.g., pancreatic or thyroid cancers occurring at least one year after initiation of the study drug) to the initial exposure.

The dynamic nature of exposure to exenatide was also measured to allow for the assessment of risk associated with cumulative exposure to exenatide. In this time-dependent analysis, exposure was classified by ascertaining the time-dependent cumulative dose and separately, duration of exposure, across the study period. Cumulative exenatide dose was calculated using the number of exenatide dispensings, days supplied, and dosage formulation of the drug—taken as the sum of the micrograms of each dose over all doses dispensed to the patient. Cumulative exenatide duration was measured by summing the days supplied across each unique dispensing over time, including a grace period to allow for modest non-adherence. Patients who refilled a study drug within 31 days following the end of days supplied of the previous dispensing were considered to be continuously using the drug.

For BYETTA 5 mcg, injected twice daily from a pen containing 60 doses, cumulative dose was calculated as 300 mcg (60 doses*5 mcg per dose) multiplied by the total number of pens in follow-up. For BYETTA 10 mcg, also injected twice daily from a pen containing 60 doses, cumulative dose was calculated as 600 mcg (60 doses*10 mcg per dose) multiplied by the total number of pens dispensed in follow-up. For example, if a patient was dispensed 5 BYETTA 5 mcg pens in follow-up, their cumulative dose was 1,500 mcg (300 mcg per pen*5 pens). BYDUREON is a once weekly injection of 2,000 mcg. Due to the different

bioavailability of BYDUREON and BYETTA, BYDUREON was assumed to be equivalent to BYETTA 10 mcg BID (20 mcg daily).

When possible, cumulative OAD dose was calculated in the same manner. For example, a patient with 10 dispensings of metformin in follow-up, each with a strength of 500 mg and a quantity of 30 days, had a cumulative metformin dose of 150,000 mg. However, many OAD claims were missing information on drug strength. When claims were missing insulin strength, we used 100 USP, the typical dose. Combination drugs were often missing information on strength. In these cases, we extracted the strength from the national drug code label to understand the common dosages. We then calculated the average dose (weighted by the percentage of claims with that dose) based on similar drugs with similar observed dosages and multiplied this estimated average strength by the observed quantity.

When the average strength of a drug was very different from other drugs in the same group (e.g., 60 mg or 120 mg 3 times per day for nateglinide and 0.5 mg, 1 mg, or 2 mg before each meal for repaglinide) we standardized the doses before creating tertiles of cumulative dose across all patients who initiated that type of OAD. For example, we multiplied the repaglinide dose by 100 before creating tertiles across all non-SU.

Although person-time and events in the first year of follow-up were excluded from the main analyses, study drug dispensings in the first year of follow-up contributed to cumulative exposure measures (cumulative duration and dose). For example, a patient used BYETTA 5 mcg BID (10 mcg per day) daily for 1 year (months 0-12), discontinued use in year 2 (months 13-24), resumed daily use in years 3 and 4 (months 25-48), and was diagnosed with pancreatic cancer at 48 months. This patient had a total cumulative exenatide duration of 3 years (years 1, 3, and 4) and a total cumulative dose of 10,950 mcg (3,650 in year 1 +3,650 in year 3 + 3,650 in year 4).

This patient had a total of 4 years of follow-up but contributed 3 years of person-time to the main analysis and the as treated analysis (years 2-4) in which the first year of follow-up was excluded. In the as treated analysis, the cumulative drug exposure was treated as a time-dependent variable such that each person-day that contributed to the analysis was attributed to the exposure category with the highest cumulative exposure (cumulative dose or duration) as of that day.

In the analysis of cumulative drug duration, the patient's first year of follow-up was excluded. Person-time in year 2 was attributed to the category "≥ 1 to < 2 years" cumulative exenatide duration because they had reached total cumulative duration of 1 year of exenatide at the end of year 1. Person-time in year 3 was also attributed to the category "≥ 1 to < 2 years" cumulative exenatide duration because they did not reach a cumulative duration of 2 years until the end of year 3. Person-time in year 4 was attributed to the category "≥ 2 to < 3 years" cumulative exenatide duration. This patient contributed no person-time to the cumulative exenatide duration categories "> 0 to 1 year" and "≥ 3 years".

In the analysis of cumulative dose, the first year of follow-up was excluded. The patient reached a cumulative dose of 3,650 at the end of their first year of follow-up (10 mcg per day for 365 days) and discontinued use during their second year of follow-up; therefore person-time in year 2 was attributed to the cumulative exenatide dose category "> 1,500 to 6,325 mcg". They resumed taking exenatide again in year 3 and reached a cumulative exenatide dose of 6,325 mcg near the end of year 3. Therefore the patient contributed the majority of their person-time in year 3 to the cumulative exenatide dose category "> 1,500 to 6,325 mcg" and person-time at the end of year 3 was attributed to the category "> 1,500 to 6,325 mcg". Person-time in year 4 and pancreatic cancer event were attributed to the category "> 6,325 mcg". This patient contributed no person-time to the category "≤ 1,500 mcg".

By design, the exenatide-unexposed person-time was assumed to be exposed to one or more OADs. The use and switching status of OADs among exenatide initiators over time was tracked for both exenatide and OAD initiator cohorts, and concomitant OAD use was adjusted for as a time-dependent covariate in multivariable models.

9.4.2 Outcome

9.4.2.1 Outcome identification in claims

The primary outcomes were newly diagnosed pancreatic cancer and thyroid neoplasms occurring at least one year following cohort entry. We identified outcomes using the previous study's (19) validated algorithms that defined a pattern of claims that were highly suggestive of true cancer (see Appendix 4 for algorithms and 5 for ICD-9-CM codes). These algorithms were based on diagnosis and procedure codes from the claims data and required the presence of surgery, chemotherapy, and radiotherapy, and the absence of corresponding benign neoplasms. The algorithms were re-validated in the extension period (01 August 2010 to 30 June 2015) via clinician adjudicator review of medical records in a subset of identifiable ORD patients.

9.4.3 Medical record abstraction and adjudication in the extension period

9.4.3.1 Review of claims profiles to select medical records of interest

The medical records of cases from both exposure cohorts were sought. The set of case medical records sought included patients matched and unmatched via propensity score (in order to provide enough information for algorithm validation given the rare occurrence of pancreatic cancer and thyroid neoplasms).

Each potential case was assigned a case date corresponding to the first date of diagnosis in the claims data. A chronological listing of claims data (claims profiles) of the identified cases in the identifiable portion of the ORD were extracted. These included claims from 3 months before through 6 months after the claims-based diagnosis date.

A clinical consultant conducted a detailed review of the claims profiles and decided which claim corresponded to the facility or provider with the medical record most likely to contain the information necessary for case adjudication. The clinician consultant selected 2 providers

(primary and alternate) for each case in order to maximize the chance to abstract available medical records. Records were first sought from the primary provider and, if not available, the alternate provider. The order of preference for choosing types of providers for medical record abstraction (primary and alternate) was as follows:

1. The hospital where the patient was diagnosed or treated for pancreatic cancer or thyroid neoplasms;

2. The surgeon associated with pancreatectomy or thyroidectomy;

3. Medical specialists (e.g., endocrinologist, oncologist) who treated the patients for pancreatic cancer or thyroid neoplasms;

4. Other (e.g., consultation, primary care physician).

9.4.3.2 Medical record abstraction

Providers were contacted via paper mail with copies of IRB approval, privacy board approval, and a brief description of the study. Medical record abstractors then followed-up with the providers via phone to ask permission to access specific patients' medical records for the purpose of collecting data related to the outcome of interest.

The date of the claim corresponding to a selected primary or alternate provider was set as the date of service (not necessarily the same as the case date). Study drug exposure status was blinded in medical records. Medical record abstraction included information relevant to case adjudication from 9 months prior through 6 months after the outcome date. The abstractors were additionally trained to blind protected health information (e.g., patient names, patient identification numbers) and study exposures in the medical records. Abstractors checked the quality control of blinding in a sample of 10% of medical records as did the Optum research associate before review by the clinical adjudicators.

9.4.3.3 Outcome adjudication

A medical record adjudication form was developed for each outcome (Appendix 6) including the criteria necessary to confirm the neoplasms of interest. There were 2 panels of adjudicators with each adjudication panel comprised of 2 adjudicators; the pancreatic cancer panel included one oncologist with expertise in pancreatic cancer and one general oncologist, and the thyroid cancer panel included one specialist in thyroid neoplasms and one general oncologist. The adjudicators reviewed the medical records blinded to exposure status and recorded information on key diagnostic questions, case status, event onset date, and tumor stage. Discrepant adjudications on case status, event onset date, tumor stage, and type of cancer were resolved by consensus among the 2 adjudicators within a panel. Each medical record was adjudicated as a definite, probable, possible, or non-diagnostic case. Only definite and probable cases were considered confirmed cases in the calculation of positive predictive value [PPV].

9.4.4 Potential confounders

9.4.4.1 Claims covariates

Covariates derived from claims data included demographics, diagnoses, medical procedures, drug use, and health care utilization. These covariates were assessed in the 9-month baseline period (unless otherwise noted) and included the following:

- Demographics
  - Age, sex
  - Geographic area
  - Cohort entry year
- Diabetes severity indicators
  - Use of oral antidiabetic medication
  - Dispensings of one, 2, or 3 study medications within 45 days of cohort entry
  - Peripheral neuropathy
  - Nephropathy
  - Retinopathy
- Cardiovascular disease indicators
  - Hypertension
  - Hyperlipidemia
  - Hypertriglyceridemia
  - Ischemic heart disease
  - Myocardial infarction
  - Congestive heart failure
  - Stroke
- Other factors
  - Health care utilization (e.g., the number of days hospitalized, hospitalization within 45 days of cohort entry date, number of physician visits, emergency department visits, and facility and pharmacy costs, etc.)

9.4.4.2 Covariates abstracted from medical records

Covariates that are captured poorly in claims data were abstracted from available case and control medical records. Existing records were used from cases in the previous study period (01 June 2005 through 31 July 2010) for covariate abstraction. In addition, new records were sought for cases in the extension period (01 August 2010 to 30 June 2015), for new cases identified in the previous study period, and for controls in the entire study period (01 June 2005 to 30 June 2015). A chronological listing of claims from 3 months before through 6 months after the control index date (corresponding to the case outcome date) was created for each control. A clinical consultant conducted a detailed review of the claims profiles and decided which claim corresponded to the facility or provider with the medical record most likely to contain the covariate information of interest. Trained abstractors contacted primary providers (and alternate providers when necessary) to ask for patient records from 9 months prior through 6 months after the control index date.

The following covariates were abstracted from medical records of cases and controls in the nested case-control study:

- Race/ethnicity
- Height and weight/BMI
- Smoking
- Alcohol use
- Blood pressure
- Family history of cancers including pancreatic and thyroid cancers
- Personal history of medical conditions, separately for pancreatic and thyroid cancer (e.g., pancreatic and thyroid diseases, gallstones, cholecystectomy, non-alcoholic fatty liver disease)
- Hemoglobin A1c and C-reactive protein
- Exposure to ionizing radiation and low-iodine diet (for thyroid cancer only)

9.5 Data sources and measurement

The patients included in this study were drawn from proprietary research databases containing eligibility and pharmacy and medical claims data for enrollees of commercial health plans in the US. The data included person-identifiable and de-identified health insurance claims from the ORD and de-identified health insurance claims from Impact.

9.5.1 Optum Research Database

The proprietary ORD contains medical claims, pharmacy claims, and laboratory results (for a subset of patients) with linked enrollment information covering the period from 1993 to the present. For 2015, data relating to approximately 13.5 million patients with both medical and pharmacy benefit coverage were available. The population was geographically diverse and fairly representative of the US population.

Claims for pharmacy services are typically submitted electronically by the pharmacy at the time prescriptions are filled. These claims include all outpatient prescription pharmacy services provided and covered by the health plan. Pharmacy claims data include drug name, dosage form, drug strength, fill date, days of supply, financial information, and de-identified patient and prescriber codes, allowing for longitudinal tracking of medication refill patterns and changes in medications.

Medical claims or encounter data are collected from all available health care sites (inpatient hospital, outpatient hospital, emergency room, physician's office, surgery center, etc.) for virtually all types of provided services, including specialty, preventive, and office-based treatments. Medical claims and coding conforms to insurance industry standards. Medical claims include: multiple ICD-9-CM diagnosis, ICD-9-CM procedure, Current Procedural Terminology [CPT], or Healthcare Common Procedure Coding System [HCPCS] codes; site of service codes; provider specialty codes; revenue codes (for facilities); paid amounts; and other information. Typically, facility claims do not include medications dispensed in hospital.

Most pharmacy claims are added to the research database within 6 weeks of dispensing. After approximately 6 months following the delivery of services, the medical data are complete. On average, individuals are enrolled in the health plan for 2.6 years.

9.5.2 Impact National Benchmark Database™

The Impact National Benchmark Database is a comprehensive, de-identified US health care claims database that, similar to the ORD, is representative of the non-elderly, commercially-insured population in the US. The database contains inpatient, outpatient, and pharmacy claims, lab results, and enrollment information. More than 75% of patients in the database have both medical and pharmacy benefits and, on average, 25.1 months of enrollment and claims information; the annual attrition rate is roughly 15-25%. The data are collected from more than 46 health plans, covering 9 census regions.

Membership in the Impact database could have overlapped somewhat with membership in the ORD. Internal Optum processes were used to identify overlapping periods of membership prior to integration with the ORD so that patients appearing in the ORD analytic cohort did not also appear in the Impact analytic cohort.

9.6 Bias

In the cohort analysis, exenatide initiators were matched to OAD initiators on propensity scores in order to balance patient characteristics between cohorts and reduce bias due to confounding. We excluded patients with the lowest 2% of propensity scores in the exenatide cohort and the top 2% of propensity scores in the OAD cohort to further reduce potential residual confounding from unmeasured patient characteristics such as frailty (24). Any characteristics that remained unbalanced after propensity score matching (weighted standardized difference > 0.1) were included in multivariable adjusted regression models.

We validated the outcome algorithms using medical records from a subset of identifiable patients in the ORD. Trained abstractors blinded study drug exposure status in the medical records used for case adjudication. The abstraction firm performed a quality control [QC] check of 10% of all records to ensure that blinding was accurate. Additionally, an Optum Research Associate did a QC check of 10% of blinded medical records before releasing the medical records to the clinician adjudicators.

In the nested case-control study, controls were frequency matched to cases on number of visits in the baseline period, age, sex, 6-month calendar block, and type of visit (in- or out-patient). Covariate information that is not well captured in claims data (e.g., BMI, smoking status, alcohol use) was abstracted from the medical records of cases and controls, allowing for statistical adjustment for these factors.

In addition to the time-fixed (“intention-to-treat”) analyses which allocated all events to the initiating drug, we performed time-dependent (“as treated”) analyses of cumulative dose and duration of the study drug. The models of time-varying exenatide and OAD exposure

additionally adjusted for switching to OAD during follow-up among the exenatide initiators. This allowed us to explore the dynamic nature of exenatide exposure.

Finally, we used the formulas presented by Greenland and Neutra to examine the potential for detection bias (29) and we applied the rule-out approach presented by Schneeweiss (30) to explore the extent to which residual confounding could explain the results. This approach estimates the effect of residual confounding over a wide range of magnitudes of association between an unmeasured confounder and outcome (disease) [RR_{CD}] and between exenatide exposure and the unmeasured confounder [OR_{EC}]. Generated figures quantify how strong an unmeasured confounder must be to fully explain the observed findings (the apparent relative risk [ARR]).

9.7 Study size

9.7.1 Cohort Study

Based on the final cohort study sample size (47,946 exenatide initiators matched to 84,443 OAD initiators) and the observed incidence rate of pancreatic cancer of 0.00045 per person per year in the OAD initiators, power for the pancreatic cancer cohort study was estimated as 90% to detect a HR of 2.0 for a two-sided significance level of 0.05. Using the same matching ratio of OAD to exenatide initiators and a thyroid cancer incidence rate of 0.00044 per person per year among the OAD initiators, power was also 90% to detect a HR of 2.0.

Table D Statistical Power for the Pancreatic Cancer Cohort Study

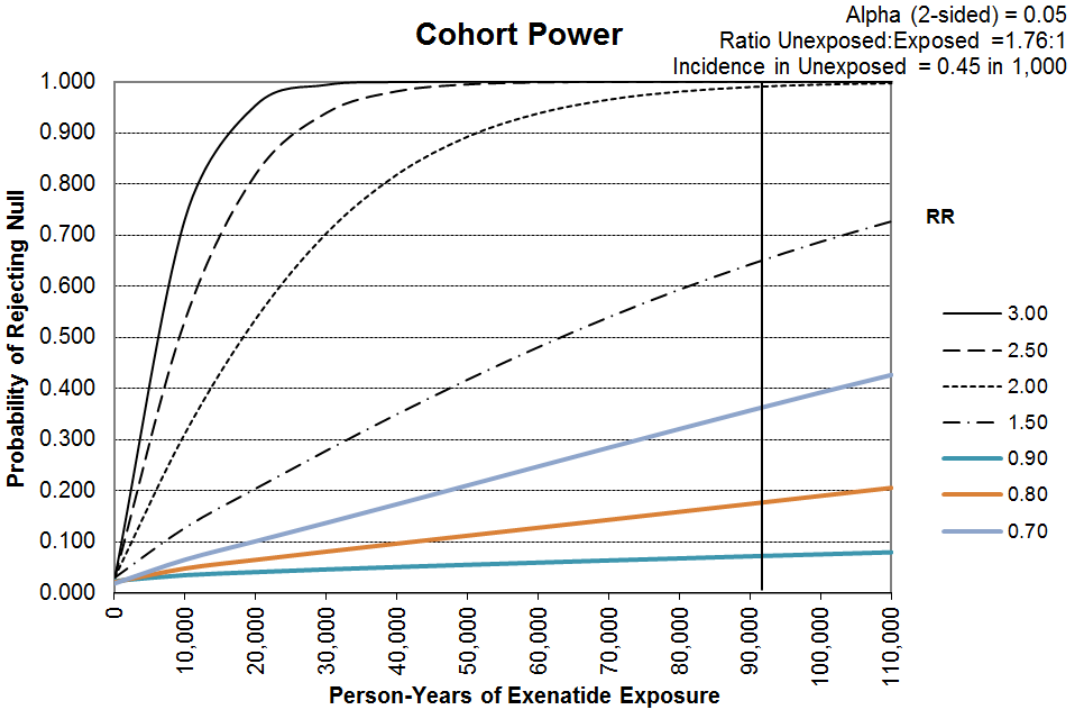
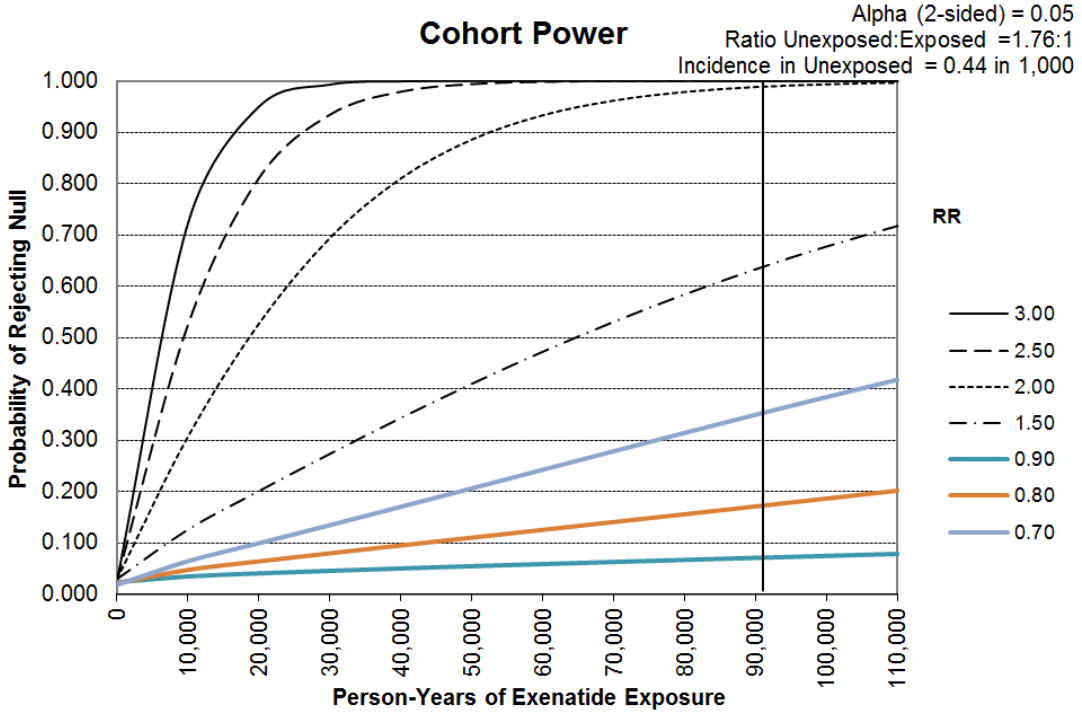


Table E Statistical Power for the Thyroid Cancer Cohort Study



9.7.2 Nested Case-Control Study

Based on the final sample sizes of the nested case-control studies, the study power for the pancreatic cancer analysis is estimated as 80% to detect an RR of 2.0 for a two-sided significance level of 0.05. This calculation uses the observed prevalence of exenatide exposure among controls (24% or 70 of 296 controls) and the number of controls per case (3.4 or 296 controls/86 pancreatic cancer cases). Using the same assumptions with the exception of a control-to-case ratio of 3.6 (296 controls/83 cases) for thyroid cancer, there is also an estimated power of 80% to detect an RR of 2.0. Although conditional logistic regression models were used (conditioned on risk sets), the sample size calculation was based on unmatched cases and controls (as in the study protocol). Power calculations used Dr. Kenneth Rothman's EpiSheet (www.krothman.org) (31, 32).

Table F Statistical Power for the Pancreatic Cancer Nested Case-Control Study

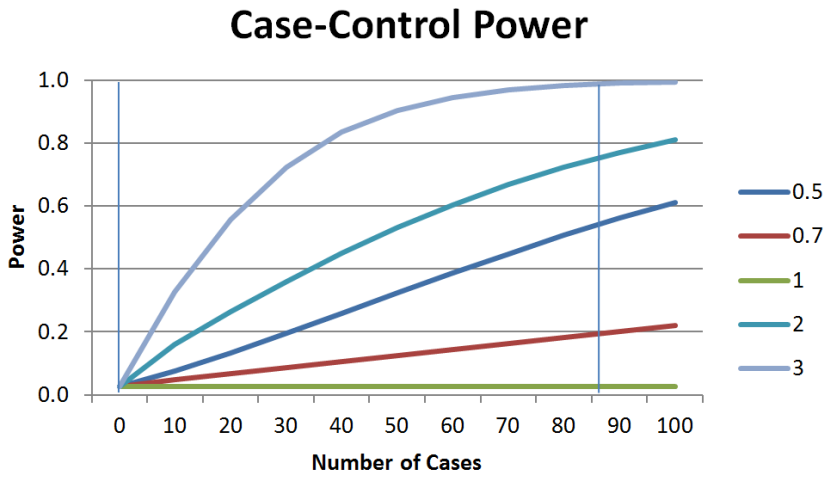
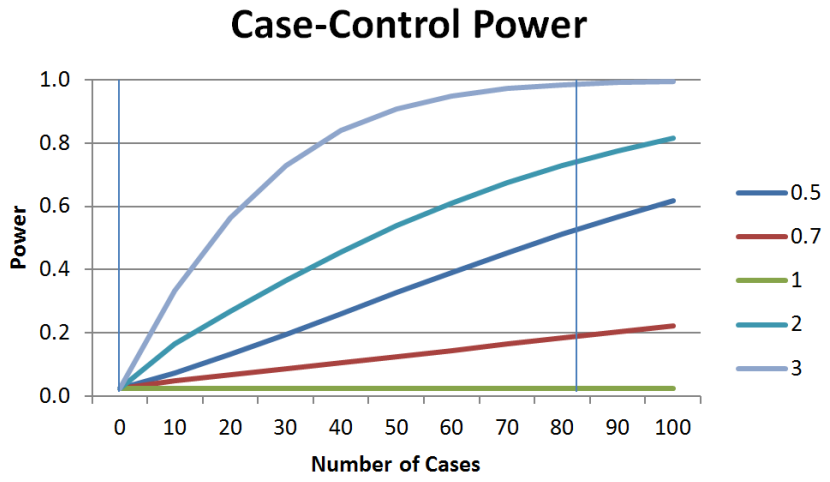


Table G Statistical Power for the Thyroid Cancer Nested Case-Control Study



9.8 Data transformation

Data transformations have been described in section 9.4 (Variables) and 9.9 (Statistical Methods). Combined analyses pooled the ORD and Impact cohorts together, creating one overall exenatide cohort and one overall OAD cohort. The same specifications for variable definitions were followed in each dataset (using a common data model) to pool directly at the patient level. Both databases are owned and operated by Optum, reside within the same firewalls at Optum, and exist in similar formats. All data management and analyses up to the point of the pooled analyses were run in parallel in the ORD and Impact. Any patients included in both the ORD and Impact were de-duplicated prior to pooling.

9.9 Statistical methods

An overview of analyses include the following (see Appendix 7 for a detailed summary):

- Combined person-time from the ORD and the Impact databases:
  - Cohort analysis of pancreatic cancer
  - Cohort analysis of thyroid cancer
  - Cohort analysis of thyroid neoplasm subgroups
  - Sensitivity analyses
- ORD cohorts only:
  - Cohort analysis of pancreatic cancer
  - Cohort analysis of thyroid cancer
  - Nested case-control analysis (malignancies only)
- Impact database cohorts only:
  - Cohort analysis of pancreatic cancer
  - Cohort analysis of thyroid cancer

9.9.1 Main summary measures

Categorical variables were summarized by frequency and percentage and continuous variables by mean and standard deviation or median and interquartile range. Incidence rates (per 1,000 person-years) and corresponding 95% confidence intervals [CIs] were used to summarize the rate of each outcome in follow-up. The RR of each outcome in follow-up was summarized using hazards ratios [HR] and RRs and corresponding 95% CIs. Main analyses were presented for the combined data as well as each database separately. Heterogeneity between databases was tested using an interaction term (exenatide*database indicator) in models of pancreatic and thyroid cancer.

9.9.2 Main statistical methods

9.9.2.1 Positive predictive value and sensitivity of outcome algorithms

PPV was calculated as the number of medical record-confirmed cases (adjudicated as definite or probable) identified by the restricted outcome algorithm divided by the number of total cases identified by the restricted algorithm. There was no restricted algorithm for MTC, therefore the MTC PPV was calculated using the relaxed algorithm.

A measure of sensitivity was calculated as the fraction of cases identified by the restricted algorithm among the medical record-confirmed cases. Because the cases for medical record confirmation were identified using a more sensitive, "relaxed" algorithm (Appendix 4), the medical record-confirmed set provides a reasonable denominator for estimating the sensitivity of the restricted algorithms. This is a conditional sensitivity calculation (conditional on meeting the relaxed algorithm criteria). With these rare outcomes, it is difficult to estimate the number of false negatives from a random sample of the study population. With this modified calculation, sensitivity will be underestimated if the number of medical record-confirmed cases identified by the relaxed but not restricted algorithm (cell c) is greater than the number of false negatives that would have observed among all study patients. Sensitivity would be

overestimated if cell c is less than the number of false negatives that would have been observed among all study patients.

Table H Description of Positive Predictive Value and Sensitivity Calculations Among Cases Identified by the Relaxed Algorithm

		Medical record-confirmed: Yes	Medical record-confirmed: No
Identified by the restricted algorithm	Yes	a	b
	No	c	d
		Total confirmed a+c	Total not confirmed b+d

PPV = a/(a+b)
Sensitivity = a/(a+c)

9.9.2.2 Follow-up

Patients were followed from drug initiation until the end of follow-up, defined as the first occurrence of a study outcome, disenrollment from the health plan, or the end of the study period (30 June 2015 for ORD and 31 March 2015 for Impact). Patients could have had more than one outcome in follow-up (e.g., one pancreatic cancer and one thyroid neoplasm). In this case, follow-up time was calculated separately for each outcome. Person-time for newly diagnosed thyroid cancer was calculated in totality (time to first thyroid outcome) and by neoplasm group (benign tumor and MTC and non-MTC cancers).

At-risk person-time for each outcome was calculated from one-year post drug initiation until the end of follow-up. Person-time within the first year of follow-up was not considered at-risk for the primary analysis as the outcomes occurring during this period were unlikely to be affected by use of the initiated medications given the expected long latency of the outcomes.

Follow-up person-time, starting one-year after drug initiation, was summed and characterized in totality and stratified by duration of follow-up (1 to < 2 years, ≥ 2 to < 3 years, and ≥ 3 years). These categories were pre-defined in the study protocol. Each patient could have contributed to multiple categories of duration of follow-up if they were followed for 2 years or more. For example, if a patient was followed for a total of 5 years, their first year of follow-up was excluded from the main results, they contributed a year of person-time to the category "1 to < 2 years", a year of person-time to the category "≥ 2 to < 3 years", and 2 years of person-time to the category "≥ 3 years".

9.9.2.3 Incidence rate and rate ratio estimation

The number of outcome events and total person-time was summed for each cohort overall as well as by duration of follow-up. IRs were calculated as the number of events occurring at least one year after drug initiation divided by the sum of person-years at risk (excluding the

first year of follow-up). IRs were also calculated separately in subgroups of patients with and without concurrent use of insulins. Concurrent use of insulins and the study exposure (exenatide or OAD) was defined as the use of insulin within 32 days before and after cohort entry. Any insulin use beyond the 32-day window was defined as non-concurrent use.

Kaplan-Meier plots for pancreatic and thyroid cancer were generated to depict the cumulative probability of event-free time among the propensity score matched cohorts. Cox proportional hazards regression models were used to estimate the HRs and 95% CIs of newly diagnosed pancreatic cancer and thyroid neoplasms among exenatide initiators compared with OAD initiators (overall and by duration of follow-up). The Cox models conditioned on the matching ratio (1:1 or 1:2). In analyses using the combined data, the Cox models additionally conditioned on database. Multivariable Cox models adjusted for any variables that were unbalanced after propensity score matching (weighted standardized difference > 0.1 among 1:1 matched patients or 1:2 matched, separately by database).

The main analysis was an "intention-to-treat" or "as matched" analyses (as opposed to the "time-on-drug" or "as treated" analysis described in section 9.9.2.4). This analysis holds the original exposure assignment constant throughout the entire follow-up period.

9.9.2.4 Analysis of cumulative exposure (time-on-drug)

Person-time

Each patient's person-time was classified into different categories of cumulative dose and cumulative duration of study drug use. With this classification, patients could contribute person-time to multiple categories of cumulative dose or duration, according to that patient's actual use. Like the intention-to-treat analysis, cumulative dose and duration were calculated separately for each outcome among patients with multiple outcomes and person-time and outcomes in the first year of follow-up were excluded. However, all study drug dispensings occurring within the first year of follow-up were included in the summations of cumulative dose and duration. For example, cumulative dose included all dispensings in the first year of follow-up and patients taking exenatide every day for the first year of follow-up would contribute their first day of follow-up to the cumulative drug duration category > 1 to < 2 years. Example cumulative dose and duration calculations are described on pages 12 to 14 of the study protocol (20).

Relative risk estimation

Poisson models were used to estimate the RR and 95% CI for each outcome according to cumulative dose and cumulative duration of study drug use. Cumulative dose and duration were treated as time-dependent exposures in the model. With Poisson regression, there is no exact equivalent to stratified Cox models. Instead of stratifying on matching ratio and database indicators (in analyses using the combined data), Poisson models were weighted by matching ratio: exenatide initiators were weighted as one patient, OAD initiators matched 1:1 were weighted as one patient, and OAD initiators matched 1:2 were weighted as 1/2 patient. It is only possible to weight on one factor in Poisson models, therefore a database indicator was included as a covariate in analyses using the combined data.

To address potential residual confounding introduced when patients switch drug regimens during follow-up, the dynamic use of concomitant antidiabetic drugs was captured and treated as time-dependent covariates. Age at time of each switch was also included as a time-dependent covariate in the cumulative exenatide exposure models. In multivariable models, additional covariates that were unbalanced after propensity-score matching were included.

9.9.2.5 Nested case-control study

We conducted a nested case-control study to investigate the potential for residual confounding of the association between exenatide exposure and pancreatic and thyroid cancer by unmeasured confounders that are captured poorly in claims data. These analyses used conditional logistic regression (conditioning on 6-month calendar block) and evaluated risk of pancreatic and thyroid malignancies only. Multivariable logistic regression models included the following medical record-abstracted covariates: BMI, smoking status, alcohol use, systolic blood pressure, hemoglobin A1c, and race. Multivariable logistic regression models also included baseline claims covariates that were potential confounders (risk factors for the outcome, associated with exenatide status, and not on the causal pathway), including age, number of antidiabetic drugs, metformin, pharmacy cost, and number of drugs dispensed. These logistic regression models did not include information on time-to-event or follow-up time, however the resulting odds ratios [ORs] can be interpreted as incidence rate ratios due to the risk set (6-month calendar block) sampling of controls. With this type of control sampling, the control patients represent a random, unbiased sample of the source populations which gave rise to the cases.

9.9.3 Missing values

The main cohort analysis assumed the data was complete and correct (e.g., patients without a diagnosis code did not have that disease, patients without a procedure code did not have that procedure, and patients without a drug dispensing did not have that drug). Some patients had drug claims with missing dose information. In these cases, we used an estimated average dose (see section 9.4.1 for details).

In the nested case-control study, we used multiple imputation to account for missing data on important covariates extracted from medical records (33). Specifically, we used a chained equation approach (fully conditional specification) due to a mix of continuous and categorical abstracted covariates with missing data (34). This approach assumes data are missing at random [MAR] and improves the validity and/or efficiency of analyses of missing data when the MAR assumption holds. The MAR assumption of multiple imputation is less stringent than the missing completely at random assumption of a complete-case analysis (including only patients with complete data) (35).

Although the assumption of MAR is not testable, we have provided a description of the proportion of missing values and patterns of missing variables to better understand whether the MAR assumption is plausible. Also, Collins, Schafer, and Kam (2001) (36) demonstrated that in many realistic cases, a departure from the MAR assumption has only a minor impact on

estimates and standard errors. Finally, multiple imputation estimates standard errors that appropriately account for statistical uncertainty from missing data.

The imputation was based on patterns of non-missing values among variables with missing data. We multiply imputed BMI, smoking status, alcohol status, systolic blood pressure, and hemoglobin A1c when missing. The imputation model included variables most predictive of exenatide initiation, demographics, variables predictive of missingness, and variables correlated with variables to be imputed. In addition, all analytic model covariates (confounders) in the nested case-control study were included in the imputation model. Variables were considered to be confounders and included in the association model if they were predictive of the study outcome and associated with exenatide initiation but not on the causal pathway. We used 10 imputations which created 10 complete datasets with imputed values of BMI, smoking, alcohol, systolic blood pressure, and hemoglobin A1c. The conditional logistic regression association model was run separately within each of the 10 imputed datasets and then combined to produce one pooled estimate.

9.9.4 Sensitivity analyses

Several sensitivity analyses were conducted. First, person-time and events within the first 6 to 12 months after study drug initiation were included to evaluate potential bias introduced by excluding these events from the main analysis. Due to the long latency of pancreatic and thyroid cancer, these events are presumed to be unrelated to the study drug. Second, exenatide and OAD use was stratified by concurrent insulin use and stratum-specific pancreatic and thyroid cancer IRs were calculated. This stratification was performed with the possible association between insulin use and cancer in mind. Third, a nested case-control study was conducted to explore the impact of potential confounding by factors that are not captured well in claims data, such as BMI, smoking, and alcohol use. Fourth, the effects of residual confounding by smoking and obesity on observed RRs were quantified. Finally, adjusted models of cumulative dose and duration were run excluding the time-varying covariates that captured information on switching from exenatide to OAD use in follow-up and age at switch. Estimates of effect were compared with and without these time-varying variables to evaluate whether they could be mediators or colliders.

9.9.5 Amendments to the statistical analysis plan

There were no changes to the statistical analysis plan.

9.10 Quality control

[redacted]

[redacted]

10. RESULTS

10.1 Participants

10.1.1 Cohort Accrual

From 01 June 2005 through 30 June 2015, there were 87,918 patients with at least one dispensing of exenatide and 1,317,475 with at least one dispensing of any other antidiabetic drug in the ORD (Figure 1). After removing patients with less than 9 months of continuous enrollment, with prior use of the initiating drug, with a DPP-4 inhibitor or GLP-1 receptor agonist dispensing, with pancreatic or thyroid neoplasms in the 9-month baseline period, without a diagnosis of T2D during the baseline period, or without at least one OAD dispensing, 45,791 exenatide initiators and 311,047 OAD initiators met the cohort eligibility criteria.

In the Impact database, from 01 June 2005 through 31 March 2015, there were 45,496 patients with at least one dispensing of exenatide and 850,075 with at least one dispensing of any other antidiabetic drug (Figure 2). A total of 24,287 exenatide initiators and 142,616 OAD initiators met the same eligibility criteria.

10.1.2 Matched Cohorts by Propensity Score

Among the 70,078 exenatide initiators and 453,663 OAD initiators who met the study cohort eligibility criteria in the ORD and Impact, 47,946 exenatide initiators were matched to 84,443 OAD initiators (matched 1:1 or 1:2) (Figure 3). Many patients were followed for more than a year including 33,629 exenatide initiators (70%) and 49,317 OAD initiators (58%). Comparing Figures 4a and 4b to Figures 5a and 5b, the distribution of propensity scores after matching was very similar between the exenatide and OAD cohorts.

10.1.3 Nested Case-Control Study Participants

The nested case-control study included 86 confirmed pancreatic cancer cases (adjudicated as definite or probable) and 83 confirmed thyroid cancer cases (Table 1). These cases were matched to 296 controls with medical records. Medical records from a total of 304 controls were received (Table 1), however 8 controls had duplicate abstraction records (records from both the primary and alternate provider were received).

10.2 Descriptive data

10.2.1 Cohort Study

In the ORD, over 60% of patients in each of the matched cohorts were age 50 years or older, about half were female, and more than half were from the South (Table 2.1a). Similarly, over 60% of Impact patients in the matched cohorts were age 50 years or older and half were female, however more than 60% of patients came from the Northeast (Table 2.1b).

Exenatide initiators were matched to OAD initiators within calendar blocks of 6 months to take into account any changes in exenatide prescribing over time. Therefore, propensity score models were customized in an automated fashion for each 6-month calendar block within each database. Tables 2.2a (ORD) and 2.2b (Impact) describe the balance of the 100 most prevalent variables among all propensity score models and all variables forced into the propensity score models (*a priori* variables and variables with the top 10 highest c-statistics). Almost all baseline characteristics were balanced after matching in the ORD, with the exception of number of antidiabetic drugs, metformin use, and pharmacy cost. The only characteristics that remained unbalanced after matching in Impact were the number of antidiabetic drugs and the number of drugs dispensed.

All baseline malignancies were balanced among matched patients, with a weighted standardized difference less than 0.1 (Table 2.2.1a in ORD and 2.2.1b in Impact). In the matched cohorts, about 2-3% of patients had a personal history of malignant neoplasm and the most common cancers were colon, skin, breast, and prostate.

More than 50% of exenatide and OAD initiators had at least one antidiabetic medication within 45 days of cohort entry, and the majority, about 40%, had 6-10 unique drugs dispensed (Table 2.3a in ORD and 2.3b in Impact). In both databases, exenatide initiators tended to have more unique drugs dispensed and more diabetes drug dispensings in baseline compared to OAD initiators: a median of 7 diabetes drug dispensings among exenatide initiators and 6 among OAD initiators. Median pharmacy costs were somewhat higher among exenatide initiators compared to OAD initiators and slightly more exenatide initiators used metformin compared to OAD initiators in both databases.

Tables 2.4a in ORD and 2.4b in Impact display characteristics of the matched cohorts stratified by duration of follow-up. All characteristics were balanced within strata of 1 to < 2 years follow-up, 2 to < 3 years follow-up, and 3 or more years follow-up (weighted standardized difference < 0.1). Tables 3.1a in ORD and 3.1b in Impact describe the top 200 most frequently recorded diagnoses during the 9-month baseline period in the claims data amongst all matched and unmatched exenatide and OAD initiators. Besides diabetes, these included disorders of lipoid metabolism, hypertension, general symptoms, respiratory symptoms, screening for malignant neoplasms, and overweight. Tables 3.2a and 3.2b include the top 200 most common baseline procedures which were office visits, hemoglobin A1c measurement, and lipid panels. Tables 3.3a and 3.3b list the top 200 drugs dispensed among exenatide and OAD initiators. These included hypoglycemics, lipotropics, and hypotensives.

10.2.2 Nested Case-Control Study

Tables 4.1 (pancreatic cancer) and 4.2 (thyroid cancer) present medical record-derived characteristics of nested case-control study patients. Overall, race, smoking status, alcohol use, and hemoglobin A1c were similar between exenatide and OAD initiators with pancreatic cancer. However, among pancreatic cancer cases, exenatide initiators tended to have a lower BMI and lower blood pressure compared to OAD initiators. Race, alcohol use, blood pressure, and hemoglobin A1c were similar between exenatide and OAD initiators with thyroid cancer; however, exenatide initiators were more likely to be obese, less likely to smoke, and more likely to have a history of thyroid disease compared to OAD initiators. Exenatide and OAD controls were similar overall with the exception that exenatide controls tended to have a higher BMI and were less likely to smoke compared to OAD controls.

Tables 5.1 (pancreatic cancer) and 5.2 (thyroid cancer) compare claims-derived characteristics between cases and controls. Pancreatic cancer cases were more likely to be male compared to controls whereas thyroid cancer cases were more likely to be female. Pancreatic cancer cases tended to have more pancreas-related procedures in baseline compared to controls including the measurement of amylase and endoscopic retrograde cholangiopancreatography. Similarly, thyroid cancer cases tended to have more thyroid procedures in baseline than controls including measurement of thyrotropin releasing hormone, T3 and T4 testing, thyroid imaging, ultrasound of the head and neck, thyroid biopsy, and thyroid operations.

10.3 Outcome data

10.3.1 Medical Review and Assessment of Algorithm Performance

Table 1 presents data on the medical records identified, sought, and retrieved from the ORD for validation of pancreatic cancer, thyroid cancer, and benign thyroid neoplasm. A total of 185 pancreatic cancer cases, 129 thyroid cancer cases, and 92 benign thyroid neoplasm cases were identified using the relaxed algorithm in the study population prior to matching. Medical records were sought for the majority of patients, with no primary or alternate providers identified for 9 pancreatic cancer cases and one benign thyroid neoplasm case. Among medical records sought, 299 of 396 (76%) case medical records were received and among all medical records received, 226 of 299 (76%) cases were confirmed (cases adjudicated as definite or probable). All pancreatic and thyroid cancer cases identified in the claims data were matched to 464 controls for the nested case-control study. Primary and alternate providers were identified for all controls and 66% of control medical records were received.

Table 6.1 presents the PPV for each algorithm overall (2005 to 2015) as well as separately by the previous study period (2005 to 2010) and the extension period (2010 to 2015). Overall PPVs ranged from 78% to 97% for pancreatic cancer, thyroid cancer, non-MTC, MTC, and benign thyroid neoplasm. Comparing the extension period to the previous study period, PPVs were lower for pancreatic (77% vs. 88%) and thyroid cancer (87% vs. 95%).

A measure of sensitivity was calculated as the fraction of cases identified by the restricted algorithm among the medical record-confirmed cases. This estimated sensitivity ranged from 68% to 86% for pancreatic cancer, thyroid cancer, and non-MTC, but was much lower for

benign thyroid neoplasm (36%, 95% CI 26% to 48%). Sensitivity was generally higher in the extension period compared to the previous study period (72% vs. 54% for pancreatic cancer and 86% vs. 69% for thyroid cancer).

Table 6.2 compares matched exenatide initiators to OAD initiators by type of pancreatic disease and pancreatic diagnostic procedures in follow-up. The purpose of this stratification was to evaluate the potential for detection bias in follow-up. A few diagnostic procedures were more common among exenatide initiators compared to OAD initiators, including lipase and amylase measurement, abdominal ultrasound, and abdominal pain. Before the BYETTA pancreatitis warning label was added in October 2007, the prevalence of diagnostic procedures was balanced between exenatide and OAD initiators. Table 6.3 presents the same comparison for thyroid cancer. Similarly, thyrotropin releasing hormone measurement, T3 and T4 testing, thyroid imaging, and ultrasound of the head and neck were more common in exenatide initiators compared to OAD initiators in follow-up. Although there was a small degree of imbalance in thyroid diagnostic procedures before the first two articles were published linking exenatide to MTC in rodents in March 2010, the relative degree of imbalance was greater afterwards. The MTC warning was included on the BYDUREON label when it was first approved in January 2012, near the end of the study period.

10.4 Main results

10.4.1 Pancreatic cancer

10.4.1.1 Time-Fixed Analysis

A total of 75 pancreatic cancers were identified (after the first year of follow-up) in the combined database using the restricted algorithms (Table 7). Compared to OAD cases, exenatide cases had a slightly shorter median cumulative duration of drug use at the time of case diagnosis (1.1 years among exenatide cases and 1.4 years among OAD cases). Overall pancreatic cancer IRs were 0.34 (95% CI 0.23 to 0.48) per 1,000 persons per year in the exenatide cohort and 0.45 (95% CI 0.32 to 0.60) in the OAD cohort. In the combined database, pancreatic cancer incidence rates were lower in exenatide initiators compared to OAD initiators in 1 to < 3 years, and similar in ≥ 3 years of follow-up, however all IR 95% CIs overlapped. The same was true within the ORD and Impact separately.

The overall HR for pancreatic cancer among patients with more than one year of follow-up in the combined database was 0.77 (95% CI 0.48 to 1.24) comparing exenatide initiators to propensity score-matched OAD initiators. After adjusting for covariates that were unbalanced after propensity-score matching (number of antidiabetic drugs, metformin, pharmacy cost, and number of drugs dispensed), the adjusted HR was 0.76 (95% CI 0.47 to 1.21). No crude or adjusted HRs were statistically significant within strata of duration of follow-up or database. The proportional hazards assumption was verified for the Cox models presented in Table 7 and in all Cox models presented in this report.

The results were generally similar in both OAD and Impact databases, although the HR for pancreatic cancer was slightly lower in the Impact database compared to the ORD. There was no statistically significant heterogeneity by database: p-values 0.46 for overall follow-up, 0.54

for > 1 to < 2 years follow-up, 0.80 for ≥ 2 to < 3 years follow-up, and 0.85 for ≥ 3 years follow-up.

The Kaplan-Meier plot of survival time to incidence of pancreatic cancer (Figure 6), including events and person-time in the first year of follow-up, shows a separation of the exenatide and OAD survival curve 95% CI bands between zero and 6 months of follow-up and 2-3 years of follow-up. In these 2 time periods, the probability of pancreatic cancer was higher among OAD users compared to matched exenatide users.

10.4.1.2 Time-Dependent Analysis

Table 8 presents an analysis of cumulative exenatide duration in the combined database. The adjusted models included all unbalanced propensity score variables (number of antidiabetic drugs, metformin, pharmacy cost, and number of drugs dispensed) as well as time-varying indicators for switching to each of the 7 types of OADs during follow-up among exenatide initiators and age at the time of switch (see Appendix 3 for a list of OAD drugs). Compared to non-use, there were no clear trends in pancreatic cancer IRs or HRs across categories of cumulative exenatide duration. Comparing each category of cumulative exenatide duration to the same duration of OAD use, there was no apparent trend in pancreatic cancer IRs or HRs across categories of cumulative drug duration (Table 8.1). Finally, looking within OAD initiators only, there appeared to be no trend in IRs or HRs across different categories of cumulative OAD duration (Table 8.2). Median cumulative drug duration was about one year for exenatide initiators and about 1.3 years for OAD initiators (Figures 7-12).

There were no statistically significant trends in pancreatic cancer IRs or HRs across categories of cumulative exenatide dose (≤ 1,500 mcg, > 1,500 to 6,325 mcg, and > 6,325 mcg) compared to non-use (Table 9). BYETTA is typically administered as 10 mcg twice daily and BYDUREON 2mg (2,000 mcg) injected once weekly, however due to differing bioavailability, BYDUREON was presumed equivalent to BYETTA 10 mcg twice daily (3, 4). Table 9.1 presents pancreatic cancer IRs and HRs within tertiles of cumulative exenatide and OAD dose. Likewise, there was no apparent trend across tertiles of cumulative exenatide and OAD dose. Within the OAD cohort separately, there were no clear trends comparing tertiles 2 and 3 of cumulative OAD dose to tertile 1 (Table 9.2).

10.4.2 Thyroid cancer

10.4.2.1 Time-fixed Analysis

One hundred thyroid cancer cases were identified in the combined database using the restricted algorithms, excluding events in the first year of follow-up (Table 10). Thyroid cancer IRs were somewhat higher in the exenatide cohort compared to the OAD cohort: 0.62 (95% CI 0.47 to 0.81) per 1,000 persons per year and 0.44 (95% CI 0.32 to 0.59), respectively, however the 95% CIs overlapped substantially. There were no obvious IR trends across duration of follow-up in the combined or individual databases. Overall, exenatide cases had a somewhat shorter median cumulative duration of drug use at the time of case diagnosis (0.8 years) compared to OAD cases (1.1 years).

The overall HR for thyroid cancer among patients with one or more years of follow-up was 1.46 (95% CI 0.97 to 2.18) comparing exenatide initiators to OAD initiators in the combined dataset. After adjusting for unbalanced propensity score variables, the adjusted HR was 1.46 (95% CI 0.98 to 2.19). In the ORD, among patients with more than one year of follow-up, exenatide use was associated with a statistically significant increased risk of thyroid cancer compared to OAD use: crude HR 1.78 (95% CI 1.06 to 2.97) and adjusted HR 1.78 (95% CI 1.06 to 2.99). In Impact, the overall HR among patients with more than one year of follow-up was 1.05 (95% CI 0.54 to 2.01) and adjusted HR 1.05 (95% CI 0.54 to 2.04) indicating no association between exenatide use and risk of thyroid cancer. No other stratum-specific HRs were statistically significant and there was complete overlap of thyroid cancer-free survival time 95% CI bands for exenatide and matched OAD initiators during the entire follow-up period (Figure 13), indicating a similar survival probability of thyroid cancer in the two cohorts. There was no statistically significant heterogeneity by database: p-values 0.22 for overall follow-up, 0.10 for > 1 to < 2 years follow-up, 0.90 for ≥ 2 to < 3 years follow-up, and 0.77 for ≥ 3 years follow-up.

10.4.2.2 Time-Dependent Analysis

An analysis of cumulative duration of exenatide use and risk of thyroid cancer in the combined database is presented in Tables 11, 11.1, and 11.2. Compared to non-use, there were no clear trends in thyroid cancer IRs or HRs across categories of cumulative duration of exenatide use (Table 11). However, there were few events among exenatide initiators with a cumulative duration greater than one year. Similarly, there were no observed IR or HR trends across categories of cumulative exenatide duration compared to the same duration of OAD use (Table 11.1). Looking across categories of cumulative duration of OAD use separately, there was a suggestion of a possible stronger inverse association between cumulative duration of OAD use and risk of thyroid cancer with shorter compared to longer OAD use, however no HRs were statistically significant (Table 11.2).

No trends in thyroid cancer IRs or HRs were observed across categories of cumulative exenatide dose (versus non-use) (Table 12). Median cumulative drug duration was about one year for exenatide initiators and about 1.3 years for OAD initiators (Figures 14-19). Likewise, there were no trends across tertiles of cumulative exenatide and OAD dose (Table 12.1) or across tertiles of cumulative OAD dose separately (Table 12.2).

10.5 Other analyses

10.5.1 Pancreatic cancer

10.5.1.1 Including Events and Person-Time in the First Year of Follow-Up

In a sensitivity analysis that included person-time and events within the first 6 to 12 months of follow-up, the overall HR for pancreatic cancer among patients with 6 or more months of follow-up was 0.70 (95% CI 0.47 to 1.05) for exenatide initiators compared to OAD initiators in the combined database (Table 7.1). After adjusting for unbalanced propensity score variables, the HR was 0.69 (95% CI 0.46 to 1.03). In addition, IRs were highest among

exenatide and OAD initiators in the first 6 to 12 months of follow-up. Median follow-up time was about two years for exenatide initiators (Table 7.2, Figures 20-22).

10.5.1.2 Concurrent Insulin Use

Pancreatic cancer IRs were similar among exenatide initiators with vs. without concurrent use of insulins in the combined database: IRs were 0.3 per 1,000 persons per year among exenatide initiators with concurrent insulin use and 0.4 among exenatide initiators without concurrent insulin use (Table 13). Likewise, IRs were similar among OAD initiators with vs. without concurrent use of insulin (0.5 and 0.4 per 1,000 persons per year, respectively).

10.5.1.3 Nested case-control study

In unadjusted logistic regression models, exenatide use was associated with a lower risk of pancreatic cancer compared to OAD use, RR 0.17 (95% CI 0.06 to 0.50) (Table 14). In multiply imputed models that adjusted for medical record-derived (BMI, smoking, alcohol, systolic blood pressure, hemoglobin A1c, and race) and frequency matching factors (age, gender, visit type on index (in- or outpatient), number of inpatient visits in 6-month calendar period (risk set), and number of outpatient visits in 6-month calendar period), the RR of pancreatic cancer for exenatide use compared to OAD use was attenuated but still statistically significant: 0.48 (95% CI 0.25 to 0.91). When we additionally adjusted for some claims-derived characteristics that were unbalanced between cases and controls, that were associated with exenatide exposure, that were not on the causal pathway, and that had a moderate-to-high prevalence among controls, including number of antidiabetic drugs, pharmacy cost, and blood sugar diagnostics, the adjusted RR was similar (RR 0.44, 95% CI 0.22 to 0.88, data not shown).

10.5.1.4 Residual Confounding Analysis

Figures 23 and 24 explore residual confounding of the association between exenatide use and pancreatic cancer by smoking and obesity. These figures display the observed pancreatic cancer HR (apparent relative risk or ARR) plotted against associations between the exposure and confounder (OR_{EC}) and associations between the confounder and the outcome (RR_{CD}) of varying strength. The area to the upper right of the curve represents combinations of the OR_{EC} and RR_{CD} required to produce an ARR as or more extreme given the true association between exenatide and pancreatic cancer is null. Combinations to the lower left of the curve are not sufficient to fully explain the ARR.

In Figure 23, the green line represents the observed prevalence of current smoking (medical record-derived) among nested case-control study controls, 21% (Table 4.1). The blue line represents a smoking prevalence of 15% and the purple line a prevalence of 25%. Based on the observed current smoking prevalence (green line), the OR_{EC} and RR_{CD} would have to be quite strong to explain the observed adjusted HR of 0.76 if the true HR was 1.0. For example, exenatide users would need to be less than half as likely to smoke compared to non-users and smoking would need to be associated with at least a 6 times higher RR of pancreatic cancer. The red dot represents the observed association between exenatide and current smoking using medical record-abstracted data among controls, OR 0.26 (3 exenatide controls currently

smoking (a), 36 exenatide controls not currently smoking (b), 34 OAD controls currently smoking (c), 106 OAD controls not currently smoking (d), OR = (a*d)/(b*c) = (3*106)/(36*34), Table 4.1) and the observed association between smoking and pancreatic cancer in the literature, RR 1.7 for current versus never smoking (37, 38). Therefore, it is unlikely that residual confounding by smoking explains the observed association between exenatide use and pancreatic cancer.

In Figure 24, the green line represents the observed prevalence of obesity (medical record-derived) among nested case-control study controls, 75% (Table 4.1). Regardless of RR_{CD}, exenatide users would have had to have less than half the odds of obesity compared to non-users to explain the ARR. The red dot represents observed associations. Exenatide controls were actually more than twice as likely to be obese compared to OAD controls in the nested case-control study, OR 2.65 (Table 4.1). In the literature, obese ($\geq$ 30 kg/m^2) individuals have 2.08 times the odds of pancreatic cancer compared to non-obese individuals (< 25 kg/m^2) (39). Therefore, residual confounding by obesity alone is unlikely to explain the observed HR of 0.76 for pancreatic cancer comparing exenatide initiators to OAD initiators.

10.5.2 Thyroid cancer

10.5.2.1 Including Events and Person-Time in the First Year of Follow-Up

Table 10.1 presents results from a sensitivity analysis including events and person-time within the first 6 to 12 months of follow-up. Thyroid cancer IRs were highest among exenatide and OAD initiators within 6 to 12 months after initiating the study drug. Overall, including events and person-time in the first 6 to 12 months of follow-up, the crude HR for thyroid cancer comparing exenatide to OAD initiators was 1.35 (95% CI 0.96 to 1.92) and adjusted HR 1.36 (95% CI 0.96 to 1.94) in the combined database. No HRs were statistically significant for any strata of duration of follow-up. Median follow-up time was about two years for exenatide initiators (Table 10.2, Figures 25-27).

10.5.2.2 Concurrent Insulin Use

In the combined database, thyroid cancer IRs were the same among exenatide initiators with vs. without concurrent insulin use: 0.6 per 1,000 persons per year (Table 13). Likewise, IRs were similar among OAD initiators with vs. without concurrent use of insulin (0.5 and 0.4 per 1,000 persons per year, respectively).

10.5.2.3 Nested case-control study

Compared to OAD use, exenatide use was not associated with risk of thyroid cancer in crude (RR 0.74, 95% CI 0.37 to 1.50) or adjusted (RR 0.87, 95% CI 0.59 to 1.29) models. Additional adjustment for some claims-derived covariates, including number of antidiabetic drugs, TZDs, thyrotropin releasing hormone, and T3/T4 testing did not materially change the RR (RR 0.92, 95% CI 0.60 to 1.40, data not shown).

10.5.2.4 Residual Confounding Analysis

Figures 28 and 29 explore residual confounding of the association between exenatide use and risk of thyroid cancer by smoking and obesity. In Figure 28, the green line represents the observed prevalence of current smoking (medical record-derived) among nested case-control study controls, 21% (Table 4.1). The blue line represents a smoking prevalence of 15% and the purple line a prevalence of 25%. Based on the observed current smoking prevalence (green line), the OR_{EC} (association between exenatide and smoking) and RR_{CD} (association between smoking and thyroid cancer) would have to be quite strong to explain the observed adjusted HR of 0.76 if the true HR was 1.0. For example, exenatide users would need to be at least 4 times as likely to smoke compared to non-users and smoking would need to be associated with at least 4 times the risk of thyroid cancer. The red dot represents the observed association between exenatide and current smoking using medical record-abstracted data among controls, OR 0.26 (Table 4.1) and the observed association between smoking and thyroid cancer in the literature, OR 0.75 for ever versus never smoking (40). Therefore, it is unlikely that residual confounding by smoking explains the observed association between exenatide use and thyroid cancer.

Figure 29 shows that the OR_{EC} and RR_{CD} for obesity would have to be extremely strong to explain the observed association between exenatide use and thyroid cancer. The red dot represents the observed associations between exenatide use and obesity in the nested case-control study, OR 2.65 (Table 4.1), and between obesity and thyroid cancer in the literature, OR 1.50 comparing obese ($\geq$ 30 kg/m^2) to non-obese ($<$ 25 kg/m^2) individuals (41). Therefore, residual confounding by obesity alone is unlikely to explain the observed HR of 1.46 for thyroid cancer comparing exenatide initiators to OAD initiators.

10.5.2.5 Subtypes of Thyroid Neoplasms

Table 15 presents IRs for thyroid neoplasm subtypes in the combined database, excluding events and person-time within the first year of follow-up. A total of 22 patients had benign thyroid neoplasm in follow-up, 5 patients had MTC, and 95 patients had non-MTC. Benign thyroid neoplasm IRs were similar for exenatide and OAD initiators, 0.12 per 1,000 persons per year and 0.11, respectively. Medullary thyroid cancer IRs were 0.02 per 1,000 persons per year among exenatide initiators and 0.03 among OAD initiators. Non-medullary thyroid cancer incidence rates were somewhat higher among exenatide compared to OAD initiators, but the 95% CIs overlapped: 0.60 (95% CI 0.45 to 0.78) per 1,000 persons per year in the exenatide cohort and 0.41 (95% CI 0.29 to 0.55) in the OAD cohort.

10.6 Adverse events/adverse reactions

No adverse events were reported (planned or unplanned) during this study.

11. DISCUSSION

11.1 Key results

This retrospective cohort study sought to quantify the incidence and risk of pancreatic cancer and thyroid neoplasms among new users of exenatide, a GLP-1 receptor agonist, compared to propensity score-matched new users of other antidiabetic medications. The matched cohorts included a total of 47,946 exenatide initiators and 84,443 OAD initiators. Baseline characteristics, including gender, age, and cohort entry date as well as baseline diagnoses, procedures and medication use were generally balanced between the cohorts. Complementary nested case-control studies of pancreatic and thyroid malignancy were conducted to explore the effect of residual confounding by patient characteristics that are poorly captured in claims data.

11.1.1 Findings for Pancreatic Cancer

11.1.1.1 Cohort Study

Compared to OAD use, exenatide use was associated with a non-statistically significant lower risk of pancreatic cancer in the time-fixed cohort analysis: adjusted HR 0.76 (95% CI 0.47 to 1.21), excluding events and person-time in the first year of follow-up. When events and person-time in the first 6 to 12 months of follow-up were included as a sensitivity analysis, assuming these events were unlikely to have been caused by the study drug due to the long latency of pancreatic cancer, HRs were similar within strata of 6 to 12 months of follow-up vs. > 1 to 2 years of follow-up.

The pancreatic cancer incidence rate was slightly higher in the ORD compared to the Impact database, however there were fewer cases and fewer patients in the Impact population and the 95% confidence intervals from the two databases overlapped. Pancreatic cancer incidence rates were highest in the first 6 to 12 months of follow-up yet IR 95% CIs overlapped for all strata of follow-up time. Although the study drug was not the first antidiabetic drug initiated by patients, these results are similar to those reported in the literature indicating higher rates of cancer within the first year after initiating glucose-lowering drugs. This short-term elevated risk of cancer observed in the literature among patients newly diagnosed with or treated for diabetes may be due to protopathic bias, reverse causality, or detection bias (42). For example, declining glucose control is a symptom of some forms of pancreatic cancer (43, 44) that may lead to modification of antidiabetic drug regimens to help control worsening symptoms, such as switching to exenatide, other GLP-1 receptor agonists, or DPP-4 inhibitors. By excluding events and person-time in the first year of follow-up from our main analyses, we minimized this particular bias. However, it is possible that a one-year exclusion may be too short given the long latency period for pancreatic and thyroid cancer.

Seventy percent (33,629 of 47,946) of exenatide initiators had more than one year of follow-up compared to 58% (49,317 of 84,443) of OAD initiators. This suggests that the exenatide cohort may have had a greater opportunity to develop pancreatic cancer due to longer overall follow-up, however, the time-to-event analysis accounts for this through risk-set formation.

When the main results were stratified by duration of follow-up, adjusted HRs were closer to the null among patients with longer duration of follow-up: HR 0.54 (95% CI 0.23 to 1.30) for > 1 to < 2 years of follow-up, HR 0.66 (95% CI 0.24 to 1.85) for ≥ 2 to < 3 years of follow-up, and HR 1.02 (95% CI 0.51 to 2.06) for ≥ 3 years of follow-up, yet all 95% CIs overlapped substantially for these three strata.

No trends were observed in the time-varying analysis across categories of either cumulative exenatide duration or dose. Importantly, we assumed that the time-dependent covariates (age and OAD use) were not mediators or colliders in the time-on-drug analyses; otherwise, the estimates could be biased (45). We expect that this assumption holds for age. While age is associated with exenatide use and pancreatic or thyroid cancer, it is not on the causal pathway between exenatide and these outcomes. Age is not a collider because both exenatide and cancers do not directly cause increased age. Regarding OAD use as a collider, the use of exenatide may cause concomitant use of OADs, but the development of cancers is less likely to cause concomitant use of OADs (with the possible exception of protopathic effects of pancreatic cancer). Therefore, collider bias (e.g., selection bias) was not anticipated.

To evaluate the possibility that time-varying OAD use was a mediator, we additionally ran models with and without this variable. Changes in the effect estimates toward the null could indicate confounding or OAD-mediation (e.g., that conditioning on the mediator blocks a portion of the causal path between exenatide exposure and pancreatic cancer). In the combined database, the adjusted HRs for pancreatic cancer with versus without adjusting for time-varying OAD use were 0.84 versus 0.77 for patients with less than one year of cumulative exenatide duration compared to non-use, 0.67 versus 0.60 for one to < 2 years of cumulative exenatide duration, 1.09 versus 0.97 for 2 to < 3 years cumulative exenatide duration, and 0.89 versus 0.78 for 3 or more years of cumulative exenatide duration. Comparing models of pancreatic cancer and cumulative exenatide dose in the combined database, HRs with and without adjustment were 0.63 versus 0.57 for patients with a cumulative exenatide dose of 1,500 mcg or less, 0.86 versus 0.78 for a cumulative exenatide dose of 1,501 to 6,325 mcg, and 0.99 versus 0.88 for a cumulative exenatide dose greater than 6,325 mcg (data not shown). Overall, the difference in effect estimates with and without adjustment was minimal and therefore time-varying OAD use is unlikely to be a mediator.

11.1.1.2 Nested Case-Control Study

In a nested case-control study that additionally adjusted for BMI, smoking, alcohol, systolic blood pressure, hemoglobin A1c, and race, the inverse association between exenatide use and risk of pancreatic cancer was statistically significant: RR 0.48 (95% CI 0.25 to 0.91). This finding could indicate that residual confounding by factors poorly captured in claims data biased our main cohort results to the null. However, due to the relatively small number of cases, we were unable to include all unbalanced medical record- and claims-derived variables in the adjusted nested case-control study models and it is possible that residual confounding remained. A general rule-of-thumb of good statistics practice is to require about 10 events for each additional covariate to risk over-fitting a regression model (46). With 86 pancreatic cancers and 83 thyroid cancers, we were limited to about 8 covariates.

Furthermore, we were unable to adjust for some important pancreatic cancer risk factors such as liver cirrhosis, and family history. This information was more often observed in case medical records, as expected, and often not discussed in control records. Finally, although the multiple imputation assumption of MAR is not testable, we have provided a description of the proportion of missing values and patterns of missing variables in Table 4.1 to better understand whether the MAR assumption is plausible. Without multiple imputation, too few patients had complete data on all covariates to compute stable adjusted RRs using the complete case method.

11.1.2 Findings for Thyroid Cancer

11.1.2.1 Cohort Study

In the time-fixed cohort analysis, exenatide initiators had a non-statistically significant increased risk of thyroid cancer compared to OAD initiators: adjusted HR 1.46 (95% CI 0.98 to 2.19), excluding events and person-time in the first year of follow-up. However, this positive association was only present in ORD patients (adjusted HR 1.78, 95% CI 1.06 to 2.99) and not in Impact patients (adjusted HR 1.05, 95% CI 0.54 to 2.04). Very few observed cases were MTC therefore our results apply primarily to non-MTC.

In the time-varying analysis, there were no clear trends across categories of cumulative exenatide duration or dose. If an association between exenatide and thyroid cancer were to exist, we might expect to see stronger associations with longer cumulative duration of exenatide use due to the long latency of cancer. If a dose-response relationship between exenatide and thyroid cancer were to exist, we would expect to see stronger associations within strata of higher cumulative dose. However, a non-dose response relationship does not rule out causality as some exposures have a threshold effect where a minimum exposure is sufficient to cause a disease.

Cumulative duration analyses ignored information on cumulative dose and vice versa. For example, patients taking low dose Byetta would take twice as long (twice the cumulative duration) to reach a particular cumulative dose compared to patients taking high dose BYETTA. However, the two measures are not independent: duration of use is partly captured in the cumulative dose analyses, assuming that patients in the highest cumulative dose category tended to have a longer cumulative duration of use. Similarly, patients with longer cumulative duration of use are likely to have higher total cumulative doses.

To evaluate the possibility that time-varying OAD use was a mediator, we additionally ran time-on-drug models with and without adjustment for time-varying OAD. In the combined database, the adjusted HRs for thyroid cancer with versus without adjusting for time-varying OAD and age were 1.53 versus 1.53 for patients with less than one year of cumulative exenatide duration compared to non-use, 1.09 versus 1.10 for one to < 2 years of cumulative exenatide duration, 1.66 versus 1.67 for 2 to < 3 years cumulative exenatide duration, and 0.72 versus 0.74 for 3 or more years of cumulative exenatide duration. Therefore, there appeared to be little confounding or mediation of the association between cumulative exenatide duration and risk of thyroid cancer by time-varying OAD and age. The same was true for cumulative

exenatide dose: in the combined database, HRs with and without adjustment were 1.59 versus 1.57 for patients with a cumulative exenatide dose of 1,500 mcg or less, 1.28 versus 1.29 for a cumulative exenatide dose of 1,501 to 6,325 mcg, and 1.16 versus 1.15 for a cumulative exenatide dose greater than 6,325 mcg (data not shown).

11.1.2.2 Nested Case-Control Study

In contrast, in the nested case-control study within a subset of ORD patients, exenatide use was not associated with risk of thyroid cancer: adjusted RR 0.87 (95% CI 0.59 to 1.29). This could indicate that the main study results were biased due to residual confounding by factors that are poorly captured in claims data. However, we were unable to adjust the nested case-control study analysis for some other important thyroid cancer risk factors that are poorly captured in claims data due to limited data abstraction, especially among controls, such as a low iodine diet, radiation exposure, and family history. Furthermore, it is possible that residual confounding may bias the nested case-control study results as the adjusted models were limited to a short list of covariates due to the relatively small number of outcomes. Although it is impossible to test the multiple imputation assumption of MAR in the nested case-control study, the proportion of missing values and patterns of missing variables (Table 4.2) does not suggest that this assumption is false.

Cases in the nested case-control study overlapped substantially with those included in the cohort study, however the nested case-control study included additional patients who were not matched in the cohort study and excluded cases that were not confirmed by medical record review. The nested case-control study included cases in the first year following drug initiation whereas the cohort study excluded these cases. The cumulative exenatide and OAD duration of cases in the cohort study is expected to be similar to that of cases in the nested case-control study. Since the control patients in the nested case-control study were randomly sampled, we expect them to be representative of the case source population in terms of cumulative duration of drug use and duration of follow-up.

11.1.3 Other Literature

Few epidemiology studies have examined the association between GLP-1 receptor agonists and risk of pancreatic or thyroid cancer. Despite a potential signal of disproportionate adverse pancreatic events among exenatide users (47), two studies using claims data reported no association between exenatide use and risk of pancreatic cancer (16, 17) and a third found no association between liraglutide use compared to use of other antidiabetic therapies and pancreatic cancer (18). To date, clinical studies show no increased risk of thyroid malignancy with liraglutide or exenatide use (12-14), however cases of MTC have been reported during post-approval use of liraglutide (15).

11.2 Strengths

With more than 30,000 exenatide initiators matched to more than 50,000 OAD initiators in the cohort study and close to 200,000 person-years of follow-up, we had acceptable statistical precision despite the rarity of pancreatic and thyroid cancers. Using propensity score matching, we were able to successfully balance exenatide and OAD initiators at the beginning

of follow-up on a wide range of potential confounders. Balance remained at the beginning of each category of follow-up time (e.g., 1 to < 2 years, ≥ 2 to < 3 years). Detailed prescription data provided the opportunity to additionally examine cumulative exenatide dose and duration in relation to cancer risk. Clinician adjudicated medical records revealed good validity of the pancreatic and thyroid cancer algorithms used in the cohort study. Medical records additionally provided data on important risk factors that are not adequately captured in claims data and these additional risk factors were adjusted for in the nested case-control studies which were limited to clinician verified pancreatic and thyroid cancers. Both the cohort and nested case-control studies were adequately powered for these rare outcomes.

11.3 Limitations

11.3.1 General Limitations of Using Claims Data

This study is based on an analysis of automated medical and prescription claims, supplemented by information abstracted from the medical records of a subset of patients. While claims data are extremely valuable for the efficient and effective examination of health care outcomes, treatment patterns, health care resource utilization, and costs, all claims databases have certain inherent limitations because the claims are collected for the purpose of payment and not research. Presence of a claim for a filled prescription does not indicate that the medication was consumed or that it was taken as prescribed. Medications filled over the counter or provided as samples by the physician will not be observed in the claims data. Presence of a diagnosis code on a medical claim is not indicative of the positive presence of disease, as the diagnosis code may be incorrectly coded or included as rule-out criteria rather than actual disease.

11.3.2 Nested Case-Control Study Patient Selection

Controls were selected and frequency matched to cases identified by the relaxed algorithms. Some of these cases were not included in the nested-case control study if medical records were not received or if the case was not confirmed. All controls with medical records were retained in the analysis as long as they were from a 6-month calendar block that included a confirmed case, otherwise they were dropped from the analysis. Therefore, the frequency matching of cases to controls within 6-month calendar blocks on the number of visits in the baseline period, age, sex, and visit type (in- or out-patient) on index date did not necessarily hold in the final analyses.

11.3.3 Detection Bias

Since medical claims are used to justify the service and not to clinically describe a patient, there often exist discrepancies between diagnoses associated with claims and actual clinical diagnoses, including comorbidities. This discrepancy could be differential with respect to drug exposure if physicians who treat patients with exenatide monitored their patients differently and followed up on their patients differently (e.g., abdominal pain reports). This form of detection bias would be expected to be less of a problem for the more severe forms of the outcomes (such as hospitalized cases) and for medical record-confirmed outcomes, but it could be substantial for minor manifestations. If physicians were more likely to warn patients

on exenatide about abdominal pain rather than those on OADs, such patients might contact their physicians more readily with complaints. Similarly, physicians might be more inclined to evaluate (and attach a provisional diagnosis to) mild abdominal pain reported by a patient on exenatide than the same minimal pain in patients on OADs.

In 2007, the FDA issued a safety alert for exenatide and the development of acute pancreatitis, and this and subsequent announcements about a potential link between GLP-1 receptor agonists and thyroid cancer could have led to increased surveillance and differential detection of pancreatic or thyroid cancer among exenatide users. A comparison of the percentage of exenatide and OAD initiators receiving diagnoses and/or diagnostic work-ups for pancreatic or thyroid symptoms revealed some differences between cohorts, however it is difficult to know if these differences are due to true differences in disease risk or due to differential monitoring. The greater prevalence of pancreatic disease diagnostic procedures among exenatide initiators compared to OAD initiators was only present after the 2007 warning, suggesting that the warning may indeed have led to increased monitoring of patients taking exenatide. The prevalence of thyroid disease diagnostic procedures was slightly higher among exenatide users compared to OAD users before the first articles were published suggesting a link between exenatide use and MTC in rodents in 2010. However the relative imbalance was larger after 2010, indicating that detection bias may have resulted in upward bias of the thyroid cancer estimates, as well. These studies were published about two years before BYDUREON was approved with a warning label regarding MTC.

This type of detection bias likely would have biased the results upward, e.g., leading to a spurious association or overestimation of the association of exenatide and thyroid and/or pancreatic cancer. While we did not observe a statistically significant association between exenatide use and risk of either outcome, there was a non-statistically significant positive association with thyroid cancer. Furthermore, the positive association between exenatide use and risk of thyroid cancer was statistically significant among ORD patients (adjusted HR 1.78, 95% CI 1.06 to 2.99) but not Impact patients (adjusted HR 1.05, 95% CI 0.54 to 2.04).

We evaluated the presence and magnitude of potential detection bias using the correction factor proposed by Greenland and Neutra (29). This correction factor is the probability of the detection-related procedure among OAD initiators (p_{12}) divided by the probability among exenatide initiators (p_{11}). Matched exenatide initiators were 30 to 75% more likely to have the following pancreatic-related diagnostic procedures in follow-up: lipase measurement, amylase measurement, abdominal ultrasound, and abdominal pain. They were also 33 to 67% more likely to have thyrotropin-releasing hormone, T3 and T4 testing, thyroid imaging, and ultrasound of the head and neck. The correction factor ranged from 0.60 to 0.77 for each of these diagnostic factors. A range of observed and corrected HRs is shown below. Again, it is difficult to know what degree of differential detection in follow-up is due to true differences in disease risk versus differential detection.

Table I Observed and Corrected Hazard Ratios

	2005 - 2015			
	Exenatide (P_{11})	**OAD (P_{12})**	**P_{11}/P_{12}**	**Correction factor P_{12}/P_{11}**
Pancreatic cancer diagnostic factors				
Lipase	8%	5%	1.6	0.63
Amylase	7%	4%	1.75	0.57
Abdominal ultrasound	13%	10%	1.3	0.77
Abdominal pain	21%	16%	1.31	0.76
Thyroid cancer diagnostic factors				
TRH	40%	30%	1.33	0.75
T3,T4 testing	27%	19%	1.42	0.7
Thyroid imaging	6%	4%	1.5	0.67
Head & neck US	5%	3%	1.67	0.6

Observed HR	Corrected HR $P_{12}/P_{11} = 0.57$	Corrected HR $P_{12}/P_{11} = 0.60$	Corrected HR $P_{12}/P_{11} = 0.75$	Corrected HR $P_{12}/P_{11} = 0.77$
0.60	0.34	0.36	0.45	0.46
0.76	0.43	0.46	0.57	0.59
0.80	0.46	0.48	0.60	0.62
1.00	0.57	0.60	0.75	0.77
1.20	0.68	0.72	0.90	0.92
1.40	0.80	0.84	1.05	1.08
1.46	0.83	0.88	1.10	1.12
1.60	0.91	0.96	1.20	1.23

The estimated correction factors and the imbalance in diagnostic procedures between exenatide and OAD initiators suggest potential detection bias for both pancreatic and thyroid cancer. Based on correction factors ranging from 0.57 to 0.77 for pancreatic cancer, the observed HR of 0.76 in the cohort study would be corrected to 0.43-0.59. Similarly, based on correction factors ranging from 0.60 to 0.75 for thyroid cancer, the observed HR of 1.46 would be corrected to an HR 0.88 to 1.10.

11.3.4 Depletion of Susceptibles

In the main analyses, we excluded person-time and cancer events that occurred in the first year following initial exenatide or OAD exposure under the assumption that cancers diagnosed shortly after the start of drug exposure cannot be causally attributed to the drug. Among the matched patients, 70% of exenatide initiators were event-free and remained under observation through the first year compared to 58% of OAD initiators. Pancreatic cancer IRs were 0.55 per 1,000 person–years in the first six months and 0.49 per 1,000 person-years for

the second six months for exenatide initiators and 1.05 and 0.92 for OAD initiators, respectively; thyroid cancer IRs were 0.82 and 0.71 per 1,000 person-years for exenatide initiators and 0.95 and 0.68 for OAD initiators, respectively.

One possible explanation for this difference is that there were more patients with a higher risk of cancer due to unmeasured factors or more patients with preclinical cancer in the OAD group at the time of treatment initiation. If exenatide and OAD patients had the same cancer risk at treatment initiation, then depletion of susceptibles may have occurred where the highest risk OAD patients differentially experienced events in the first year and were therefore excluded from the analysis. This would potentially lead to lower average cancer risk among the OAD initiators at the start of the second year and a lower subsequent cancer incidence rate for this group.

In the first year of follow-up, pancreatic cancer incidence rates were higher for OAD compared to exenatide initiators whereas thyroid cancer incidence rates were similar. When events and person-time in the first year of follow-up were included, HRs were consistent with the main analysis (data not shown).

11.3.5 Short Average Duration of Enrollment in Claims Data

For patients in the ORD and Impact databases, like nearly all commercial health insurance claims databases in the US, duration of follow-up can be limited due to individuals changing health insurance plans. Within the ORD, patients are enrolled for an average of 2 years. For patients on an antidiabetic drug with 9 months of continuous enrollment, the average duration of enrollment increases to approximately 5 years (19). Because cancer outcomes tend to have long latency periods, in a modification of the as-matched analysis, person-time was categorized according to length of follow-up. Person-time that occurs later in follow-up is more likely to give rise to pancreatic and thyroid cancer, allowing empirical assessment of the latency period of the outcomes.

Given that many pancreatic (48, 49) and thyroid cancers (50, 51) have a latency period of more than a decade, longer than the 10-year study period, follow-up time in this study may not be sufficient to allow for complete observation of the study outcomes even when using the combination of two large claims databases. Indeed, the median follow-up time was about 2 years for exenatide initiators. In addition to a short average duration of enrollment in claims data, the majority of patients included were age 70 years or younger. A wider age range may have provided more power to study pancreatic cancer since more than 80% of pancreatic cancers occur in individuals aged 60 to 80 years and more than half of pancreatic adenocarcinomas, the most common type of exocrine pancreatic cancer, occur in individuals over age 70 (39). In contrast, thyroid cancer is common in younger ages, with the highest incidence rates observed in the second through fourth decades of life (52).

11.3.6 Power

As shown in section 9.7 (study size), estimated power was sufficient to detect a RR/HR of 2 or greater but not RRs/HRs closer to one.

11.3.7 Misclassification of Exposure

In this study, an intention-to-treat analysis was applied that has the advantage of preserving the randomization-like features of the propensity score matching but risks misclassification of the exposure. Such exposure misclassification might provide conservative estimates of effect as patients switch exposure status throughout the course of the follow-up; however, the attribution of remote outcomes to the baseline exposure status that occurs with this analysis is appropriate for cancer outcomes with a long latency period. To account for the effect of cumulative exenatide exposure on the risk of study outcomes and to reduce potential exposure misclassification, a time-dependent exposure analysis was additionally conducted. There were no clear trends in risk of pancreatic or thyroid cancer across categories of either cumulative exenatide duration or cumulative exenatide dose, however the median cumulative exenatide duration was relatively short – a little under one year. The median cumulative OAD duration was also short – slightly more than one year.

11.3.8 Misclassification of Outcomes

Cohort study outcomes were identified using validated algorithms, which may have misclassified some cases and non-cases. However, compared with outcomes identified solely based on diagnosis codes within the claims data, this algorithm approach is expected to increase the specificity of outcome ascertainment, reducing the misclassification of outcomes in estimated RRs. All PPVs were generally high (78% or higher) for pancreatic and thyroid cancer. As expected, the estimated sensitivity was lower for the benign thyroid neoplasm algorithm compared to the pancreatic and thyroid cancer algorithms, likely a result of claims data catching more severe cases and fewer benign cases. Therefore incidence rates of benign thyroid neoplasm are likely to be underestimated.

In the main analysis, cancers occurring within the first year of study drug initiation were excluded to reduce potential reverse causality and because these cancers were unlikely to be caused by the study drug. Although pre-specified, this is an arbitrary cut off and it is possible that some cases occurring in the first 1-2 years of follow-up may have been in the early stages of development well before study drug initiation began. Indeed, some data suggest that many pancreatic (48, 49) and thyroid cancers (50, 51) have a latency period more than a decade, longer than the 10-year study period.

It is possible that some pancreatic cancers that were not diagnosed before death were missed. However, symptoms of pancreatic cancer are typically not mild and therefore we expect that the majority of true cases will have a diagnosis in claims data. Furthermore, we expect the proportion of missed diagnoses to be the same among the exenatide and OAD cohorts and in this case, the RR estimates would be unbiased.

11.3.9 Misclassification of Covariates

Claims data capture smoking and obesity status poorly, and both lifestyle factors may be confounders of the association between exenatide use and risk of pancreatic or thyroid cancer. Obesity is an important risk factor for pancreatic (39) and thyroid cancer (41), and obese patients may be more likely to use exenatide given that exenatide is preferentially prescribed

to patients with poorly-controlled diabetes. While smokers are more likely to develop pancreatic cancer (37, 38), smoking appears to have a seemingly protective effect on the development of thyroid cancer (40). However, analyses that quantified the degree of confounding needed to explain the observed associations indicated that residual confounding by smoking or obesity was unlikely to explain these results.

Data on additional potential confounders that are not captured well in claims data were abstracted from medical records. While medical records were selected to confirm outcomes, control records were selected to gather covariate information. Therefore, it is possible that the types of medical records selected and received for cases could have contained different types of information compared to controls. For example, medical records related to outcome confirmation may be more likely to have some discussion of important risk factors such as family history whereas control records may be less likely to explore outcome-specific family or personal histories.

11.4 Interpretation

These results do not suggest an increased risk of pancreatic cancer with exenatide use. We observed a non-statistically significant inverse association between exenatide use and risk of pancreatic cancer. A similar inverse association was observed in a nested-case control study that additionally controlled for medical record-abstracted covariates such as BMI, smoking status, and alcohol use. Exenatide initiators in the nested case-control study had a statistically significant lower risk of pancreatic cancer compared to OAD initiators. This inverse association was observed despite the suggestion of possible detection bias that may have led to an overestimate of the risk of pancreatic cancer among exenatide initiators.

It is possible that this inverse association could be due to confounding by prescribing patterns, for example, if physicians are concerned about a potential increased risk of pancreatic disease with exenatide use, as indicated in the prescribing information, they may hesitate to prescribe exenatide to individuals with a family or personal history of pancreatic disease. Although the nested case-control study attempted to abstract information on family and personal history of pancreatic disease, this information was often missing from case medical records and even more often missing from control records. It is expected that this detailed history might be discussed more often with suspected pancreatic cancer patients than with controls. Hence, despite adjusting for some medical record-derived covariates that are captured poorly in claims data, the nested case-control study, like the cohort study, did not adjust for some important risk factors such as family history. Furthermore, the nested case-control study was restricted to a limited number of covariates and did not adjust for all unbalanced medical record- and claims-derived variables.

In general, the extended follow-up (2005 to 2015) cohort study results agree with the results observed in the previous study period (2005 to 2010) (19), but the inverse association was stronger in the overall study period compared to the previous study period. The previous report did not pool results across databases and did not include a nested case-control study.

These extended follow-up results are also similar to an analysis of exenatide and pancreatic cancer reported in the literature: this 2007 to 2009 retrospective cohort study using claims data found no difference in pancreatic cancer risk comparing OAD users with at least 365 days of exenatide use versus OAD users without exenatide use, OR 1.54 (95% CI 0.49 to 4.87) (17). An additional study within the FDA Adverse Event Reporting System (FAERS) database reported an elevated odds of pancreatic cancer among exenatide users compared to users of comparator drugs (47), however this FAERS study has several, serious methodological flaws such as non-confirmed events, known reporting bias, and a lack of adjustment for confounders (53).

Overall, the association between exenatide use and risk of thyroid cancer was not statistically significant, however we observed a statistically significant increased risk of thyroid cancer among ORD patients but not Impact patients. Yet there were no trends in risk across cumulative exenatide dose or duration and a nested-case control study within a subset of ORD patients showed no association between exenatide use and risk of thyroid cancer. When interpreting the trends across cumulative exenatide dose and duration, it is important to note that median cumulative exenatide duration was about one year and median follow-up among exenatide initiators was about 2 years.

It is possible that the conflicting results between the cohort and nested-case control study are due to residual confounding by medical record-derived factors in the cohort study. However, the nested case-control study was limited to a small number of covariates and did not adjust for all unbalanced medical record- or claims-derived covariates. Neither the cohort nor nested case-control study adjusted for some important thyroid cancer risk factors that are poorly captured in claims data, including a low iodine diet, radiation therapy, and family and personal history of thyroid disease. Another difference between the cohort and nested case-control studies was the identification of thyroid cancers: cases were identified using a validated algorithm in the cohort study in comparison to medical record confirmed cases in the nested case-control study. Nevertheless, using the thyroid algorithm, the proportion of false positives and false negatives would be the same in the cohort study for exenatide and OAD initiators and, therefore, all relative estimates would be unbiased. Finally, there was a suggestion of possible detection bias that may have led to an overestimate of the risk of thyroid cancer among exenatide initiators.

One previous study using the FAERS database reported an elevated odds of thyroid cancer among exenatide users compared to users of comparator drugs (47), however this study has several, serious methodological flaws and its findings are questionable (53). No other studies have had the power to examine exenatide use and risk of thyroid cancer.

11.5 Generalizability

Patients in ORD and Impact are geographically diverse and fairly representative of the non-elderly, commercially-insured US population. Therefore, these results may not be generalizable to non-insured or elderly individuals.

12. OTHER INFORMATION

This study used identifiable and de-identified insurance claims data. To comply with HIPAA Privacy Regulations, we sought a Waiver of Patient Authorization for access to protected health information from a privacy board and approval from an institutional review board for general study oversight, including use of the de-identified claims data. Confidentiality of patient records was maintained at all times. This study report contains aggregate data only and does not identify individual patients or physicians.

13. CONCLUSION

The results of the cohort study suggest that exenatide use was not associated with an increased risk of pancreatic or thyroid cancer. A nested case-control study within the ORD that adjusted for additional chart-derived covariates found no elevation in risk of pancreatic or thyroid cancer with exenatide use. Given the long latency period of pancreatic and thyroid cancer, and the relatively short follow-up for many patients, these results should be interpreted with caution.

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15. TABLES

Table 1. Proportion of Medical Records Identified and Acquired for Pancreatic Cancer and Thyroid Neoplasms during the Extension Period, Optum Research Database 8/1/2010−6/30/2015

	Pancreatic Cancer (N= 185)				Thyroid Cancer (N= 129)				Benign Thyroid Neoplasm (N= 92)				Controls (N= 464)			
	Exenatide (N= 9)		OADs (N= 176)		Exenatide (N= 25)		OADs (N= 104)		Exenatide (N= 12)		OADs (N= 80)		Exenatide (N= 109)		OADs (N= 355)	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Identified in Claims Data*	9	100.0	176	100.0	25	100.0	104	100.0	12	100.0	80	100.0	109	100.0	355	100.0
Retained After Profile Review (Charts Sought)*	9	100.0	167	94.9	25	100.0	104	100.0	12	100.0	79	98.8	109	100.0	355	100.0
Charts Received*	6	66.7	123	73.7	17	68.0	83	79.8	11	91.7	59	74.7	73	67.0	231	65.1
Number of Confirmed Cases**	4	66.7	82	66.7	12	70.6	71	85.5	8	72.7	49	83.1	N/A	N/A	N/A	N/A

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.

*Number of cases or number of controls. The same patient may be counted twice if they had more than one type of cancer. Some patients were identified as a control for more than one case. No controls were also cases.

** Inclusion of definite cases and probable cases from adjudication

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Based on relaxed algorithms

Table 2.1a. Characteristics of Exenatide Initiators and Other Antidiabetic Drug Initiators on the Date of Cohort Entry, Optum Research Database 6/1/2005−6/30/2015

	All (N= 356,838)					Matched (N= 89,503)					Not Matched (N= 267,335)	
	Exenatide (N= 45,791)		OADs (N= 311,047)		Standardized	Exenatide (N= 32,191)		OADs (N= 57,312)		Standardized	Exenatide (N= 13,600)	
Characteristic	**N**	**%**	**N**	**%**	**Difference**	**N**	**%**	**N**	**%**	**Difference**	**N**	**%**
Age												
≤ 39	4,770	10.4	32,122	10.3	0.00	3,479	10.8	6,035	10.5	0.01	1,291	9.5
40-49	11,367	24.8	67,801	21.8	0.08	7,841	24.4	13,855	24.2	0.00	3,526	25.9
50-59	18,411	40.2	112,644	36.2	0.09	12,616	39.2	22,423	39.1	0.00	5,795	42.6
60-69	10,041	21.9	76,569	24.6	0.07	7,284	22.6	13,288	23.2	0.01	2,757	20.3
≥ 70	1,202	2.6	21,911	7.0	0.22	971	3.0	1,711	3.0	0.01	231	1.7
Sex												
Male	21,184	46.3	180,817	58.1	0.26	15,361	47.7	27,509	48.0	0.01	5,823	42.8
Female	24,607	53.7	130,230	41.9	0.26	16,830	52.3	29,803	52.0	0.01	7,777	57.2
Geographic Area												
Northeast	2,902	6.3	22,446	7.2	0.04	2,078	6.5	3,648	6.4	0.00	824	6.1
Midwest	11,649	25.4	81,030	26.1	0.01	8,192	25.4	14,712	25.7	0.00	3,457	25.4
South	25,704	56.1	167,444	53.8	0.05	18,047	56.1	31,984	55.8	0.00	7,657	56.3
West	5,536	12.1	40,123	12.9	0.03	3,874	12.0	6,968	12.2	0.00	1,662	12.2
Unknown	0	0.0	4	0.0	0.01	0	0.0	0	0.0	−	0	0.0
Cohort Entry Year												
2005	3,639	7.9	23,887	7.7	0.01	2,295	7.1	4,260	7.4	0.02	1,344	9.9
2006	12,281	26.8	46,867	15.1	0.31	8,198	25.5	13,217	23.1	0.01	4,083	30.0
2007	9,087	19.8	36,909	11.9	0.23	6,385	19.8	10,455	18.2	0.00	2,702	19.9
2008	6,633	14.5	37,921	12.2	0.08	5,028	15.6	9,213	16.1	0.00	1,605	11.8
2009	4,085	8.9	32,295	10.4	0.05	3,039	9.4	5,808	10.1	0.00	1,046	7.7
2010	2,266	4.9	28,627	9.2	0.17	1,626	5.1	3,277	5.7	0.01	640	4.7
2011	1,753	3.8	26,493	8.5	0.21	1,215	3.8	2,437	4.3	0.00	538	4.0
2012	2,095	4.6	22,650	7.3	0.12	1,497	4.7	2,806	4.9	0.01	598	4.4
2013	1,697	3.7	22,316	7.2	0.16	1,280	4.0	2,575	4.5	0.00	417	3.1
2014	1,514	3.3	21,985	7.1	0.18	1,093	3.4	2,185	3.8	0.00	421	3.1
2015	741	1.6	11,097	3.6	0.13	535	1.7	1,079	1.9	0.00	206	1.5

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.
Standardized difference is calculated by the difference between the 2 proportions divided by the pooled standard deviation.
Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 2.1b. Characteristics of Exenatide Initiators and Other Antidiabetic Drug Initiators on the Date of Cohort Entry, Impact National Benchmark Database 6/1/2005−3/31/2015

	All (N= 166,903)					Matched (N= 42,886)					Not Matched (N= 124,017)	
	Exenatide (N= 24,287)		OADs (N= 142,616)		Standardized	Exenatide (N= 15,755)		OADs (N= 27,131)		Standardized	Exenatide (N= 8,532)	
Characteristic	**N**	**%**	**N**	**%**	**Difference**	**N**	**%**	**N**	**%**	**Difference**	**N**	**%**
Age												
≤ 39	1,983	8.2	11,542	8.1	0.00	1,373	8.7	2,304	8.5	0.01	610	7.1
40-49	5,541	22.8	28,192	19.8	0.08	3,530	22.4	6,001	22.1	0.00	2,011	23.6
50-59	9,943	40.9	54,533	38.2	0.06	6,303	40.0	10,764	39.7	0.00	3,640	42.7
60-69	6,335	26.1	42,278	29.6	0.08	4,225	26.8	7,407	27.3	0.01	2,110	24.7
≥ 70	485	2.0	6,071	4.3	0.14	324	2.1	655	2.4	0.01	161	1.9
Sex												
Male	11,918	49.1	85,063	59.6	0.23	7,876	50.0	13,772	50.8	0.00	4,042	47.4
Female	12,369	50.9	57,553	40.4	0.23	7,879	50.0	13,359	49.2	0.00	4,490	52.6
Geographic Area												
Northeast	15,463	63.7	89,271	62.6	0.02	9,918	63.0	17,031	62.8	0.00	5,545	65.0
Midwest	2,609	10.7	17,340	12.2	0.05	1,746	11.1	3,071	11.3	0.00	863	10.1
South	4,850	20.0	29,252	20.5	0.01	3,174	20.1	5,536	20.4	0.01	1,676	19.6
West	1,176	4.8	5,553	3.9	0.05	791	5.0	1,308	4.8	0.00	385	4.5
Unknown	189	0.8	1,200	0.8	0.01	126	0.8	185	0.7	0.01	63	0.7
Cohort Entry Year												
2005	3,105	12.8	21,865	15.3	0.08	1,904	12.1	3,685	13.6	0.03	1,201	14.1
2006	7,281	30.0	25,868	18.1	0.29	4,567	29.0	7,106	26.2	0.02	2,714	31.8
2007	5,553	22.9	22,115	15.5	0.20	3,797	24.1	6,135	22.6	0.01	1,756	20.6
2008	2,775	11.4	14,761	10.4	0.04	1,915	12.2	3,441	12.7	0.01	860	10.1
2009	1,584	6.5	12,471	8.7	0.09	1,079	6.8	1,969	7.3	0.01	505	5.9
2010	838	3.5	10,850	7.6	0.19	626	4.0	1,291	4.8	0.01	212	2.5
2011	702	2.9	9,044	6.3	0.18	417	2.6	797	2.9	0.00	285	3.3
2012	789	3.2	7,866	5.5	0.12	526	3.3	969	3.6	0.00	263	3.1
2013	689	2.8	8,035	5.6	0.15	448	2.8	867	3.2	0.00	241	2.8
2014	789	3.2	7,831	5.5	0.12	387	2.5	714	2.6	0.00	402	4.7
2015	182	0.7	1,910	1.3	0.06	89	0.6	157	0.6	0.00	93	1.1

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.
Standardized difference is calculated by the difference between the 2 proportions divided by the pooled standard deviation.
Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 2.2a. Prevalence of Common Baseline* Characteristics, Optum Research Database 6/1/2005−6/30/2015

	All (N= 356,838)					Matched (N= 89,503)					Not Matched (N= 267,335)	
	Exenatide (N= 45,791)		OADs (N= 311,047)		Standardized Difference	Exenatide (N= 32,191)		OADs (N= 57,312)		Standardized Difference	Exenatide (N= 13,600)	
Characteristic	**N**	**%**	**N**	**%**		**N**	**%**	**N**	**%**		**N**	**%**
Other lab	41,422	90.5	263,666	84.8	0.18	28,788	89.4	51,149	89.2	0.00	12,634	92.9
Procedure codes not elsewhere specified	40,628	88.7	260,791	83.8	0.15	28,257	87.8	50,292	87.8	0.00	12,371	91.0
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A detailed history; A detailed examination; Medical decision making of moderate complexity	38,518	84.1	234,654	75.4	0.23	26,515	82.4	46,839	81.7	0.00	12,003	88.3
Glycated hemoglobin test	37,567	82.0	227,227	73.1	0.23	25,906	80.5	45,816	79.9	0.01	11,661	85.7
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: An expanded problem focused history; An expanded problem focused examination; Medical decision making of low complexity.	35,227	76.9	218,492	70.2	0.16	24,405	75.8	43,021	75.1	0.01	10,822	79.6
Other therapeutic procedure	32,126	70.2	206,770	66.5	0.08	22,281	69.2	39,314	68.6	0.01	9,845	72.4
Lipid panel	33,225	72.6	199,544	64.2	0.19	22,885	71.1	40,476	70.6	0.00	10,340	76.0
Metformin	37,302	81.5	187,158	60.2	0.51	25,063	77.9	43,642	76.1	0.02	12,239	90.0
Male	21,184	46.3	180,817	58.1	0.26	15,361	47.7	27,509	48.0	0.01	5,823	42.8
Microscopic exam (smear culture)	27,561	60.2	166,130	53.4	0.15	18,668	58.0	33,342	58.2	0.01	8,893	65.4
Statins	27,011	59.0	162,152	52.1	0.15	18,319	56.9	32,521	56.7	0.00	8,692	63.9
Comprehensive metabolic panel	25,768	56.3	151,935	48.8	0.16	17,489	54.3	30,890	53.9	0.00	8,279	60.9
Ace Inhibitors	21,759	47.5	144,034	46.3	0.03	15,039	46.7	27,338	47.7	0.02	6,720	49.4
Blood sugar diagnostics	26,076	56.9	136,428	43.9	0.28	17,088	53.1	30,040	52.4	0.01	8,988	66.1
1 Anti-diabetic medication within 45 days of index	18,707	40.9	135,271	43.5	0.05	13,862	43.1	25,119	43.8	0.01	4,845	35.6
Other diagnostic radiology	20,264	44.3	122,901	39.5	0.10	13,681	42.5	24,156	42.1	0.00	6,583	48.4
Sulfonylureas	23,404	51.1	116,343	37.4	0.29	14,436	44.8	24,971	43.6	0.01	8,968	65.9
50-59 years of age	18,411	40.2	112,644	36.2	0.09	12,616	39.2	22,423	39.1	0.00	5,795	42.6
Electrocardiogram	13,881	30.3	103,075	33.1	0.07	9,511	29.5	17,366	30.3	0.02	4,370	32.1
Automated hemogram	15,208	33.2	101,732	32.7	0.01	10,521	32.7	18,876	32.9	0.01	4,687	34.5
Lipotropics	21,876	47.8	94,069	30.2	0.38	14,427	44.8	24,447	42.7	0.00	7,449	54.8
Microalbumin quantitative	17,246	37.7	93,763	30.1	0.17	11,371	35.3	20,118	35.1	0.00	5,875	43.2
Analgesics, narcotics	14,575	31.8	91,601	29.4	0.05	9,867	30.7	17,837	31.1	0.02	4,708	34.6
General symptoms	14,960	32.7	89,470	28.8	0.09	9,937	30.9	17,111	29.9	0.01	5,023	36.9
Ophthalmologic/otologic diagnosis/treatment	14,390	31.4	80,381	25.8	0.13	9,498	29.5	16,686	29.1	0.00	4,892	36.0
Encounter for other and unspecified procedure and aftercare	12,882	28.1	81,432	26.2	0.04	8,655	26.9	15,352	26.8	0.00	4,227	31.1
Midwest	11,649	25.4	81,030	26.1	0.01	8,192	25.4	14,712	25.7	0.00	3,457	25.4
Nonoperative urinary measurements	11,864	25.9	78,557	25.3	0.02	8,251	25.6	14,769	25.8	0.00	3,613	26.6
Prophylactic vaccinations	12,216	26.7	74,427	23.9	0.07	8,338	25.9	14,817	25.9	0.00	3,878	28.5
60-69 years of age	10,041	21.9	76,569	24.6	0.07	7,284	22.6	13,288	23.2	0.01	2,757	20.3
Urine creatinine assay	13,948	30.5	71,898	23.1	0.17	9,035	28.1	15,557	27.1	0.02	4,913	36.1
Thiazolidinediones in baseline	20,108	43.9	65,597	21.1	0.52	11,678	36.3	19,645	34.3	0.01	8,430	62.0

Table 2.2a. Prevalence of Common Baseline* Characteristics. Optum Research Database 6/1/2015-6/30/2015

	All (N= 356,838)					Matched (N= 89,503)					Not Matched (N= 267,335)	
	Exenatide (N= 45,791)		OADs (N= 311,047)		Standardized Difference	Exenatide (N= 32,191)		OADs (N= 57,312)		Standardized Difference	Exenatide (N= 13,600)	
Characteristic	**N**	**%**	**N**	**%**		**N**	**%**	**N**	**%**		**N**	**%**
Unlisted miscellaneous pathology test	9,914	21.7	68,488	22.0	0.01	6,863	21.3	12,158	21.2	0.00	3,051	22.4
Thyrotropin releasing hormone	13,704	29.9	62,122	20.0	0.24	8,491	26.4	14,623	25.5	0.01	5,213	38.3
Durable medical equipment, miscellaneous (Group 1)	9,982	21.8	63,094	20.3	0.04	6,776	21.0	11,965	20.9	0.00	3,206	23.6
Radiographic procedure	10,083	22.0	62,443	20.1	0.05	6,846	21.3	12,330	21.5	0.01	3,237	23.8
Nonsteroidal antiinflammatory drugs (NSAIDs)	10,343	22.6	60,728	19.5	0.08	7,017	21.8	12,583	22.0	0.01	3,326	24.5
Basic metabolic panel	9,291	20.3	57,988	18.6	0.04	6,226	19.3	11,129	19.4	0.01	3,065	22.5
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A problem focused history; A problem focused examination; Straightforward medical decision making.	10,183	22.2	56,082	18.0	0.11	6,781	21.1	11,615	20.3	0.01	3,402	25.0
Insulins	13,373	29.2	50,364	16.2	0.32	6,662	20.7	11,828	20.6	0.02	6,711	49.3
Vaginal delivery	10,733	23.4	51,098	16.4	0.18	6,859	21.3	11,353	19.8	0.02	3,874	28.5
Penicillins	8,613	18.8	52,125	16.8	0.06	5,852	18.2	10,378	18.1	0.00	2,761	20.3
General medical examination	6,722	14.7	53,824	17.3	0.07	4,831	15.0	9,060	15.8	0.01	1,891	13.9
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A comprehensive history; A comprehensive examination; Medical decision making of high complexity.	9,768	21.3	50,439	16.2	0.14	6,284	19.5	10,830	18.9	0.01	3,484	25.6
Immunization administration; 1 vaccine	8,516	18.6	50,152	16.1	0.07	5,833	18.1	10,355	18.1	0.00	2,683	19.7
Calcium channel blocking agents	7,026	15.3	49,741	16.0	0.02	4,841	15.0	8,873	15.5	0.01	2,185	16.1
Hypotensives, angiotensin receptor antagonist	10,874	23.7	45,582	14.7	0.24	6,889	21.4	11,815	20.6	0.01	3,985	29.3
2 Anti-diabetic medications within 45 days of index	10,378	22.7	45,488	14.6	0.22	6,782	21.1	11,410	19.9	0.02	3,596	26.4
Acid-suppressing drugs	8,205	17.9	47,024	15.1	0.08	5,418	16.8	9,677	16.9	0.01	2,787	20.5
Other and unspecified disorders of back	7,709	16.8	46,593	15.0	0.05	5,244	16.3	9,200	16.1	0.00	2,465	18.1
Quinolones	8,030	17.5	46,025	14.8	0.08	5,339	16.6	9,451	16.5	0.01	2,691	19.8
Macrolides	8,326	18.2	45,624	14.7	0.10	5,543	17.2	9,819	17.1	0.00	2,783	20.5
Obesity	10,052	22.0	43,573	14.0	0.22	5,815	18.1	10,099	17.6	0.00	4,237	31.2
Urinalysis; automated with microscopy	6,545	14.3	45,605	14.7	0.01	4,491	14.0	8,618	15.0	0.03	2,054	15.1
Non-alcohol sedatives	7,442	16.3	41,054	13.2	0.09	4,991	15.5	8,729	15.2	0.00	2,451	18.0
Preventive visit; established patient, 18-39 years	7,270	15.9	40,471	13.0	0.09	4,880	15.2	8,668	15.1	0.00	2,390	17.6
Serotonin specific reuptake inhibitor (SSRIs)	8,118	17.7		12.6	0.15	5,353	16.6	9,186	16.0	0.01	2,765	20.3
Office consultation for a new or established patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical decision making of moderate complexity.	8,793	19.2	37,676	12.1	0.20	5,448	16.9	9,013	15.7	0.01	3,345	24.6
Eye exam treatment	7,244	15.8	38,673	12.4	0.10	4,682	14.5	8,397	14.7	0.01	2,562	18.8
West	5,536	12.1	40,123	12.9	0.03	3,874	12.0	6,968	12.2	0.00	1,662	12.2

Table 2.2a. Prevalence of Common Baseline* Characteristics. Optum Research Database 6/1/2015-6/30/2015

	All (N= 356,838)					Matched (N= 89,503)					Not Matched (N= 267,335)	
	Exenatide (N= 45,791)		OADs (N= 311,047)		Standardized Difference	Exenatide (N= 32,191)		OADs (N= 57,312)		Standardized Difference	Exenatide (N= 13,600)	
Characteristic	**N**	**%**	**N**	**%**		**N**	**%**	**N**	**%**		**N**	**%**
Emergency department visit for the evaluation and management of a patient, which requires these 3 key components within the constraints imposed by the urgency of the patient's clinical condition and/or mental status: A comprehensive history; A comprehensive examination; and Medical decision making of high complexity.	3,669	8.0	40,079	12.9	0.17	2,474	7.7	4,786	8.4	0.02	1,195	8.8
Quantitative glucose assay	6,301	13.8	36,932	11.9	0.06	4,128	12.8	7,496	13.1	0.01	2,173	16.0
Tissue exam by pathologist	5,868	12.8	36,605	11.8	0.03	3,923	12.2	6,876	12.0	0.00	1,945	14.3
Symptoms involving skin and other integumentary tissue	6,035	13.2	35,815	11.5	0.05	3,970	12.3	6,764	11.8	0.01	2,065	15.2
Physical therapy exercises/manipulation	6,905	15.1	34,171	11.0	0.13	4,471	13.9	7,696	13.4	0.00	2,434	17.9
Symptoms involving digestive system	4,382	9.6	34,462	11.1	0.05	3,038	9.4	5,702	9.9	0.02	1,344	9.9
Chest x-ray	3,068	6.7	34,689	11.2	0.17	2,082	6.5	3,887	6.8	0.01	986	7.3
Subsequent hospital care	2,629	5.7	34,943	11.2	0.21	1,709	5.3	3,389	5.9	0.03	920	6.8
Osteoarthrosis and allied disorders	5,403	11.8	32,000	10.3	0.05	3,595	11.2	6,331	11.0	0.00	1,808	13.3
Fibrates	6,235	13.6	30,790	9.9	0.12	3,951	12.3	7,072	12.3	0.01	2,284	16.8
Thiazide and related diuretics	5,288	11.5	31,292	10.1	0.05	3,518	10.9	6,370	11.1	0.01	1,770	13.0
Anticonvulsants	5,507	12.0	30,974	10.0	0.07	3,663	11.4	6,721	11.7	0.02	1,844	13.6
Magnetic resonance imaging	4,946	10.8	31,487	10.1	0.02	3,225	10.0	5,857	10.2	0.01	1,721	12.7
Thyroid hormones	6,415	14.0	29,365	9.4	0.15	4,152	12.9	7,058	12.3	0.01	2,263	16.6
Insulin glargine	8,653	18.9	26,119	8.4	0.32	4,006	12.4	6,873	12.0	0.01	4,647	34.2
Loop diuretics	5,737	12.5	28,187	9.1	0.11	3,588	11.1	5,975	10.4	0.01	2,149	15.8
Gastroesophageal reflux disease	4,561	10.0	29,332	9.4	0.02	3,104	9.6	5,621	9.8	0.01	1,457	10.7
Free thyroxine assay	6,515	14.2	26,896	8.6	0.18	3,912	12.2	6,433	11.2	0.02	2,603	19.1
Refraction	5,268	11.5	27,854	9.0	0.09	3,429	10.7	5,991	10.5	0.00	1,839	13.5
Skeletal muscle relaxants	4,826	10.5	27,505	8.8	0.06	3,274	10.2	5,902	10.3	0.01	1,552	11.4
Anti-anxiety drugs	4,720	10.3	27,404	8.8	0.05	3,165	9.8	5,678	9.9	0.01	1,555	11.4
Acute sinusitis	5,159	11.3	26,497	8.5	0.10	3,464	10.8	5,964	10.4	0.01	1,695	12.5
Office consultation for a new or established patient, which requires these 3 key components: A detailed history; A detailed examination; and Medical decision making of low complexity.	5,201	11.4	26,413	8.5	0.10	3,463	10.8	5,893	10.3	0.00	1,738	12.8
Radioisotope scan/function	4,564	10.0	26,705	8.6	0.05	2,948	9.2	5,208	9.1	0.01	1,616	11.9
Other and unspecified anemias	3,367	7.4	27,023	8.7	0.05	2,260	7.0	4,343	7.6	0.02	1,107	8.1
Cardiac stress tests	4,825	10.5	25,549	8.2	0.08	3,124	9.7	5,395	9.4	0.00	1,701	12.5
Specimen handling	4,741	10.4	25,527	8.2	0.08	3,223	10.0	5,614	9.8	0.00	1,518	11.2
Hypothyroidism	5,140	11.2	24,279	7.8	0.12	3,320	10.3	5,527	9.6	0.02	1,820	13.4
Disorders of fluid, electrolyte, and acid-base balance	2,222	4.9	27,105	8.7	0.16	1,526	4.7	3,078	5.4	0.03	696	5.1
Hospitalization within 45 days of index	965	2.1	28,283	9.1	0.32	685	2.1	1,483	2.6	0.02	280	2.1
Emergency department visit for the evaluation and management of a patient, which requires these 3 key components: A detailed history; A detailed examination; and Medical decision making of moderate complexity.	3,038	6.6	26,202	8.4	0.07	2,107	6.5	3,998	7.0	0.02	931	6.8

Table 2.2a. Prevalence of Common Baseline* Characteristics. Optum Research Database 6/1/2015-6/30/2015

	All (N= 356,838)					Matched (N= 89,503)					Not Matched (N= 267,335)	
	Exenatide (N= 45,791)		OADs (N= 311,047)		Standardized Difference	Exenatide (N= 32,191)		OADs (N= 57,312)		Standardized Difference	Exenatide (N= 13,600)	
Characteristic	**N**	**%**	**N**	**%**		**N**	**%**	**N**	**%**		**N**	**%**
Symptoms involving head and neck	3,468	7.6	25,519	8.2	0.02	2,394	7.4	4,450	7.8	0.01	1,074	7.9
Beta-adrenergic agents	4,442	9.7	24,450	7.9	0.07	2,906	9.0	5,169	9.0	0.01	1,536	11.3
Diabetic supplies	2,648	5.8	25,464	8.2	0.10	1,951	6.1	3,645	6.4	0.01	697	5.1
Diagnostic ultrasound abdomen	3,209	7.0	24,659	7.9	0.04	2,194	6.8	3,940	6.9	0.01	1,015	7.5
Critical care procedure	568	1.2	10,563	3.4	0.15	375	1.2	708	1.2	0.00	193	1.4
Peripheral neuropathy	5,146	11.2	24,352	7.8	0.12	3,079	9.6	5,224	9.1	0.00	2,067	15.2
Nephritis and nephropathy, not specified as acute or chronic	622	1.4	3,299	1.1	0.03	380	1.2	595	1.0	0.01	242	1.8
Retinopathy	2,480	5.4	13,070	4.2	0.06	1,534	4.8	2,830	4.9	0.01	946	7.0
Hypertension	32,720	71.5	209,390	67.3	0.09	22,489	69.9	39,740	69.3	0.01	10,231	75.2
Hyperlipidemia	36,469	79.6	214,415	68.9	0.26	24,967	77.6	43,726	76.3	0.01	11,502	84.6
Ischemic heart disease	5,799	12.7	41,214	13.3	0.02	3,911	12.1	6,909	12.1	0.00	1,888	13.9
Myocardial infarction	669	1.5	7,582	2.4	0.08	449	1.4	832	1.5	0.00	220	1.6
Congestive heart failure	1,473	3.2	13,831	4.4	0.07	985	3.1	1,806	3.2	0.01	488	3.6
Stroke/TIA	828	1.8	9,399	3.0	0.09	553	1.7	1,001	1.7	0.00	275	2.0
Thyrotropin releasing hormone	13,704	29.9	62,122	20.0	0.24	8,491	26.4	14,623	25.5	0.01	5,213	38.3
T3, T4 testing	9,444	20.6	43,002	13.8	0.19	5,843	18.2	10,030	17.5	0.01	3,601	26.5
Computerized tomography (CT), soft tissue neck	216	0.5	1,720	0.6	0.01	142	0.4	262	0.5	0.00	74	0.5
Thyroid imaging	772	1.7	5,918	1.9	0.02	512	1.6	949	1.7	0.00	260	1.9
Ultrasound of head and neck	1,058	2.3	3,660	1.2	0.09	583	1.8	937	1.6	0.01	475	3.5
Biopsy thyroid	229	0.5	1,020	0.3	0.03	129	0.4	222	0.4	0.00	100	0.7
Thyroidectomy	31	0.1	109	0.0	0.01	11	0.0	27	0.0	0.01	20	0.1
Other operations on thyroid	2	0.0	23	0.0	0.00	0	0.0	1	0.0	0.01	2	0.0
Lipase	1,137	2.5	8,876	2.9	0.02	779	2.4	1,429	2.5	0.01	358	2.6
Amylase	1,122	2.5	7,950	2.6	0.01	773	2.4	1,367	2.4	0.00	349	2.6
Abdominal ultrasound	2,149	4.7	16,172	5.2	0.03	1,462	4.5	2,676	4.7	0.01	687	5.1
Biopsy of pancreas	1	0.0	18	0.0	0.01	0	0.0	0	0.0	–	1	0.0
Pancreatectomy	4	0.0	40	0.0	0.00	0	0.0	0	0.0	–	4	0.0
Endobronchial ultrasound	3	0.0	88	0.0	0.02	1	0.0	3	0.0	0.00	2	0.0
Magnetic resonance imaging (MRI), abdomen	236	0.5	1,950	0.6	0.02	147	0.5	292	0.5	0.01	89	0.7
Magnetic resonance cholangiopancreatography (MRCP)	1	0.0	4	0.0	0.00	0	0.0	0	0.0	–	1	0.0
Endoscopic retrograde cholangiopancreatography (ERCP)	24	0.1	437	0.1	0.03	15	0.0	24	0.0	0.00	9	0.1
Other operations on pancreas	3	0.0	52	0.0	0.01	0	0.0	0	0.0	–	3	0.0
X-ray for pancreas	80	0.2	711	0.2	0.01	53	0.2	94	0.2	0.00	27	0.2
Micro exam of pancreas	0	0.0	0	0.0	–	0	0.0	0	0.0	–	0	0.0
Abdominal pain	5,579	12.2	40,180	12.9	0.02	3,843	11.9	6,883	12.0	0.01	1,736	12.8
Other nonspecific abnormal serum enzyme levels	451	1.0	3,737	1.2	0.02	299	0.9	563	1.0	0.00	152	1.1

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.

Standardized difference is calculated by the difference between the 2 proportions divided by the pooled standard deviation.

* Baseline includes 9-month period prior to drug initiation

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 2.2.1a. Prevalence of Malignances During the 9-Month Baseline Period, Optum Research Database 6/1/2005−6/30/2015

	All (N= 356,838)					Matched (N= 89,503)				
	Exenatide (N= 45,791)		OADs (N= 311,047)		Standardized Difference	Exenatide (N= 32,191)		OADs (N = 57,312)		Standardized Difference
Baseline Malignancies	**N**	**%**	**N**	**%**		**N**	**%**	**N**	**%**	
Malignant neoplasm of lip	2	0.0	39	0.0	0.01	2	0.0	5	0.0	0.00
Malignant neoplasm of tongue	4	0.0	94	0.0	0.02	4	0.0	8	0.0	0.00
Malignant neoplasm of major salivary glands	6	0.0	53	0.0	0.00	6	0.0	9	0.0	0.00
Malignant neoplasm of gum	0	0.0	16	0.0	0.01	0	0.0	2	0.0	0.01
Malignant neoplasm of floor of mouth	1	0.0	18	0.0	0.01	1	0.0	1	0.0	0.00
Malignant neoplasm of other and unspecified parts of mouth	3	0.0	43	0.0	0.01	3	0.0	2	0.0	0.00
Malignant neoplasm of oropharynx	5	0.0	78	0.0	0.01	5	0.0	4	0.0	0.01
Malignant neoplasm of nasopharynx	1	0.0	37	0.0	0.01	1	0.0	5	0.0	0.01
Malignant neoplasm of hypopharynx	1	0.0	16	0.0	0.01	1	0.0	2	0.0	0.00
Malignant neoplasm of other and ill-defined sites within the lip, oral cavity, and pharynx	3	0.0	49	0.0	0.01	3	0.0	1	0.0	0.01
Malignant neoplasm of esophagus	3	0.0	139	0.0	0.02	3	0.0	9	0.0	0.00
Malignant neoplasm of stomach	4	0.0	155	0.0	0.02	3	0.0	19	0.0	0.02
Malignant neoplasm of small intestine, including duodenum	2	0.0	59	0.0	0.01	1	0.0	5	0.0	0.01
Malignant neoplasm of colon	104	0.2	1,326	0.4	0.04	72	0.2	149	0.3	0.01
Malignant neoplasm of rectum, rectosigmoid junction, and anus	67	0.1	712	0.2	0.02	45	0.1	76	0.1	0.00
Malignant neoplasm of liver and intrahepatic bile ducts	14	0.0	298	0.1	0.03	8	0.0	22	0.0	0.01
Malignant neoplasm of gallbladder and extrahepatic bile ducts	4	0.0	50	0.0	0.01	1	0.0	4	0.0	0.00
Malignant neoplasm of retroperitoneum and peritoneum	8	0.0	72	0.0	0.00	6	0.0	12	0.0	0.00
Malignant neoplasm of other and ill-defined sites within the digestive organs and peritoneum	4	0.0	62	0.0	0.01	3	0.0	9	0.0	0.01
Malignant neoplasm of nasal cavities, middle ear, and accessory sinuses	5	0.0	32	0.0	0.00	5	0.0	4	0.0	0.01

Table 2.2.1a. Prevalence of Malignances During the 9-Month Baseline Period, Optum Research Database 6/1/2005−6/30/2015

	All (N= 356,838)					Matched (N= 89,503)				
	Exenatide (N= 45,791)		OADs (N= 311,047)		Standardized Difference	Exenatide (N= 32,191)		OADs (N = 57,312)		Standardized Difference
Baseline Malignancies	**N**	**%**	**N**	**%**		**N**	**%**	**N**	**%**	
Malignant neoplasm of larynx	7	0.0	139	0.0	0.02	4	0.0	11	0.0	0.00
Malignant neoplasm of trachea, bronchus, and lung	51	0.1	1,202	0.4	0.06	36	0.1	101	0.2	0.02
Malignant neoplasm of pleura	2	0.0	36	0.0	0.01	1	0.0	4	0.0	0.00
Malignant neoplasm of thymus, heart, and mediastinum	4	0.0	45	0.0	0.01	3	0.0	5	0.0	0.00
Malignant neoplasm of other and ill-defined sites within the respiratory system and intrathoracic organs	0	0.0	13	0.0	0.01	0	0.0	0	0.0	−
Malignant neoplasm of bone and articular cartilage	8	0.0	174	0.1	0.02	5	0.0	14	0.0	0.01
Malignant neoplasm of connective and other soft tissue	18	0.0	228	0.1	0.01	13	0.0	37	0.1	0.01
Malignant melanoma of skin	79	0.2	556	0.2	0.00	55	0.2	85	0.1	0.01
Other and unspecified malignant neoplasm of skin	495	1.1	3,675	1.2	0.01	330	1.0	575	1.0	0.00
Malignant neoplasm of female breast	495	1.1	3,338	1.1	0.00	347	1.1	688	1.2	0.01
Malignant neoplasm of male breast	5	0.0	43	0.0	0.00	5	0.0	2	0.0	0.01
Kaposi's sarcoma	2	0.0	20	0.0	0.00	1	0.0	4	0.0	0.00
Malignant neoplasm of uterus, part unspecified	26	0.1	181	0.1	0.00	18	0.1	32	0.1	0.00
Malignant neoplasm of cervix uteri	19	0.0	150	0.0	0.00	11	0.0	18	0.0	0.00
Malignant neoplasm of placenta	0	0.0	2	0.0	0.00	0	0.0	0	0.0	−
Malignant neoplasm of body of uterus	91	0.2	524	0.2	0.01	66	0.2	99	0.2	0.01
Malignant neoplasm of ovary and other uterine adnexa	39	0.1	371	0.1	0.01	33	0.1	64	0.1	0.00
Malignant neoplasm of other and unspecified female genital organs	4	0.0	75	0.0	0.01	1	0.0	10	0.0	0.01
Malignant neoplasm of prostate	260	0.6	3,429	1.1	0.06	208	0.6	417	0.7	0.01
Malignant neoplasm of testis	18	0.0	146	0.0	0.00	14	0.0	18	0.0	0.01
Malignant neoplasm of penis and other male genital organs	2	0.0	34	0.0	0.01	2	0.0	5	0.0	0.00
Malignant neoplasm of bladder	95	0.2	814	0.3	0.01	69	0.2	95	0.2	0.01

Table 2.2.1a. Prevalence of Malignances During the 9-Month Baseline Period, Optum Research Database 6/1/2005−6/30/2015

	All (N= 356,838)					Matched (N= 89,503)				
	Exenatide (N= 45,791)		OADs (N= 311,047)		Standardized Difference	Exenatide (N= 32,191)		OADs (N = 57,312)		Standardized Difference
Baseline Malignancies	**N**	**%**	**N**	**%**		**N**	**%**	**N**	**%**	
Malignant neoplasm of kidney and other and unspecified urinary organs	88	0.2	774	0.2	0.01	68	0.2	92	0.2	0.01
Malignant neoplasm of eye	10	0.0	69	0.0	0.00	7	0.0	7	0.0	0.01
Malignant neoplasm of brain	16	0.0	464	0.1	0.04	12	0.0	42	0.1	0.02
Malignant neoplasm of other and unspecified parts of nervous system	10	0.0	98	0.0	0.01	8	0.0	5	0.0	0.01
Malignant neoplasm of other endocrine glands and related structures	28	0.1	118	0.0	0.01	19	0.1	14	0.0	0.01
Malignant neoplasm of other and ill-defined sites	25	0.1	302	0.1	0.02	19	0.1	32	0.1	0.00
Secondary and unspecified malignant neoplasm of lymph nodes	35	0.1	899	0.3	0.05	22	0.1	94	0.2	0.03
Secondary malignant neoplasm of respiratory and digestive systems	32	0.1	1,044	0.3	0.06	21	0.1	100	0.2	0.03
Secondary malignant neoplasm of other specified sites	34	0.1	1,270	0.4	0.07	22	0.1	130	0.2	0.04
Malignant neoplasm without specification of site	36	0.1	847	0.3	0.05	24	0.1	69	0.1	0.02
Lymphosarcoma and reticulosarcoma and other specified malignant tumors of lymphatic tissue	61	0.1	507	0.2	0.01	43	0.1	82	0.1	0.00
Hodgkin's disease	35	0.1	252	0.1	0.00	25	0.1	24	0.0	0.01
Other malignant neoplasms of lymphoid and histiocytic tissue	89	0.2	1,162	0.4	0.04	66	0.2	141	0.2	0.01
Multiple myeloma and immunoproliferative neoplasms	17	0.0	395	0.1	0.03	12	0.0	69	0.1	0.03
Lymphoid leukemia	34	0.1	449	0.1	0.02	26	0.1	45	0.1	0.00
Myeloid leukemia	43	0.1	417	0.1	0.01	26	0.1	72	0.1	0.02
Monocytic leukemia	2	0.0	32	0.0	0.01	2	0.0	2	0.0	0.00
Other specified leukemia	0	0.0	18	0.0	0.01	0	0.0	2	0.0	0.01
Leukemia of unspecified cell type	9	0.0	245	0.1	0.03	8	0.0	23	0.0	0.01
Neuroendocrine tumors	7	0.0	128	0.0	0.02	6	0.0	10	0.0	0.00
Personal history of malignant neoplasm	1,327	2.9	10,549	3.4	0.03	916	2.8	1,641	2.9	0.00

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.
Standardized difference is calculated by the difference between the 2 proportions divided by the pooled standard deviation.
Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 2.2b. Prevalence of Common Baseline* Characteristics, Impact National Benchmark Database 6/1/2005−3/31/2015

	All (N= 166,903)					Matched (N= 42,886)					Not Matched (N= 124,017)	
	Exenatide (N= 24,287)		OAD (N= 142,616)		Standardized Difference	Exenatide (N= 15,755)		OADs (N= 27,131)		Standardized Difference	Exenatide (N= 8,532)	
Characteristic	**N**	**%**	**N**	**%**		**N**	**%**	**N**	**%**		**N**	**%**
Other Lab	20,018	82.4	109,573	76.8	0.14	12,740	80.9	21,733	80.1	0.01	7,278	85.3
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: An expanded problem focused history; An expanded problem focused examination; Medical decision making of low complexity.	19,586	80.6	105,695	74.1	0.16	12,514	79.4	21,360	78.7	0.00	7,072	82.9
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A detailed history; A detailed examination; Medical decision making of moderate complexity.	20,156	83.0	104,528	73.3	0.25	12,658	80.3	21,669	79.9	0.00	7,498	87.9
Other therapeutic procedure	16,590	68.3	94,734	66.4	0.04	10,696	67.9	18,454	68.0	0.01	5,894	69.1
Metformin	20,022	82.4	89,346	62.6	0.48	12,421	78.8	21,010	77.4	0.01	7,601	89.1
Disorders of lipoid metabolism	17,544	72.2	89,989	63.1	0.21	11,015	69.9	18,852	69.5	0.00	6,529	76.5
Glycated hemoglobin test	16,748	69.0	89,482	62.7	0.14	10,633	67.5	18,127	66.8	0.01	6,115	71.7
Northeast	15,463	63.7	89,271	62.6	0.02	9,918	63.0	17,031	62.8	0.00	5,545	65.0
Male	11,918	49.1	85,063	59.6	0.23	7,876	50.0	13,772	50.8	0.00	4,042	47.4
Statins	15,610	64.3	79,485	55.7	0.18	9,781	62.1	16,758	61.8	0.00	5,829	68.3
Lipid panel	14,299	58.9	76,108	53.4	0.12	9,010	57.2	15,492	57.1	0.00	5,289	62.0
Hypercholesterolemia	14,788	60.9	74,155	52.0	0.19	9,125	57.9	15,772	58.1	0.02	5,663	66.4
Microscopic exam (smear culture)	12,949	53.3	69,919	49.0	0.09	8,151	51.7	14,049	51.8	0.01	4,798	56.2
Blood sugar diagnostics	14,988	61.7	65,602	46.0	0.33	9,009	57.2	15,175	55.9	0.00	5,979	70.1
Ace inhibitors	11,591	47.7	66,936	46.9	0.02	7,425	47.1	12,962	47.8	0.01	4,166	48.8
1 Anti-diabetic medication within 45 days of index	9,635	39.7	63,019	44.2	0.09	6,702	42.5	11,611	42.8	0.01	2,933	34.4
Lipotropics	13,518	55.7	54,563	38.3	0.37	8,376	53.2	13,987	51.6	0.01	5,142	60.3
Sulfonylureas	12,607	51.9	54,725	38.4	0.28	7,293	46.3	12,325	45.4	0.01	5,314	62.3
50-59 years of age	9,943	40.9	54,533	38.2	0.06	6,303	40.0	10,764	39.7	0.00	3,640	42.7
Electrocardiogram	8,751	36.0	53,950	37.8	0.04	5,520	35.0	9,542	35.2	0.01	3,231	37.9
Other diagnostic radiology	8,956	36.9	45,681	32.0	0.11	5,423	34.4	9,226	34.0	0.00	3,533	41.4
Microalbumin quantitative	8,410	34.6	41,498	29.1	0.12	5,173	32.8	8,704	32.1	0.01	3,237	37.9
60-69 years of age	6,335	26.1	42,278	29.6	0.08	4,225	26.8	7,407	27.3	0.01	2,110	24.7
Anti-hyperlipidemic - HMG CoA reductase inhibitors	5,560	22.9	41,647	29.2	0.15	3,549	22.5	6,501	24.0	0.00	2,011	23.6
Analgesics, narcotics	7,110	29.3	38,557	27.0	0.05	4,373	27.8	7,569	27.9	0.01	2,737	32.1
Symptoms involving respiratory system and other chest symptoms	6,718	27.7	38,398	26.9	0.01	4,101	26.0	7,047	26.0	0.00	2,617	30.7
Thiazolidinediones	10,589	43.6	31,879	22.4	0.49	5,841	37.1	9,729	35.9	0.02	4,748	55.6
Miscellaneous medication administration	7,215	29.7	33,592	23.6	0.14	4,245	26.9	7,172	26.4	0.00	2,970	34.8
Beta-adrenergic blocking agents	5,936	24.4	34,047	23.9	0.01	3,734	23.7	6,606	24.3	0.02	2,202	25.8
Urine creatinine assay	6,847	28.2	32,737	23.0	0.12	4,161	26.4	6,939	25.6	0.01	2,686	31.5
General symptoms	6,466	26.6	33,027	23.2	0.08	3,859	24.5	6,545	24.1	0.00	2,607	30.6

[redacted] * Characteristics, Impact National Benchmark Database 6/1/2005−3/31/2015

	All (N= 166,903)					Matched (N= 42,886)					Not Matched (N= 124,017)	
	Exenatide (N= 24,287)		OAD (N= 142,616)		Standardized Difference	Exenatide (N= 15,755)		OADs (N= 27,131)		Standardized Difference	Exenatide (N= 8,532)	
Characteristic	N	%	N	%		N	%	N	%		N	%
Routine chest x-ray	4,860	20.0	33,588	23.6	0.09	2,978	18.9	5,283	19.5	0.02	1,882	22.1
Special investigations and examinations	6,224	25.6	31,937	22.4	0.08	3,908	24.8	6,567	24.2	0.01	2,316	27.1
Durable medical equipment, miscellaneous (Group 1)	5,970	24.6	31,009	21.7	0.07	3,771	23.9	6,302	23.2	0.01	2,199	25.8
General medical examination	4,874	20.1	31,855	22.3	0.06	3,165	20.1	5,549	20.5	0.00	1,709	20.0
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A problem focused history; A problem focused examination; Straightforward medical decision making.	6,130	25.2	28,390	19.9	0.13	3,669	23.3	6,198	22.8	0.00	2,461	28.8
South	4,850	20.0	29,252	20.5	0.01	3,174	20.1	5,536	20.4	0.01	1,676	19.6
Durable medical equipment and supplies	5,446	22.4	28,361	19.9	0.06	3,253	20.6	5,588	20.6	0.00	2,193	25.7
NSAIDs	5,200	21.4	27,186	19.1	0.06	3,276	20.8	5,590	20.6	0.00	1,924	22.6
Eye exam treatment	5,843	24.1	26,457	18.6	0.14	3,553	22.6	5,963	22.0	0.00	2,290	26.8
Preventive visit; established patient, 18-39 years	5,113	21.1	27,045	19.0	0.05	3,238	20.6	5,406	19.9	0.02	1,875	22.0
Acid-suppressing drugs	5,333	22.0	26,053	18.3	0.10	3,220	20.4	5,491	20.2	0.00	2,113	24.8
Flu vaccine, 3 yrs & >, split virus	5,391	22.2	25,051	17.6	0.12	3,393	21.5	5,695	21.0	0.00	1,998	23.4
Need for prophylactic vaccination and inoculation against certain viral diseases	5,007	20.6	24,585	17.2	0.09	3,126	19.8	5,208	19.2	0.01	1,881	22.0
Hypotensives, angiotensin receptor antagonist	6,349	26.1	23,207	16.3	0.26	3,690	23.4	6,093	22.5	0.00	2,659	31.2
Vaginal Delivery	6,255	25.8	23,075	16.2	0.24	3,456	21.9	5,617	20.7	0.01	2,799	32.8
Penicillins	4,657	19.2	24,303	17.0	0.06	2,860	18.2	4,910	18.1	0.01	1,797	21.1
2 Anti-diabetic medications within 45 days of index	5,883	24.2	22,382	15.7	0.22	3,463	22.0	5,624	20.7	0.02	2,420	28.4
Insulins	7,755	31.9	20,421	14.3	0.44	3,291	20.9	5,448	20.1	0.01	4,464	52.3
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A comprehensive history; A comprehensive examination; Medical decision making of high complexity.	4,982	20.5	21,712	15.2	0.14	2,907	18.5	4,737	17.5	0.01	2,075	24.3
Encounter for other and unspecified procedure and aftercare	3,976	16.4	22,068	15.5	0.02	2,361	15.0	4,024	14.8	0.00	1,615	18.9
Calcium channel blocking agents	3,903	16.1	22,126	15.5	0.02	2,418	15.3	4,346	16.0	0.02	1,485	17.4
Office consultation for a new or established patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical decision making of moderate complexity.	5,410	22.3	20,398	14.3	0.21	3,122	19.8	5,033	18.6	0.01	2,288	26.8
Macrolides	4,483	18.5	21,318	14.9	0.10	2,715	17.2	4,817	17.8	0.02	1,768	20.7
Other disorders of soft tissues	4,167	17.2	21,302	14.9	0.06	2,471	15.7	4,264	15.7	0.01	1,696	19.9
Quantitative glucose assay	3,873	15.9	21,059	14.8	0.03	2,401	15.2	4,222	15.6	0.01	1,472	17.3
Non-alcohol sedatives	4,119	17.0	19,786	13.9	0.09	2,517	16.0	4,327	15.9	0.01	1,602	18.8
Quinolones	4,048	16.7	19,856	13.9	0.08	2,423	15.4	4,176	15.4	0.01	1,625	19.0

Table 2.2b. Prevalence of Common Baseline* Characteristics, Impact National Benchmark Database 6/1/2005−3/31/2015

	All (N= 166,903)					Matched (N= 42,886)					Not Matched (N= 124,017)	
	Exenatide (N= 24,287)		OAD (N= 142,616)		Standardized Difference	Exenatide (N= 15,755)		OADs (N= 27,131)		Standardized Difference	Exenatide (N= 8,532)	
Characteristic	**N**	**%**	**N**	**%**		**N**	**%**	**N**	**%**		**N**	**%**
Electrocardiogram report	2,568	10.6	21,126	14.8	0.14	1,551	9.8	2,847	10.5	0.02	1,017	11.9
Prostate specific antigen	2,724	11.2	20,292	14.2	0.10	1,795	11.4	3,235	11.9	0.01	929	10.9
Glucose blood test	3,701	15.2	18,171	12.7	0.07	2,204	14.0	3,783	13.9	0.00	1,497	17.5
Echocardiogram	3,077	12.7	18,474	13.0	0.01	1,833	11.6	3,192	11.8	0.01	1,244	14.6
General health panel	3,154	13.0	17,948	12.6	0.01	1,992	12.6	3,421	12.6	0.00	1,162	13.6
Urinalysis; automated with mircroscopy	2,761	11.4	17,825	12.5	0.04	1,807	11.5	3,146	11.6	0.00	954	11.2
Other diagnostic ultrasound	3,143	12.9	17,397	12.2	0.02	1,882	11.9	3,284	12.1	0.01	1,261	14.8
Tissue exam by pathologist	3,229	13.3	17,209	12.1	0.04	1,965	12.5	3,264	12.0	0.01	1,264	14.8
Thiazide and related diuretics	3,354	13.8	17,050	12.0	0.06	2,050	13.0	3,597	13.3	0.01	1,304	15.3
Midwest	2,609	10.7	17,340	12.2	0.05	1,746	11.1	3,071	11.3	0.00	863	10.1
Gastric acid secretion reducers	4,170	17.2	15,652	11.0	0.19	2,519	16.0	4,099	15.1	0.00	1,651	19.4
Nonspecific findings on examination of blood	2,160	8.9	17,599	12.3	0.12	1,438	9.1	2,552	9.4	0.00	722	8.5
Obesity	4,761	19.6	14,883	10.4	0.27	2,407	15.3	3,922	14.5	0.01	2,354	27.6
Office consultation for a new or established patient, which requires these 3 key components: A detailed history; A detailed examination; and Medical decision making of low complexity.	3,560	14.7	15,331	10.7	0.12	2,126	13.5	3,553	13.1	0.00	1,434	16.8
Glucocorticoids	2,663	11.0	15,300	10.7	0.01	1,627	10.3	2,923	10.8	0.02	1,036	12.1
Fibrates	3,204	13.2	13,428	9.4	0.13	1,873	11.9	3,240	11.9	0.01	1,331	15.6
Insulin glargine	5,167	21.3	11,010	7.7	0.40	1,991	12.6	3,243	12.0	0.01	3,176	37.2
Transferase; aspartate amino (AST) (SGOT)	2,859	11.8	13,161	9.2	0.09	1,751	11.1	2,869	10.6	0.01	1,108	13.0
Thyroid hormones	3,324	13.7	12,669	8.9	0.16	1,991	12.6	3,324	12.3	0.00	1,333	15.6
Subsequent hospital care	1,316	5.4	14,669	10.3	0.20	777	4.9	1,444	5.3	0.02	539	6.3
Anticonvulsants	2,903	12.0	13,034	9.1	0.10	1,683	10.7	2,938	10.8	0.01	1,220	14.3
Physical therapy exercises/manipulation	3,135	12.9	12,660	8.9	0.13	1,787	11.3	2,996	11.0	0.00	1,348	15.8
Automated hemogram	1,921	7.9	13,857	9.7	0.07	1,230	7.8	2,226	8.2	0.01	691	8.1
Symptoms involving skin and other integumentary tissue	2,639	10.9	13,114	9.2	0.06	1,572	10.0	2,578	9.5	0.01	1,067	12.5
Loop diuretics	3,130	12.9	12,601	8.8	0.13	1,777	11.3	2,912	10.7	0.00	1,353	15.9
Osteoarthrosis and allied disorders	2,691	11.1	12,547	8.8	0.08	1,579	10.0	2,652	9.8	0.01	1,112	13.0
Beta-adrenergic agents	2,569	10.6	12,382	8.7	0.07	1,535	9.7	2,713	10.0	0.01	1,034	12.1
Radioisotope scan/function	2,481	10.2	12,081	8.5	0.06	1,444	9.2	2,525	9.3	0.02	1,037	12.2
Chest x-ray	1,359	5.6	13,164	9.2	0.15	822	5.2	1,507	5.6	0.02	537	6.3
Other disorders of urethra and urinary tract	2,206	9.1	12,118	8.5	0.02	1,410	8.9	2,357	8.7	0.00	796	9.3
Symptoms involving digestive system	1,816	7.5	12,220	8.6	0.04	1,137	7.2	2,038	7.5	0.01	679	8.0
Doppler color flow	2,366	9.7	11,668	8.2	0.05	1,397	8.9	2,388	8.8	0.01	969	11.4
Total creatinine kinase (CK), (CPK) assay	2,304	9.5	11,387	8.0	0.05	1,384	8.8	2,259	8.3	0.01	920	10.8
Peripheral enthesopathies and allied syndromes	2,498	10.3	10,724	7.5	0.10	1,460	9.3	2,436	9.0	0.00	1,038	12.2
Skeletal muscle relaxants	2,194	9.0	11,026	7.7	0.05	1,341	8.5	2,359	8.7	0.01	853	10.0
CT Scan Abdomen	1,651	6.8	11,463	8.0	0.05	1,044	6.6	1,750	6.5	0.01	607	7.1
Topical anti-inflammatory steroidal	2,189	9.0	10,647	7.5	0.06	1,351	8.6	2,367	8.7	0.01	838	9.8

Table 2.2b. Prevalence of Common Baseline* Characteristics, Impact National Benchmark Database 6/1/2005−3/31/2015

	All (N= 166,903)					Matched (N= 42,886)					Not Matched (N= 124,017)	
	Exenatide (N= 24,287)		OAD (N= 142,616)		Standardized Difference	Exenatide (N= 15,755)		OADs (N= 27,131)		Standardized Difference	Exenatide (N= 8,532)	
Characteristic	**N**	**%**	**N**	**%**		**N**	**%**	**N**	**%**		**N**	**%**
Nasal anti-inflammatory steroids	2,378	9.8	10,443	7.3	0.09	1,409	8.9	2,483	9.2	0.01	969	11.4
Hospitalization within 45 days of index	498	2.1	12,204	8.6	0.31	352	2.2	696	2.6	0.02	146	1.7
Critical care procedure	186	0.8	3,804	2.7	0.16	124	0.8	233	0.9	0.01	62	0.7
Peripheral neuropathy	2,802	11.5	9,438	6.6	0.18	1,438	9.1	2,299	8.5	0.01	1,364	16.0
Nephritis and nephropathy, not specified as acute or chronic	297	1.2	1,164	0.8	0.04	157	1.0	257	0.9	0.00	140	1.6
Retinopathy	1,522	6.3	5,935	4.2	0.10	841	5.3	1,471	5.4	0.01	681	8.0
Hypertension	15,101	62.2	83,306	58.4	0.08	9,512	60.4	16,295	60.1	0.00	5,589	65.5
Hyperlipidemia	18,977	78.1	93,327	65.4	0.30	11,947	75.8	20,348	75.0	0.00	7,030	82.4
Ischemic heart disease	3,294	13.6	18,757	13.2	0.01	1,955	12.4	3,459	12.7	0.02	1,339	15.7
Myocardial infarction	317	1.3	3,107	2.2	0.07	189	1.2	323	1.2	0.00	128	1.5
Congestive heart failure	791	3.3	5,396	3.8	0.03	471	3.0	757	2.8	0.01	320	3.8
Stroke/TIA in baseline	433	1.8	3,788	2.7	0.06	258	1.6	503	1.9	0.02	175	2.1
Thyrotropin releasing hormone	7,202	29.7	31,011	21.7	0.19	4,234	26.9	7,147	26.3	0.00	2,968	34.8
T3, T4 testing	4,045	16.7	15,398	10.8	0.18	2,271	14.4	3,754	13.8	0.00	1,774	20.8
Computerized tomography (CT), soft tissue neck	105	0.4	802	0.6	0.02	55	0.3	103	0.4	0.01	50	0.6
Thyroid imaging	70	0.3	220	0.2	0.03	42	0.3	73	0.3	0.01	28	0.3
Ultrasound of head and neck	602	2.5	1,729	1.2	0.10	314	2.0	485	1.8	0.01	288	3.4
Biopsy thyroid	107	0.4	523	0.4	0.01	58	0.4	112	0.4	0.01	49	0.6
Thyroidectomy	15	0.1	39	0.0	0.02	3	0.0	9	0.0	0.01	12	0.1
Other operations on thyroid	3	0.0	10	0.0	0.01	0	0.0	1	0.0	0.01	3	0.0
Lipase	472	1.9	3,537	2.5	0.04	300	1.9	538	2.0	0.01	172	2.0
Amylase	500	2.1	3,391	2.4	0.02	312	2.0	544	2.0	0.00	188	2.2
Abdominal ultrasound	1,189	4.9	7,605	5.3	0.02	722	4.6	1,235	4.6	0.00	467	5.5
Biopsy of pancreas	0	0.0	4	0.0	0.01	0	0.0	0	0.0	−	0	0.0
Pancreatectomy	1	0.0	20	0.0	0.01	0	0.0	0	0.0	−	1	0.0
Endobronchial ultrasound	1	0.0	18	0.0	0.01	0	0.0	1	0.0	0.01	1	0.0
Magnetic resonance imaging (MRI), abdomen	146	0.6	1,121	0.8	0.02	79	0.5	143	0.5	0.00	67	0.8
Magnetic resonance cholangiopancreatography (MRCP)	1	0.0	14	0.0	0.01	0	0.0	0	0.0	−	1	0.0
Endoscopic retrograde cholangiopancreatography (ERCP)	12	0.0	240	0.2	0.04	7	0.0	9	0.0	0.01	5	0.1
Other operations on pancreas	0	0.0	23	0.0	0.02	0	0.0	0	0.0	−	0	0.0
X-ray for pancreas	36	0.1	271	0.2	0.01	15	0.1	35	0.1	0.01	21	0.2
Micro exam of pancreas	0	0.0	0	0.0	−	0	0.0	0	0.0	−	0	0.0
Abdominal pain	2,586	10.6	16,038	11.2	0.02	1,622	10.3	2,808	10.3	0.00	964	11.3
Other nonspecific abnormal serum enzyme levels	155	0.6	1,099	0.8	0.02	95	0.6	161	0.6	0.00	60	0.7

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.

Standardized difference is calculated by the difference between the 2 proportions divided by the pooled standard deviation.

* Baseline includes 9-month period prior to drug initiation

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 2.2.1b. Prevalence of Baseline Malignances During the 9-Month Baseline Period, Impact National Benchmark Database 6/1/2005−3/31/2015

	All (N= 166,903)					Matched (N= 42,886)				
	Exenatide (N= 24,287)		OADs (N= 142,616)		Standardized Difference	Exenatide (N= 15,755)		OADs (N= 27,131)		Standardized Difference
Baseline Malignancies	**N**	**%**	**N**	**%**		**N**	**%**	**N**	**%**	
Malignant neoplasm of lip	3	0.0	16	0.0	0.00	3	0.0	3	0.0	0.01
Malignant neoplasm of tongue	3	0.0	39	0.0	0.01	1	0.0	2	0.0	0.00
Malignant neoplasm of major salivary glands	2	0.0	21	0.0	0.01	1	0.0	3	0.0	0.01
Malignant neoplasm of gum	0	0.0	4	0.0	0.01	0	0.0	0	0.0	–
Malignant neoplasm of floor of mouth	1	0.0	15	0.0	0.01	1	0.0	3	0.0	0.01
Malignant neoplasm of other and unspecified parts of mouth	1	0.0	35	0.0	0.02	1	0.0	2	0.0	0.00
Malignant neoplasm of oropharynx	1	0.0	37	0.0	0.02	1	0	3	0.0	0.00
Malignant neoplasm of nasopharynx	2	0.0	22	0.0	0.01	1	0.0	3	0.0	0.00
Malignant neoplasm of hypopharynx	1	0.0	4	0.0	0.00	0	0.0	0	0.0	–
Malignant neoplasm of other and ill-defined sites within the lip, oral cavity, and pharynx	0	0.0	24	0.0	0.02	0	0.0	3	0.0	0.02
Malignant neoplasm of esophagus	0	0.0	90	0.1	0.04	0	0.0	7	0.0	0.02
Malignant neoplasm of stomach Malignant	3	0.0	94	0.1	0.03	2	0.0	7	0.0	0.01
neoplasm of small intestine, including duodenum	1	0.0	28	0.0	0.01	1	0.0	6	0.0	0.01
Malignant neoplasm of colon	55	0.2	612	0.4	0.04	43	0.3	84	0.3	0.00
Malignant neoplasm of rectum, rectosigmoid junction, and anus Malignant	28	0.1	390	0.3	0.04	21	0.1	54	0.2	0.01
neoplasm of liver and intrahepatic bile ducts	4	0.0	182	0.1	0.04	4	0.0	15	0.1	0.01
Malignant neoplasm of gallbladder and extrahepatic bile ducts	2	0.0	34	0.0	0.01	1	0.0	4	0.0	0.01
Malignant neoplasm of retroperitoneum and peritoneum	4	0.0	38	0.0	0.01	1	0.0	4	0.0	0.01
Malignant neoplasm of other and ill-defined sites within the digestive organs and peritoneum	0	0.0	43	0.0	0.02	0	0.0	5	0.0	0.02
Malignant neoplasm of nasal cavities, middle ear, and accessory sinuses	3	0.0	23	0.0	0.00	3	0.0	3	0.0	0.01
Malignant neoplasm of larynx	10	0.0	78	0.1	0.01	8	0.1	8	0.0	0.01
Malignant neoplasm of trachea, bronchus, and lung	37	0.2	628	0.4	0.06	24	0.2	63	0.2	0.02
Malignant neoplasm of pleura	0	0.0	23	0.0	0.02	0	0.0	3	0.0	0.01
Malignant neoplasm of thymus, heart, and mediastinum	4	0.0	21	0.0	0.00	3	0.0	4	0.0	0.01

Table 2.2.1b. Prevalence of Baseline Malignances During the 9-Month Baseline Period, Impact National Benchmark Database 6/1/2005−3/31/2015

	All (N= 166,903)					Matched (N= 42,886)				
	Exenatide (N= 24,287)		OADs (N= 142,616)		Standardized Difference	Exenatide (N= 15,755)		OADs (N= 27,131)		Standardized Difference
Baseline Malignancies	**N**	**%**	**N**	**%**		**N**	**%**	**N**	**%**	
Malignant neoplasm of other and ill-defined sites within the respiratory system and intrathoracic organs	2	0.0	9	0.0	0.00	0	0.0	0	0.0	–
Malignant neoplasm of bone and articular cartilage	8	0.0	94	0.1	0.02	6	0.0	8	0.0	0.00
Malignant neoplasm of connective and other soft tissue	17	0.1	162	0.1	0.02	6	0.0	26	0.1	0.02
Malignant melanoma of skin	42	0.2	287	0.2	0.01	23	0.1	53	0.2	0.01
Other and unspecified malignant neoplasm of skin	259	1.1	1,536	1.1	0.00	154	1.0	307	1.1	0.01
Malignant neoplasm of female breast	274	1.1	1,629	1.1	0.00	176	1.1	378	1.4	0.02
Malignant neoplasm of male breast	4	0.0	25	0.0	0.00	3	0.0	3	0.0	0.01
Kaposi's sarcoma	0	0.0	20	0.0	0.02	0	0.0	6	0.0	0.02
Malignant neoplasm of uterus, part unspecified	20	0.1	95	0.1	0.01	13	0.1	12	0.0	0.02
Malignant neoplasm of cervix uteri	13	0.1	86	0.1	0.00	8	0.1	12	0.0	0.00
Malignant neoplasm of body of uterus	56	0.2	262	0.2	0.01	37	0.2	49	0.2	0.01
Malignant neoplasm of ovary and other uterine adnexa	23	0.1	195	0.1	0.01	19	0.1	38	0.1	0.01
Malignant neoplasm of other and unspecified female genital organs	2	0.0	36	0.0	0.01	2	0.0	4	0.0	0.00
Malignant neoplasm of prostate	160	0.7	1,564	1.1	0.05	109	0.7	216	0.8	0.01
Malignant neoplasm of testis	6	0.0	74	0.1	0.01	4	0.0	10	0.0	0.01
Malignant neoplasm of penis and other male genital organs	1	0.0	16	0.0	0.01	0	0.0	1	0.0	0.01
Malignant neoplasm of bladder	64	0.3	454	0.3	0.01	45	0.3	62	0.2	0.01
Malignant neoplasm of kidney and other and unspecified urinary organs	67	0.3	397	0.3	0.00	41	0.3	50	0.2	0.02
Malignant neoplasm of eye	3	0.0	39	0.0	0.01	2	0.0	6	0.0	0.01
Malignant neoplasm of brain	9	0.0	249	0.2	0.04	5	0.0	23	0.1	0.02
Malignant neoplasm of other and unspecified parts of nervous system	4	0.0	54	0.0	0.01	2	0.0	3	0.0	0.00
Malignant neoplasm of other endocrine glands and related structures	11	0.0	67	0.0	0.00	4	0.0	10	0.0	0.01
Malignant neoplasm of other and ill-defined sites	11	0.0	185	0.1	0.03	9	0.1	17	0.1	0.01
Secondary and unspecified malignant neoplasm of lymph nodes	21	0.1	436	0.3	0.05	15	0.1	43	0.2	0.02

Table 2.2.1b. Prevalence of Baseline Malignances During the 9-Month Baseline Period, Impact National Benchmark Database 6/1/2005−3/31/2015

	All (N= 166,903)					Matched (N= 42,886)				
	Exenatide (N= 24,287)		OADs (N= 142,616)		Standardized Difference	Exenatide (N= 15,755)		OADs (N= 27,131)		Standardized Difference
Baseline Malignancies	**N**	**%**	**N**	**%**		**N**	**%**	**N**	**%**	
Secondary malignant neoplasm of respiratory and digestive systems	14	0.1	558	0.4	0.07	8	0.1	50	0.2	0.04
Secondary malignant neoplasm of other specified sites	24	0.1	685	0.5	0.07	14	0.1	67	0.2	0.03
Malignant neoplasm without specification of site	19	0.1	404	0.3	0.05	11	0.1	40	0.1	0.02
Lymphosarcoma and reticulosarcoma and other specified malignant tumors of lymphatic tissue	25	0.1	209	0.1	0.01	17	0.1	28	0.1	0.00
Hodgkin's disease	15	0.1	122	0.1	0.01	13	0.1	19	0.1	0.01
Other malignant neoplasms of lymphoid and histiocytic tissue	64	0.3	673	0.5	0.04	49	0.3	80	0.3	0.00
Multiple myeloma and immunoproliferative neoplasms	20	0.1	226	0.2	0.02	12	0.1	27	0.1	0.01
Lymphoid leukemia	18	0.1	248	0.2	0.03	12	0.1	27	0.1	0.01
Myeloid leukemia	22	0.1	197	0.1	0.02	12	0.1	28	0.1	0.01
Monocytic leukemia	2	0.0	19	0.0	0.01	1	0.0	2	0.0	0.00
Other specified leukemia	0	0.0	9	0.0	0.01	0	0.0	2	0.0	0.01
Leukemia of unspecified cell type	11	0.0	128	0.1	0.02	5	0.0	10	0.0	0.00
Neuroendocrine tumors	6	0.0	49	0.0	0.01	1	0.0	5	0.0	0.01
Personal history of malignant neoplasm	587	2.4	3,739	2.6	0.01	375	2.4	671	2.5	0.01

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.
Standardized difference is calculated by the difference between the 2 proportions divided by the pooled standard deviation.
Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 2.3a. Healthcare Utilization Baseline* Characteristics Among Exenatide Initiators and OADs Initiators, Optum Research Database 6/1/2005−6/30/2015

Characteristic	All (N= 356,838)				
	Exenatide (N= 45,791)		OADs (N= 311,047)		Standardized Difference
	N	%	N	%	
One Antidiabetic Medication within 45 Days of Cohort Entry	18,707	40.9	135,271	43.5	0.05
Two Antidiabetic Medications within 45 Days of Cohort Entry	10,378	22.7	45,488	14.6	0.22
Three and Over Antidiabetic Medications within 45 Days of Cohort Entry	5,492	12.0	10,883	3.5	0.34
Hospitalization within 45 days of Cohort Entry	965	2.1	28,283	9.1	0.32
Critical Care Evaluation and Management	568	1.2	10,563	3.4	0.15
0-5 Unique Drugs Dispensed	2,505	5.5	59,143	19.0	0.44
6-10 Unique Drugs Dispensed	15,631	34.1	136,153	43.8	0.20
11-15 Unique Drugs Dispensed	15,828	34.6	73,149	23.5	0.26
≥16 Unique Drugs Dispensed	11,827	25.8	42,602	13.7	0.32

	Mean	Median	IQR	Mean	Median	IQR	Standardized Difference
Number of Diabetes Drugs Dispensings**	8.4	8.0	4.0 - 11.0	5.0	4.0	2.0 - 8.0	0.79
Number of Diabetes Diagnoses**	4.2	3.0	2.0 - 5.0	3.8	3.0	2.0 - 4.0	0.11
Number of Physician Visits**	7.5	6.0	4.0 - 10.0	6.6	5.0	3.0 - 8.0	0.15
Number of Emergency Department Visits**	0.6	0.0	0.0 - 0.0	0.7	0.0	0.0 - 1.0	0.00
Number of Inpatient Days	0.5	0.0	0.0 - 0.0	1.5	0.0	0.0 - 0.0	0.17
Number of Inpatient Stays	0.1	0.0	0.0 - 0.0	0.2	0.0	0.0 - 0.0	0.20
Number of 3-Digit Diagnosis Codes	13.5	12.0	8.0 - 17.0	13.1	11.0	7.0 - 17.0	0.04
Number of Laboratory Tests	14.7	11.0	6.0 - 19.0	13.3	9.0	4.0 - 16.0	0.08
Number of Cardiovascular Procedures	0.7	0.0	0.0 - 1.0	0.8	0.0	0.0 - 1.0	0.06
Number of Procedures	2.7	2.0	1.0 - 4.0	2.4	2.0	1.0 - 3.0	0.10
Medical Costs ($)	2,204.8	1,130.3	541.8 - 2,506.5	2,448.4	907.5	399.4 - 2,302.2	0.05
Facility Costs ($)	3,371.0	440.0	65.9 - 2,256.8	5,899.4	380.8	31.2 - 2,701.8	0.14
Pharmacy Costs ($)	3,245.6	2,562.0	1,362.0 - 4,175.5	2,013.0	1,146.7	448.4 - 2,507.0	0.40
Days from Study Start to Index Date	1,128.6	849.0	430.0 - 1,542.0	1,566.9	1,416.0	642.0 - 2,410.0	0.47

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.

Standardized difference is calculated by the difference between the two proportions or two means divided by the pooled standard deviation.

* Baseline includes 9-month period prior to drug initiation

** One counted per day

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 2.3a. Healthcare Utilization Baseline* Characteristics Among Exenatide Initiators and OADs Initiators, Optum Research Database 6/1/2005−6/30/2015

Characteristic	Matched (N= 89,503)					Not Matched (N= 267,335)	
	Exenatide (N= 32,191)		OADs (N= 57,312)		Standardized Difference	Exenatide (N= 13,600)	
	N	%	N	%		N	%
One Antidiabetic Medication within 45 Days of Cohort Entry	13,862	43.1	25,119	43.8	0.01	4,845	35.6
Two Antidiabetic Medications within 45 Days of Cohort Entry	6,782	21.1	11,410	19.9	0.02	3,596	26.4
Three and Over Antidiabetic Medications within 45 Days of Cohort Entry	2,698	8.4	4,331	7.6	0.00	2,794	20.5
Hospitalization within 45 days of Cohort Entry	685	2.1	1,483	2.6	0.02	280	2.1
Critical Care Evaluation and Management	375	1.2	708	1.2	0.00	193	1.4
0-5 Unique Drugs Dispensed	2,211	6.9	4,588	8.0	0.02	294	2.2
6-10 Unique Drugs Dispensed	12,765	39.7	23,883	41.7	0.01	2,866	21.1
11-15 Unique Drugs Dispensed	10,792	33.5	17,773	31.0	0.04	5,036	37.0
≥16 Unique Drugs Dispensed	6,423	20.0	11,068	19.3	0.02	5,404	39.7

	Mean	Median	IQR	Mean	Median	IQR	Standardized Difference	Mean	Median	IQR
Number of Diabetes Drugs Dispensings**	7.5	7.0	4.0 - 10.0	6.7	6.0	3.0 - 9.0	0.12	10.6	10.0	6.0 - 14.0
Number of Diabetes Diagnoses**	3.9	3.0	2.0 - 5.0	3.8	3.0	2.0 - 5.0	0.00	4.9	4.0	3.0 - 6.0
Number of Physician Visits**	7.1	6.0	4.0 - 9.0	7.0	6.0	3.0 - 9.0	0.00	8.7	7.0	5.0 - 11.0
Number of Emergency Department Visits**	0.6	0.0	0.0 - 0.0	0.6	0.0	0.0 - 0.0	0.00	0.8	0.0	0.0 - 1.0
Number of Inpatient Days	0.4	0.0	0.0 - 0.0	0.5	0.0	0.0 - 0.0	0.03	0.6	0.0	0.0 - 0.0
Number of Inpatient Stays	0.1	0.0	0.0 - 0.0	0.1	0.0	0.0 - 0.0	0.02	0.1	0.0	0.0 - 0.0
Number of 3-Digit Diagnosis Codes	12.9	11.0	7.0 - 17.0	12.9	11.0	7.0 - 17.0	0.01	14.8	13.0	9.0 - 19.0
Number of Laboratory Tests	13.8	10.0	6.0 - 17.0	13.7	10.0	6.0 - 17.0	0.01	17.0	13.0	8.0 - 21.0
Number of Cardiovascular Procedures	0.7	0.0	0.0 - 1.0	0.7	0.0	0.0 - 1.0	0.01	0.8	0.0	0.0 - 1.0
Number of Procedures	2.6	2.0	1.0 - 3.0	2.6	2.0	1.0 - 3.0	0.01	3.1	2.0	1.0 - 4.0
Medical Costs ($)	2,030.3	1,014.4	487.8 - 2,276.2	2,170.1	1,003.5	468.2 - 2,327.1	0.04	2,617.6	1,455.0	713.1 - 3,047.2
Facility Costs ($)	3,114.4	381.0	56.0 - 2,012.0	3,531.9	390.0	51.4 - 2,159.7	0.03	3,978.3	614.4	94.9 - 2,911.7
Pharmacy Costs ($)	2,750.7	2,130.3	1,128.5 - 3,560.9	2,967.5	2,081.8	1,083.3 - 3,539.2	0.09	4,417.0	3,660.4	2,352.0 - 5,403.3
Days from Study Start to Index Date	1,158.3	894.0	461.0 - 1,569.0	1,218.0	965.0	490.0 - 1,679.0	0.00	1,058.4	742.0	378.0 - 1,472.5

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.
Standardized difference is calculated by the difference between the two proportions or two means divided by the pooled standard deviation.
* Baseline includes 9-month period prior to drug initiation
** One counted per day
Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 2.3b. Healthcare Utilization Baseline* Characteristics Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Impact National Benchmark Database 6/1/2005−3/31/2015

Characteristic	All (N= 166,903)				
	Exenatide (N= 24,287)		OADs (N= 142,616)		Standardized Difference
	N	%	N	%	
One Antidiabetic Medication within 45 Days of Cohort Entry	9,635	39.7	63,019	44.2	0.09
Two Antidiabetic Medications within 45 Days of Cohort Entry	5,883	24.2	22,382	15.7	0.22
Three and Over Antidiabetic Medications within 45 Days of Cohort Entry	3,268	13.5	5,778	4.1	0.35
Hospitalization within 45 days of Cohort Entry	498	2.1	12,204	8.6	0.31
Critical Care Evaluation and Management	186	0.8	3,804	2.7	0.16
0-5 Unique Drugs Dispensed	993	4.1	25,598	17.9	0.47
6-10 Unique Drugs Dispensed	7,814	32.2	62,894	44.1	0.25
11-15 Unique Drugs Dispensed	8,759	36.1	34,396	24.1	0.28
≥16 Unique Drugs Dispensed	6,721	27.7	19,728	13.8	0.36

	Mean	Median	IQR	Mean	Median	IQR	Standardized Difference
Number of Diabetes Drugs Dispensings**	8.9	8.0	5.0 - 12.0	5.3	4.0	2.0 - 8.0	0.82
Number of Diabetes Diagnoses**	4.0	3.0	2.0 - 5.0	3.4	3.0	1.0 - 4.0	0.20
Number of Physician Visits**	7.7	6.0	4.0 - 10.0	6.2	5.0	3.0 - 8.0	0.28
Number of Emergency Department Visits**	0.1	0.0	0.0 - 0.0	0.2	0.0	0.0 - 0.0	0.19
Number of Inpatient Days	0.5	0.0	0.0 - 0.0	1.4	0.0	0.0 - 0.0	0.18
Number of Inpatient Stays	0.1	0.0	0.0 - 0.0	0.2	0.0	0.0 - 0.0	0.13
Number of 3-Digit Diagnosis Codes	12.2	11.0	7.0 - 16.0	11.4	9.0	6.0 - 15.0	0.10
Number of Laboratory Tests	13.3	10.0	3.0 - 18.0	12.7	8.0	2.0 - 16.0	0.03
Number of Cardiovascular Procedures	0.9	0.0	0.0 - 1.0	1.0	0.0	0.0 - 1.0	0.03
Number of Procedures	2.9	2.0	1.0 - 4.0	2.6	2.0	1.0 - 3.0	0.08
Medical Costs ($)	3169.0	1656.8	765.0 - 3,569.2	3521.3	1258.7	527.3 - 3,197.0	0.05
Facility Costs ($)	2105.8	0.0	0.0 - 893.2	4478.3	0.0	0.0 - 1,176.9	0.16
Pharmacy Costs ($)	3314.1	2647.9	1,435.5 - 4,230.0	2033.8	1223.0	470.1 - 2,519.0	0.36
Days from Study Start to Index Date	957.4	686.0	352.0 - 1,207.0	1266.8	974.0	394.0 - 2,002.0	0.35

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.

Standardized difference is calculated by the difference between the two proportions or two means divided by the pooled standard deviation.

* Baseline includes 9-month period prior to drug initiation

** One counted per day

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 2.3b. Healthcare Utilization Baseline* Characteristics Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Impact National Benchmark Database 6/1/2005−3/31/2015

Characteristic	Matched (N= 42,886)					Not Matched (N= 124,017)	
	Exenatide (N= 15,755)		OADs (N= 27,131)		Standardized Difference	Exenatide (N= 8,532)	
	N	%	N	%		N	%
One Antidiabetic Medication within 45 Days of Cohort Entry	6,702	42.5	11,611	42.8	0.01	2,933	34.4
Two Antidiabetic Medications within 45 Days of Cohort Entry	3,463	22.0	5,624	20.7	0.02	2,420	28.4
Three and Over Antidiabetic Medications within 45 Days of Cohort Entry	1,543	9.8	2,412	8.9	0.00	1,725	20.2
Hospitalization within 45 days of Cohort Entry	352	2.2	696	2.6	0.02	146	1.7
Critical Care Evaluation and Management	124	0.8	233	0.9	0.01	62	0.7
0-5 Unique Drugs Dispensed	841	5.3	1,996	7.4	0.05	152	1.8
6-10 Unique Drugs Dispensed	6,157	39.1	10,951	40.4	0.01	1,657	19.4
11-15 Unique Drugs Dispensed	5,527	35.1	8,759	32.3	0.04	3,232	37.9
≥16 Unique Drugs Dispensed	3,230	20.5	5,425	20.0	0.02	3,491	40.9

	Mean	Median	IQR	Mean	Median	IQR	Standardized Difference	Mean	Median	IQR
Number of Diabetes Drugs Dispensings**	8.0	7.0	4.0 - 10.0	7.0	6.0	3.0 - 9.0	0.16	10.7	10.0	7.0 - 14.0
Number of Diabetes Diagnoses**	3.7	3.0	2.0 - 5.0	3.6	3.0	2.0 - 5.0	0.00	4.7	4.0	3.0 - 6.0
Number of Physician Visits**	7.0	6.0	4.0 - 9.0	6.9	6.0	4.0 - 9.0	0.00	8.8	8.0	5.0 - 11.0
Number of Emergency Department Visits**	0.1	0.0	0.0 - 0.0	0.1	0.0	0.0 - 0.0	0.01	0.1	0.0	0.0 - 0.0
Number of Inpatient Days	0.5	0.0	0.0 - 0.0	0.5	0.0	0.0 - 0.0	0.03	0.5	0.0	0.0 - 0.0
Number of Inpatient Stays	0.1	0.0	0.0 - 0.0	0.1	0.0	0.0 - 0.0	0.01	0.1	0.0	0.0 - 0.0
Number of 3-Digit Diagnosis Codes	11.5	10.0	6.0 - 15.0	11.5	10.0	6.0 - 15.0	0.02	13.6	12.0	8.0 - 17.0
Number of Laboratory Tests	12.3	9.0	3.0 - 17.0	12.3	9.0	3.0 - 17.0	0.01	15.1	11.0	4.0 - 20.0
Number of Cardiovascular Procedures	0.8	0.0	0.0 - 1.0	0.8	0.0	0.0 - 1.0	0.01	1.1	0.0	0.0 - 1.0
Number of Procedures	2.7	2.0	1.0 - 4.0	2.7	2.0	1.0 - 4.0	0.02	3.2	2.0	1.0 - 4.0
Medical Costs ($)	2,857.6	1,440.0	662.3 - 3,180.1	3,013.2	1,406.9	620.0 - 3,211.8	0.03	3,744.2	2,089.2	1,003.2 - 4,276.9
Facility Costs ($)	1,976.4	0.0	0.0 - 739.1	2,194.8	0.0	0.0 - 745.0	0.03	2,344.8	0.0	0.0 - 1,161.8
Pharmacy Costs ($)	2,785.5	2,220.0	1,181.9 - 3,614.9	2,831.3	2,053.7	1,067.7 - 3,480.5	0.05	4,290.1	3488.4	2,159.5 - 5,290.7
Days from Study Start to Index Date	949.4	706.0	366.0 - 1,200.0	983.2	733.0	372.0 - 1,308.0	0.01	972.0	642.0	335.0 - 1,218.5

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.
Standardized difference is calculated by the difference between the two proportions or two means divided by the pooled standard deviation.
* Baseline includes 9-month period prior to drug initiation
** One counted per day
Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 2.4a. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initiators by Duration of Follow-up, Optum Research Database 6/1/2005−6/30/2015

Characteristic	1 to < 2 years					2 to < 3 years				
	Exenatide (N= 6,622)		OADs (N= 13,272)		Standardized Difference	Exenatide (N= 4,359)		OADs (N= 7,474)		Standardized Difference
	N	%	N	%		N	%	N	%	
Age										
≤ 39	729	11.0	1,396	10.5	0.01	458	10.5	699	9.4	0.04
40-49	1,676	25.3	3,138	23.6	0.04	1,003	23.0	1,742	23.3	0.00
50-59	2,332	35.2	5,083	38.3	0.07	1,741	39.9	3,006	40.2	0.01
60-69	1,680	25.4	3,250	24.5	0.02	1,028	23.6	1,809	24.2	0.02
≥ 70	205	3.1	405	3.1	0.01	129	3.0	218	2.9	0.01
Number of Drugs Dispensed										
0-5 Unique drugs dispensed	482	7.3	1,076	8.1	0.00	303	7.0	586	7.8	0.01
6-10 Unique drugs dispensed	2,649	40.0	5,641	42.5	0.03	1,739	39.9	3,173	42.5	0.03
11-15 Unique drugs dispensed	2,206	33.3	4,138	31.2	0.03	1,409	32.3	2,294	30.7	0.02
≥16 Unique drugs dispensed	1,285	19.4	2,417	18.2	0.00	908	20.8	1,421	19.0	0.02
Gender										
Male	3,168	47.8	6,483	48.8	0.01	2,097	48.1	3,577	47.9	0.01
Geographic Area										
Northeast	428	6.5	827	6.2	0.00	271	6.2	480	6.4	0.01
Midwest	1,712	25.9	3,377	25.4	0.01	1,124	25.8	1,959	26.2	0.01
South	3,712	56.1	7,484	56.4	0.00	2,467	56.6	4,160	55.7	0.01
West	770	11.6	1,584	11.9	0.00	497	11.4	875	11.7	0.00
Unknown	0	0.0	0	0.0	−	0	0.0	0	0.0	−
Number of Physician Visits										
0-3 Physician visits	1,489	22.5	3,417	25.7	0.06	1,063	24.4	1,983	26.5	0.03
4-5 Physician visits	1,624	24.5	3,039	22.9	0.05	1,009	23.1	1,774	23.7	0.01
6-8 Physician visits	1,646	24.9	3,202	24.1	0.01	1,073	24.6	1,785	23.9	0.01
≥9 Physician visits	1,863	28.1	3,614	27.2	0.00	1,214	27.9	1,932	25.8	0.03
Number of Laboratory Tests										
0-4 Laboratory tests	1,194	18.0	2,469	18.6	0.00	777	17.8	1,383	18.5	0.01
5-9 Laboratory tests	1,771	26.7	3,473	26.2	0.02	1,178	27.0	2,033	27.2	0.00
10-15 Laboratory tests	1,617	24.4	3,367	25.4	0.02	1,071	24.6	1,915	25.6	0.03
>15 Laboratory tests	2,040	30.8	3,963	29.9	0.01	1,333	30.6	2,143	28.7	0.03
Stroke/transient ischemic attack	122	1.8	221	1.7	0.01	78	1.8	132	1.8	0.00
Ischemic heart disease	826	12.5	1,612	12.1	0.00	558	12.8	894	12.0	0.02
Myocardial infarction	116	1.8	193	1.5	0.02	58	1.3	119	1.6	0.02
Disorders of fluid, electrolyte, and acid-base balance	321	4.8	709	5.3	0.02	207	4.7	411	5.5	0.03
Other and unspecified anemias	488	7.4	1,005	7.6	0.01	307	7.0	551	7.4	0.02

Table 2.4a. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initiators by Duration of Follow-up, Optum Research Database 6/1/2005−6/30/2015

Characteristic	1 to < 2 years					2 to < 3 years				
	Exenatide (N= 6,622)		OADs (N= 13,272)		Standardized Difference	Exenatide (N= 4,359)		OADs (N= 7,474)		Standardized Difference
	N	%	N	%		N	%	N	%	
Acute sinusitis	719	10.9	1,332	10.0	0.02	453	10.4	776	10.4	0.00
Osteoarthrosis and allied disorders	727	11.0	1,512	11.4	0.02	503	11.5	819	11.0	0.01
Other and unspecified disorders of back	1,130	17.1	2,114	15.9	0.03	671	15.4	1,152	15.4	0.00
General symptoms	2,080	31.4	3,916	29.5	0.03	1,307	30.0	2,170	29.0	0.01
Symptoms involving skin and other integumentary issue	829	12.5	1,568	11.8	0.01	551	12.6	859	11.5	0.03
Symptoms involving head and neck	507	7.7	1,022	7.7	0.00	352	8.1	559	7.5	0.02
Symptoms involving digestive system	644	9.7	1,244	9.4	0.01	432	9.9	714	9.6	0.01
Encounter for other and unspecified procedure and aftercare	1,799	27.2	3,613	27.2	0.01	1,163	26.7	1,967	26.3	0.01
General medical examination	1,008	15.2	2,104	15.9	0.00	664	15.2	1,161	15.5	0.00
Hypothyroidism	721	10.9	1,268	9.6	0.04	465	10.7	688	9.2	0.04
Chest x-ray	425	6.4	913	6.9	0.02	302	6.9	466	6.2	0.03
Radiographic procedure	1,464	22.1	2,804	21.1	0.02	924	21.2	1,578	21.1	0.00
Basic metabolic panel	1,300	19.6	2,625	19.8	0.01	873	20.0	1,446	19.3	0.01
Comprehensive metabolic panel	3,580	54.1	7,097	53.5	0.01	2,421	55.5	4,064	54.4	0.01
Lipid panel	4,726	71.4	9,405	70.9	0.01	3,106	71.3	5,367	71.8	0.02
Urinalysis, automated, with microscopy	925	14.0	2,039	15.4	0.03	626	14.4	1,105	14.8	0.01
Albumin; urine, microalbumin, quantitative	2,309	34.9	4,729	35.6	0.02	1,559	35.8	2,622	35.1	0.02
Creatinine, other source	1,833	27.7	3,660	27.6	0.00	1,244	28.5	2,045	27.4	0.02
Glucose; quantitative, blood (except reagent strip)	861	13.0	1,754	13.2	0.01	578	13.3	976	13.1	0.01
Hemoglobin; glycosylated (A1C)	5,365	81.0	10,620	80.0	0.02	3,530	81.0	5,996	80.2	0.01
Thryroxine; free	821	12.4	1,478	11.1	0.04	548	12.6	799	10.7	0.05
Blood count; complete (CBC), automated (Hgb, Hct, RBC, WBC and platelet count) and automated differential WBC count	2,176	32.9	4,291	32.3	0.01	1,449	33.2	2,495	33.4	0.01
Level IV - Surgical pathology, gross and microscopic examination Abortion - spontaneous/missed Artery, biopsy Bone marrow, biopsy Bone exostosis Brain/meninges, other than for tumor resection Breast, biopsy, not requiring microscopic evaluation (truncated)	790	11.9	1,611	12.1	0.01	525	12.0	867	11.6	0.01
Unlisted miscellaneous pathology test	1,410	21.3	2,772	20.9	0.00	928	21.3	1,566	21.0	0.00
Immunization administration (includes percutaneous, intradermal, subcutaneous, or intramuscular injections); one vaccine (single or combination vaccine/toxoid)	1,259	19.0	2,432	18.3	0.02	853	19.6	1,340	17.9	0.04

Table 2.4a. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initiators by Duration of Follow-up, Optum Research Database 6/1/2005−6/30/2015

Characteristic	1 to < 2 years					2 to < 3 years				
	Exenatide (N= 6,622)		OADs (N= 13,272)		Standardized Difference	Exenatide (N= 4,359)		OADs (N= 7,474)		Standardized Difference
	N	%	N	%		N	%	N	%	
Ophthalmological services: medical examination and evaluation, with initiation or continuation of diagnostic and treatment program; comprehensive, established patient, one or more visits.	978	14.8	1,903	14.3	0.01	629	14.4	1,116	14.9	0.02
Determination of refractive state	714	10.8	1,364	10.3	0.02	457	10.5	845	11.3	0.03
Handling and/or conveyance of specimen for transfer from the physician's office to a laboratory	669	10.1	1,254	9.4	0.02	445	10.2	734	9.8	0.02
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A problem focused history; A problem focused examination; Straightforward medical decision making.	1,348	20.4	2,688	20.3	0.01	913	20.9	1,489	19.9	0.02
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: An expanded problem focused history; An expanded problem focused examination; Medical decision making of low complexity.	5,036	76.0	9,961	75.1	0.01	3,260	74.8	5,583	74.7	0.00
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A detailed history; A detailed examination; Medical decision making of moderate complexity.	5,497	83.0	10,837	81.7	0.02	3,613	82.9	6,056	81.0	0.04
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A comprehensive history; A comprehensive examination; Medical decision making of high complexity.	1,321	19.9	2,498	18.8	0.02	859	19.7	1,436	19.2	0.00
Subsequent hospital care, per day, for the evaluation and management of a patient, which requires at least 2 of these 3 key components: An expanded problem focused interval history; An expanded problem focused examination; Medical decision making of moderate complexity.	373	5.6	789	5.9	0.02	236	5.4	434	5.8	0.02

Table 2.4a. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initiators by Duration of Follow-up, Optum Research Database 6/1/2005−6/30/2015

Characteristic	1 to < 2 years					2 to < 3 years				
	Exenatide (N= 6,622)		OADs (N= 13,272)		Standardized Difference	Exenatide (N= 4,359)		OADs (N= 7,474)		Standardized Difference
	N	%	N	%		N	%	N	%	
Office consultation for a new or established patient, which requires these 3 key components: A detailed history; A detailed examination; and Medical decision making of low complexity.	701	10.6	1,401	10.6	0.01	482	11.1	747	10.0	0.02
Office consultation for a new or established patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical decision making of moderate complexity.	1,106	16.7	2,064	15.6	0.01	727	16.7	1,170	15.7	0.01
Emergency department visit for the evaluation and management of a patient, which requires these 3 key components: A detailed history; A detailed examination; and Medical decision making of moderate complexity.	441	6.7	886	6.7	0.00	277	6.4	469	6.3	0.00
Emergency department visit for the evaluation and management of a patient, which requires these 3 key components within the constraints imposed by the urgency of the patient's clinical condition and/or mental status: A comprehensive history; A comprehensive examination; and Medical decision making of high complexity.	538	8.1	1,092	8.2	0.00	343	7.9	604	8.1	0.01
Periodic comprehensive preventive medicine reevaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, established patient; 40-64 years.	1,008	15.2	1,962	14.8	0.01	667	15.3	1,160	15.5	0.01
Diagnostic ultrasound abdomen	468	7.1	934	7.0	0.00	298	6.8	521	7.0	0.01
Magnetic resonance imaging (MRI)	654	9.9	1,376	10.4	0.02	482	11.1	746	10.0	0.03
Nonoperative urinary measurements	1,673	25.3	3,395	25.6	0.01	1,081	24.8	1,909	25.5	0.01
Cardiac stress tests	658	9.9	1,339	10.1	0.02	453	10.4	718	9.6	0.01
Electrocardiogram	2,007	30.3	4,021	30.3	0.00	1,321	30.3	2,220	29.7	0.02
Microscopic exam (smear culture)	3,824	57.7	7,685	57.9	0.01	2,533	58.1	4,319	57.8	0.01
Radioisotope scan/function	606	9.2	1,298	9.8	0.03	431	9.9	687	9.2	0.01
Physical therapy exercises/manipulation	912	13.8	1,772	13.4	0.01	599	13.7	963	12.9	0.02
Ophthalmological/otologic diagnosis/treatment	2,000	30.2	3,821	28.8	0.03	1,260	28.9	2,207	29.5	0.02
Other diagnostic radiology	2,846	43.0	5,553	41.8	0.02	1,842	42.3	3,142	42.0	0.00

Table 2.4a. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initiators by Duration of Follow-up, Optum Research Database 6/1/2005−6/30/2015

Characteristic	1 to < 2 years					2 to < 3 years				
	Exenatide (N= 6,622)		OADs (N= 13,272)		Standardized Difference	Exenatide (N= 4,359)		OADs (N= 7,474)		Standardized Difference
	N	%	N	%		N	%	N	%	
Prophylactic vaccinations	1,795	27.1	3,429	25.8	0.03	1,187	27.2	1,909	25.5	0.04
Other therapeutic procedure	4,564	68.9	9,002	67.8	0.02	3,046	69.9	5,153	68.9	0.02
Other lab	5,909	89.2	11,821	89.1	0.00	3,934	90.3	6,689	89.5	0.02
Procedure codes not elsewhere specified	5,836	88.1	11,691	88.1	0.00	3,845	88.2	6,588	88.1	0.00
Vaginal delivery	1,375	20.8	2,607	19.6	0.01	942	21.6	1,470	19.7	0.04
Thyrotropin releasing hormone	1,712	25.9	3,408	25.7	0.01	1,174	26.9	1,920	25.7	0.01
Hypotensives, angiotensin receptor antagonist	1,376	20.8	2,755	20.8	0.02	953	21.9	1,518	20.3	0.01
Calcium channel blocking agents	1,005	15.2	2,056	15.5	0.00	692	15.9	1,176	15.7	0.01
Anti-anxiety drugs	641	9.7	1,265	9.5	0.00	404	9.3	745	10.0	0.03
Serotonin specific reuptake inhibitor (SSRIs)	1,128	17.0	2,111	15.9	0.02	701	16.1	1,118	15.0	0.02
Analgesics, narcotics	2,046	30.9	4,065	30.6	0.01	1,345	30.9	2,259	30.2	0.01
Anticonvulsants	785	11.9	1,531	11.5	0.00	489	11.2	846	11.3	0.01
Skeletal muscle relaxants	693	10.5	1,336	10.1	0.01	427	9.8	746	10.0	0.01
Beta-adrenergic agents	585	8.8	1,187	8.9	0.01	400	9.2	667	8.9	0.01
Blood sugar diagnostics	3,492	52.7	6,924	52.2	0.01	2,369	54.3	3,960	53.0	0.02
Lipotropics	2,853	43.1	5,647	42.5	0.03	1,851	42.5	3,133	41.9	0.03
Thyroid hormones	887	13.4	1,582	11.9	0.03	560	12.8	880	11.8	0.02
Thiazide and related diuretics	745	11.3	1,450	10.9	0.01	488	11.2	854	11.4	0.01
Loop diuretics	743	11.2	1,388	10.5	0.01	528	12.1	802	10.7	0.03
Penicillins	1,221	18.4	2,363	17.8	0.01	758	17.4	1,341	17.9	0.02
Macrolides	1,105	16.7	2,229	16.8	0.01	748	17.2	1,288	17.2	0.01
Quinolones	1,095	16.5	2,116	15.9	0.01	747	17.1	1,212	16.2	0.02
Durable medical equipment, miscellaneous (Group 1)	1,367	20.6	2,699	20.3	0.00	942	21.6	1,611	21.6	0.00
Diabetic supplies	417	6.3	809	6.1	0.01	282	6.5	484	6.5	0.01
Non-alcohol sedatives	1,032	15.6	1,960	14.8	0.01	668	15.3	1,134	15.2	0.01
Acid-supressing drugs	1,106	16.7	2,250	17.0	0.01	722	16.6	1,233	16.5	0.01
Metformin	5,163	78.0	10,147	76.5	0.01	3,337	76.6	5,695	76.2	0.01
Sulfonylureas	3,026	45.7	5,839	44.0	0.00	1,934	44.4	3,277	43.8	0.02
Thiazolidinediones	2,263	34.2	4,595	34.6	0.06	1,528	35.1	2,494	33.4	0.02
Insulin glargine	809	12.2	1,620	12.2	0.02	584	13.4	867	11.6	0.04
Insulins	1,373	20.7	2,630	19.8	0.00	942	21.6	1,532	20.5	0.01
Ace inhibitors	3,056	46.1	6,281	47.3	0.02	2,019	46.3	3,620	48.4	0.04
Obesity	1,249	18.9	2,333	17.6	0.02	820	18.8	1,261	16.9	0.04
Gastroesophageal reflux disease	666	10.1	1,280	9.6	0.01	395	9.1	700	9.4	0.02

Table 2.4a. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initiators by Duration of Follow-up, Optum Research Database 6/1/2005−6/30/2015

Characteristic	1 to < 2 years					2 to < 3 years				
	Exenatide (N= 6,622)		OADs (N= 13,272)		Standardized Difference	Exenatide (N= 4,359)		OADs (N= 7,474)		Standardized Difference
	N	%	N	%		N	%	N	%	
Hospitalization within 45 days of Index	139	2.1	346	2.6	0.03	95	2.2	184	2.5	0.01
1 Anti-diabetic medication within 45 days of index	2,881	43.5	5,775	43.5	0.01	1,908	43.8	3,376	45.2	0.02
2 Anti-diabetic medications within 45 days of index	1,409	21.3	2,611	19.7	0.03	918	21.1	1,501	20.1	0.01
NSAIDs	1,424	21.5	2,868	21.6	0.01	945	21.7	1,639	21.9	0.01
Fibrates	797	12.0	1,680	12.7	0.03	543	12.5	921	12.3	0.00
Statins	3,757	56.7	7,478	56.3	0.00	2,483	57.0	4,273	57.2	0.01
Critical care procedure	75	1.1	160	1.2	0.01	61	1.4	92	1.2	0.02
Nephritis and nephropathy, not specified as acute or chronic	75	1.1	148	1.1	0.01	55	1.3	76	1.0	0.02
Retinopathy	304	4.6	679	5.1	0.03	198	4.5	406	5.4	0.04
Hypertension	4,695	70.9	9,217	69.4	0.03	3,076	70.6	5,216	69.8	0.02
Congestive heart failure	199	3.0	424	3.2	0.01	138	3.2	249	3.3	0.02
Peripheral neuropathy	645	9.7	1,224	9.2	0.00	406	9.3	636	8.5	0.01
Hyperlipidemia	5,116	77.3	10,173	76.7	0.00	3,394	77.9	5,661	75.7	0.03
Thryotropin releasing hormone	1,712	25.9	3,408	25.7	0.01	1,174	26.9	1,920	25.7	0.01
T3, T4 testing	1,234	18.6	2,289	17.2	0.03	807	18.5	1,286	17.2	0.02
Computerized tomography (CT), soft tissue neck	29	0.4	64	0.5	0.01	22	0.5	33	0.4	0.01
Thyroid imaging	113	1.7	218	1.6	0.01	81	1.9	125	1.7	0.02
Ultrasound of head and neck	139	2.1	234	1.8	0.02	85	1.9	112	1.5	0.03
Biopsy thyroid	33	0.5	41	0.3	0.03	17	0.4	30	0.4	0.00
Thyroidectomy	4	0.1	7	0.1	0.00	0	0.0	2	0.0	0.02
Other operations on thyroid	0	0.0	0	0.0	−	0	0.0	0	0.0	−
Abdominal pain	778	11.7	1,553	11.7	0.00	522	12.0	888	11.9	0.00
Lipase	154	2.3	302	2.3	0.00	123	2.8	194	2.6	0.01
Amylase	149	2.3	304	2.3	0.01	110	2.5	169	2.3	0.01
Other nonspecific abnormal serum enzyme levels	68	1.0	140	1.1	0.00	45	1.0	77	1.0	0.00
Abdominal ultrasound	318	4.8	607	4.6	0.01	193	4.4	372	5.0	0.03
Biopsy of pancreas	0	0.0	0	0.0	−	0	0.0	0	0.0	−
Pancreatectomy	0	0.0	0	0.0	−	0	0.0	0	0.0	−
Endobronchial ultrasound	0	0.0	1	0.0	0.01	1	0.0	0	0.0	0.02
Magnetic resonance imaging (MRI), abdomen	36	0.5	67	0.5	0.00	18	0.4	29	0.4	0.00
Magnetic resonance cholangiopancreatography (MRCP)	0	0.0	0	0.0	−	0	0.0	0	0.0	−
Endoscopic retrograde cholangiopancreatography (ERCP)	4	0.1	4	0.0	0.01	2	0.0	5	0.1	0.01
Other operations on pancreas	0	0.0	0	0.0	−	0	0.0	0	0.0	−

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Characteristic	1 to < 2 years					2 to < 3 years				
	Exenatide (N= 6,622)		OADs (N= 13,272)		Standardized Difference	Exenatide (N= 4,359)		OADs (N= 7,474)		Standardized Difference
	N	%	N	%		N	%	N	%	
X-ray for pancreas	12	0.2	12	0.1	0.02	7	0.2	17	0.2	0.02
Micro exam of pancreas	0	0.0	0	0.0	−	0	0.0	0	0.0	−
Malignant neoplasm of lip	0	0.0	0	0.0	−	1	0.0	2	0.0	0.00
Malignant neoplasm of tongue	1	0.0	3	0.0	0.01	1	0.0	1	0.0	0.01
Malignant neoplasm of major salivary glands	1	0.0	2	0.0	0.00	2	0.0	1	0.0	0.02
Malignant neoplasm of gum	0	0.0	1	0.0	0.01	0	0.0	1	0.0	0.02
Malignant neoplasm of floor of mouth	0	0.0	1	0.0	0.02	0	0.0	0	0.0	−
Malignant neoplasm of other and unspecified parts of mouth	0	0.0	1	0.0	0.02	1	0.0	0	0.0	0.02
Malignant neoplasm of oropharynx	3	0.0	1	0.0	0.02	0	0.0	0	0.0	−
Malignant neoplasm of nasopharynx	0	0.0	3	0.0	0.02	0	0.0	0	0.0	−
Malignant neoplasm of hypopharynx	0	0.0	2	0.0	0.02	0	0.0	0	0.0	−
Malignant neoplasm of other and ill-defined sites within the lip, oral cavity, and pharynx	2	0.0	0	0.0	0.02	0	0.0	0	0.0	−
Malignant neoplasm of esophagus	0	0.0	4	0.0	0.02	0	0.0	0	0.0	−
Malignant neoplasm of stomach	1	0.0	4	0.0	0.01	0	0.0	2	0.0	0.02
Malignant neoplasm of small intestine, including duodenum	0	0.0	1	0.0	0.01	0	0.0	2	0.0	0.02
Malignant neoplasm of colon	9	0.1	39	0.3	0.03	13	0.3	22	0.3	0.00
Malignant neoplasm of rectum, rectosigmoid junction, and anus	9	0.1	17	0.1	0.00	5	0.1	16	0.2	0.03
Malignant neoplasm of liver and intrahepatic bile ducts	1	0.0	4	0.0	0.01	1	0.0	3	0.0	0.01
Malignant neoplasm of gallbladder and extrahepatic bile ducts	0	0.0	1	0.0	0.01	0	0.0	0	0.0	−
Malignant neoplasm of retroperitoneum and peritoneum	1	0.0	3	0.0	0.01	3	0.1	1	0.0	0.03
Malignant neoplasm of other and ill-defined sites within the digestive organs and peritoneum	0	0.0	2	0.0	0.02	0	0.0	1	0.0	0.02
Malignant neoplasm of nasal cavities, middle ear, and accessory sinuses	1	0.0	2	0.0	0.00	1	0.0	0	0.0	0.02
Malignant neoplasm of larynx	1	0.0	2	0.0	0.00	0	0.0	2	0.0	0.02
Malignant neoplasm of trachea, bronchus, and lung	7	0.1	24	0.2	0.02	3	0.1	9	0.1	0.02
Malignant neoplasm of pleura	0	0.0	1	0.0	0.01	1	0.0	0	0.0	0.02
Malignant neoplasm of thymus, heart, and mediastinum	0	0.0	2	0.0	0.02	1	0.0	2	0.0	0.01
Malignant neoplasm of bone and articular cartilage	0	0.0	2	0.0	0.02	0	0.0	2	0.0	0.03

Table 2.4a. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initiators by Duration of Follow-up, Optum Research Database 6/1/2005−6/30/2015

Characteristic	1 to < 2 years					2 to < 3 years				
	Exenatide (N= 6,622)		OADs (N= 13,272)		Standardized Difference	Exenatide (N= 4,359)		OADs (N= 7,474)		Standardized Difference
	N	%	N	%		N	%	N	%	
Malignant neoplasm of connective and other soft tissue	4	0.1	10	0.1	0.01	2	0.0	6	0.1	0.01
Malignant melanoma of skin	11	0.2	27	0.2	0.02	7	0.2	10	0.1	0.01
Other and unspecified malignant neoplasm of skin	74	1.1	136	1.0	0.01	51	1.2	76	1.0	0.02
Malignant neoplasm of female breast	70	1.1	165	1.2	0.02	48	1.1	102	1.4	0.02
Malignant neoplasm of male breast	1	0.0	1	0.0	0.01	0	0.0	0	0.0	−
Kaposi's sarcoma	0	0.0	2	0.0	0.02	0	0.0	0	0.0	−
Malignant neoplasm of uterus, part unspecified	8	0.1	9	0.1	0.02	2	0.0	3	0.0	0.00
Malignant neoplasm of cervix uteri	2	0.0	2	0.0	0.01	3	0.1	4	0.1	0.01
Malignant neoplasm of body of uterus	17	0.3	17	0.1	0.03	9	0.2	14	0.2	0.01
Malignant neoplasm of ovary and other uterine adnexa	8	0.1	15	0.1	0.00	7	0.2	11	0.1	0.00
Malignant neoplasm of other and unspecified female genital organs	0	0.0	0	0.0	−	1	0.0	3	0.0	0.01
Malignant neoplasm of prostate	34	0.5	101	0.8	0.03	33	0.8	64	0.9	0.01
Malignant neoplasm of testis	5	0.1	1	0.0	0.03	1	0.0	2	0.0	0.00
Malignant neoplasm of penis and other male genital organs	0	0.0	0	0.0	−	2	0.0	0	0.0	0.03
Malignant neoplasm of bladder	15	0.2	17	0.1	0.03	13	0.3	17	0.2	0.01
Malignant neoplasm of kidney and other and unspecified urinary organs	9	0.1	28	0.2	0.02	5	0.1	19	0.3	0.03
Malignant neoplasm of eye	1	0.0	3	0.0	0.00	1	0.0	0	0.0	0.02
Malignant neoplasm of brain	4	0.1	8	0.1	0.00	2	0.0	6	0.1	0.02
Malignant neoplasm of other and unspecified parts of nervous system	1	0.0	0	0.0	0.02	0	0.0	3	0.0	0.03
Malignant neoplasm of other endocrine glands and related structures	4	0.1	3	0.0	0.01	3	0.1	3	0.0	0.01
Malignant neoplasm of other and ill-defined sites	2	0.0	10	0.1	0.02	2	0.0	3	0.0	0.00
Secondary and unspecified malignant neoplasm of lymph nodes	2	0.0	24	0.2	0.05	5	0.1	7	0.1	0.01
Secondary malignant neoplasm of respiratory and digestive systems	4	0.1	17	0.1	0.03	5	0.1	9	0.1	0.00
Secondary malignant neoplasm of other specified sites	2	0.0	27	0.2	0.05	3	0.1	14	0.2	0.04
Malignant neoplasm without specification of site	7	0.1	17	0.1	0.01	4	0.1	2	0.0	0.02
Lymphosarcoma and reticulosarcoma and other specified malignant tumors of lymphatic tissue	3	0.0	16	0.1	0.03	7	0.2	9	0.1	0.01
Hodgkin's disease	7	0.1	7	0.1	0.02	5	0.1	3	0.0	0.02

Table 2.4a. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initiators by Duration of Follow-up, Optum Research Database 6/1/2005−6/30/2015

Characteristic	1 to < 2 years					2 to < 3 years				
	Exenatide (N= 6,622)		OADs (N= 13,272)		Standardized Difference	Exenatide (N= 4,359)		OADs (N= 7,474)		Standardized Difference
	N	%	N	%		N	%	N	%	
Other malignant neoplasms of lymphoid and histiocytic tissue	10	0.2	27	0.2	0.01	7	0.2	16	0.2	0.02
Multiple myeloma and immunoproliferative neoplasms	5	0.1	12	0.1	0.01	3	0.1	13	0.2	0.03
Lymphoid leukemia	5	0.1	9	0.1	0.00	6	0.1	6	0.1	0.02
Myeloid leukemia	2	0.0	15	0.1	0.03	4	0.1	8	0.1	0.01
Monocytic leukemia	1	0.0	0	0.0	0.02	0	0.0	0	0.0	−
Other specified leukemia	0	0.0	1	0.0	0.01	0	0.0	0	0.0	−
Leukemia of unspecified cell type	1	0.0	5	0.0	0.02	3	0.1	1	0.0	0.03
Neuroendocrine tumors	1	0.0	4	0.0	0.01	0	0.0	0	0.0	−
Personal history of malignant neoplasm	181	2.7	412	3.1	0.02	134	3.1	226	3.0	0.01

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.
Standardized difference is calculated by the difference between the two proportions divided by the pooled standard deviation
Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 2.4a. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initiators by Duration of Follow-Up, Optum Research Database 6/1/2005−6/30/2015

	≥ 3 years				
	Exenatide (N= 11,613)		OADs (N= 12,392)		Standardized Difference
Characteristic	N	%	N	%	
Age					
≤ 39	1,109	9.5	1,116	9.0	0.02
40-49	2,764	23.8	2,882	23.3	0.01
50-59	4,929	42.4	5,275	42.6	0.01
60-69	2,389	20.6	2,612	21.1	0.00
≥ 70	422	3.6	507	4.1	0.02
Number of Drugs Dispensed					
0-5 Unique drugs dispensed	763	6.6	1,019	8.2	0.03
6-10 Unique drugs dispensed	4,585	39.5	5,221	42.1	0.03
11-15 Unique drugs dispensed	4,003	34.5	3,770	30.4	0.07
≥16 Unique drugs dispensed	2,262	19.5	2,382	19.2	0.03
Gender					
Male	5,459	47.0	5,878	47.4	0.00
Geographic Area					
Northeast	770	6.6	791	6.4	0.01
Midwest	2,619	22.6	3,023	24.4	0.04
South	6,728	57.9	6,961	56.2	0.04
West	1,496	12.9	1,617	13.0	0.01
Unknown	0	0.0	0	0.0	−
Number of Physician Visits					
0-3 Physician visits	2,765	23.8	3,264	26.3	0.04
4-5 Physician visits	2,826	24.3	2,848	23.0	0.03
6-8 Physician visits	2,893	24.9	3,066	24.7	0.00
≥9 Physician visits	3,129	26.9	3,214	25.9	0.00
Number of Laboratory Tests					
0-4 Laboratory tests	2,210	19.0	2,479	20.0	0.01
5-9 Laboratory tests	3,101	26.7	3,380	27.3	0.01
10-15 Laboratory tests	2,997	25.8	3,118	25.2	0.02
>15 Laboratory tests	3,305	28.5	3,415	27.6	0.00
Stroke/transient ischemic attack	188	1.6	214	1.7	0.01
Ischemic heart disease	1,349	11.6	1,474	11.9	0.01
Myocardial infarction	134	1.2	152	1.2	0.00
Disorders of fluid, electrolyte, and acid-base balance	510	4.4	590	4.8	0.02

Table 2.4a. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initiators by Duration of Follow-Up, Optum Research Database 6/1/2005−6/30/2015

	≥ 3 years				
	Exenatide (N= 11,613)		OADs (N= 12,392)		Standardized Difference
Characteristic	N	%	N	%	
Other and unspecified anemias	764	6.6	901	7.3	0.02
Acute sinusitis	1,260	10.8	1,302	10.5	0.01
Osteoarthrosis and allied disorders	1,298	11.2	1,336	10.8	0.01
Other and unspecified disorders of back	1,785	15.4	1,918	15.5	0.01
General symptoms	3,466	29.8	3,511	28.3	0.03
Symptoms involving skin and other integumentary issue	1,388	12.0	1,382	11.2	0.02
Symptoms involving head and neck	803	6.9	843	6.8	0.00
Symptoms involving the digestive system	999	8.6	1,153	9.3	0.03
Encounter for other and unspecified procedure and aftercare	3,086	26.6	3,311	26.7	0.01
General medical examination	1,661	14.3	1,918	15.5	0.02
Hypothyroidism	1,196	10.3	1,173	9.5	0.02
Chest x-ray	689	5.9	757	6.1	0.01
Radiographic procedure	2,399	20.7	2,689	21.7	0.03
Basic metabolic panel	2,145	18.5	2,370	19.1	0.02
Comprehensive metabolic panel	6,250	53.8	6,451	52.1	0.03
Lipid panel	8,216	70.7	8,552	69.0	0.03
Urinalysis, automated, with microscopy	1,587	13.7	1,715	13.8	0.01
Albumin; urine, microalbumin, quantitative	3,997	34.4	4,136	33.4	0.01
Creatinine, other source	3,209	27.6	3,250	26.2	0.02
Glucose; quantitative, blood (except reagent strip)	1,488	12.8	1,607	13.0	0.01
Hemoglobin; glycosylated (A1C)	9,282	79.9	9,706	78.3	0.03
Thyroxine; free	1,356	11.7	1,250	10.1	0.04
Blood count; complete (CBC), automated (Hgb, Hct, RBC, WBC and platelet count) and automated differential WBC count	3,719	32.0	3,910	31.6	0.01
Level IV - Surgical pathology, gross and microscopic examination Abortion - spontaneous/missed Artery, biopsy Bone marrow, biopsy Bone exostosis Brain/meninges, other than for tumor resection Breast, biopsy, not requiring microscopic evaluation (truncated)	1,439	12.4	1,439	11.6	0.02
Unlisted miscellaneous pathology test	2,371	20.4	2,552	20.6	0.00

Table 2.4a. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initiators by Duration of Follow-Up, Optum Research Database 6/1/2005−6/30/2015

	≥ 3 years				
	Exenatide (N= 11,613)		OADs (N= 12,392)		Standardized Difference
Characteristic	N	%	N	%	
Immunization administration (includes percutaneous, intradermal, subcutaneous, or intramuscular injections); one vaccine (single or combination vaccine/toxoid)	1,915	16.5	2,129	17.2	0.01
Ophthalmological services: medical examination and evaluation, with initiation or continuation of diagnostic and treatment program; comprehensive, established patient, one or more visits.	1,819	15.7	2,020	16.3	0.03
Determination of refractive state	1,284	11.1	1,356	10.9	0.00
Handling and/or conveyance of specimen for transfer from the physician's office to a laboratory	1,190	10.2	1,207	9.7	0.01
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A problem focused history; A problem focused examination; Straightforward medical decision making.	2,547	21.9	2,662	21.5	0.00
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: An expanded problem focused history; An expanded problem focused examination; Medical decision making of low complexity.	8,870	76.4	9,407	75.9	0.00
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A detailed history; A detailed examination; Medical decision making of moderate complexity.	9,469	81.5	10,033	81.0	0.00
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A comprehensive history; A comprehensive examination; Medical decision making of high complexity.	2,293	19.7	2,247	18.1	0.03

Table 2.4a. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initiators by Duration of Follow-Up, Optum Research Database 6/1/2005−6/30/2015

	≥ 3 years				
	Exenatide (N= 11,613)		OADs (N= 12,392)		Standardized Difference
Characteristic	N	%	N	%	
Subsequent hospital care, per day, for the evaluation and management of a patient, which requires at least 2 of these 3 key components: An expanded problem focused interval history; An expanded problem focused examination; Medical decision making of moderate complexity.	547	4.7	688	5.6	0.04
Office consultation for a new or established patient, which requires these 3 key components: A detailed history; A detailed examination; and Medical decision making of low complexity.	1,287	11.1	1,316	10.6	0.01
Office consultation for a new or established patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical decision making of moderate complexity.	1,983	17.1	1,931	15.6	0.02
Emergency department visit for the evaluation and management of a patient, which requires these 3 key components: A detailed history; A detailed examination; and Medical decision making of moderate complexity.	682	5.9	788	6.4	0.02
Emergency department visit for the evaluation and management of a patient, which requires these 3 key components within the constraints imposed by the urgency of the patient's clinical condition and/or mental status: A comprehensive history; A comprehensive examination; and Medical decision making of high complexity.	773	6.7	883	7.1	0.02
Periodic comprehensive preventive medicine reevaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, established patient; 40-64 years.	1,782	15.3	1,938	15.6	0.01
Diagnostic ultrasound abdomen	736	6.3	794	6.4	0.00
Magnetic resonance imaging (MRI)	1,087	9.4	1,218	9.8	0.02
Nonoperative urinary measurements	2,914	25.1	3,035	24.5	0.01
Cardiac stress tests	1,085	9.3	1,178	9.5	0.01

Table 2.4a. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initiators by Duration of Follow-Up, Optum Research Database 6/1/2005−6/30/2015

	≥ 3 years				
	Exenatide (N= 11,613)		OADs (N= 12,392)		Standardized Difference
Characteristic	N	%	N	%	
Electrocardiogram	3,363	29.0	3,677	29.7	0.02
Microscopic exam (smear culture)	6,631	57.1	6,969	56.2	0.01
Radioisotope scan/function	1,011	8.7	1,105	8.9	0.01
Physical therapy exercises/manipulation	1,637	14.1	1,732	14.0	0.01
Ophthalmological/otologic diagnosis/treatment	3,560	30.7	3,811	30.8	0.01
Other diagnostic radiology	4,912	42.3	5,229	42.2	0.00
Prophylactic vaccinations	2,816	24.2	3,074	24.8	0.01
Other therapeutic procedure	7,902	68.0	8,347	67.4	0.01
Other lab	10,329	88.9	10,948	88.3	0.01
Procedure codes not elsewhere specified	10,091	86.9	10,660	86.0	0.02
Vaginal delivery	2,525	21.7	2,510	20.3	0.02
Thyrotropin releasing hormone	2,989	25.7	3,060	24.7	0.01
Hypotensives, angiotensin receptor antagonist	2,656	22.9	2,663	21.5	0.01
Calcium channel blocking agents	1,769	15.2	1,993	16.1	0.02
Anti-anxiety drugs	1,093	9.4	1,137	9.2	0.00
Serotonin specific reuptake inhibitor (SSRIs)	1,839	15.8	1,919	15.5	0.00
Analgesics, narcotics	3,404	29.3	3,701	29.9	0.02
Anticonvulsants	1,188	10.2	1,308	10.6	0.02
Skeletal muscle relaxants	1,076	9.3	1,222	9.9	0.03
Beta-adrenergic agents	990	8.5	1,032	8.3	0.00
Blood sugar diagnostics	6,197	53.4	6,545	52.8	0.01
Lipotropics	5,733	49.4	5,850	47.2	0.00
Thyroid hormones	1,555	13.4	1,595	12.9	0.00
Thiazide and related diuretics	1,258	10.8	1,458	11.8	0.03
Loop diuretics	1,237	10.7	1,220	9.8	0.01
Penicillins	2,064	17.8	2,187	17.6	0.00
Macrolides	2,051	17.7	2,092	16.9	0.01
Quinolones	1,888	16.3	2,020	16.3	0.01
Durable medical equipment, miscellaneous (Group 1)	2,426	20.9	2,616	21.1	0.01
Diabetic supplies	657	5.7	731	5.9	0.00
Non-alcohol sedatives	1,740	15.0	1,785	14.4	0.01
Acid-supressing drugs	1,926	16.6	2,046	16.5	0.01
Metformin	9,085	78.2	9,318	75.2	0.05

Table 2.4a. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initiators by Duration of Follow-Up, Optum Research Database 6/1/2005−6/30/2015

	≥ 3 years				
	Exenatide (N= 11,613)		OADs (N= 12,392)		Standardized Difference
Characteristic	N	%	N	%	
Sulfonylureas	5,256	45.3	5,300	42.8	0.01
Thiazolidinediones	4,638	39.9	4,576	36.9	0.01
Insulin glargine	1,427	12.3	1,458	11.8	0.01
Insulins	2,345	20.2	2,598	21.0	0.05
Ace inhibitors	5,417	46.6	5,937	47.9	0.03
Obesity	1,824	15.7	1,929	15.6	0.01
Gastroesophageal reflux disease	1,074	9.2	1,123	9.1	0.00
Hospitalization within 45 days of Index	220	1.9	287	2.3	0.02
1 Anti-diabetic medication within 45 days of index	5,028	43.3	5,528	44.6	0.02
2 Anti-diabetic medications within 45 days of index	2,406	20.7	2,418	19.5	0.01
NSAIDs	2,488	21.4	2,668	21.5	0.01
Fibrates	1,414	12.2	1,506	12.2	0.00
Statins	6,681	57.5	7,164	57.8	0.01
Critical care procedure	114	1.0	142	1.1	0.01
Nephritis and nephropathy, not specified as acute or chronic	122	1.1	117	0.9	0.01
Retinopathy	568	4.9	636	5.1	0.02
Hypertension	8,059	69.4	8,549	69.0	0.01
Congestive heart failure	311	2.7	334	2.7	0.00
Peripheral neuropathy	1,083	9.3	1,080	8.7	0.01
Hyperlipidemia	9,148	78.8	9,575	77.3	0.02
Thryotropin releasing hormone	2,989	25.7	3,060	24.7	0.01
T3, T4 testing	2,077	17.9	2,045	16.5	0.03
Computerized tomography (CT), soft tissue neck	41	0.4	53	0.4	0.02
Thyroid imaging	145	1.2	173	1.4	0.01
Ultrasound of head and neck	201	1.7	179	1.4	0.02
Biopsy thyroid	48	0.4	51	0.4	0.00
Thyroidectomy	5	0.0	7	0.1	0.01
Other operations on thyroid	0	0.0	1	0.0	0.01
Abdominal pain	1,316	11.3	1,350	10.9	0.01
Lipase	234	2.0	257	2.1	0.00
Amylase	252	2.2	267	2.2	0.00
Other nonspecific abnormal serum enzyme levels	91	0.8	101	0.8	0.01

Table 2.4a. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initiators by Duration of Follow-Up, Optum Research Database 6/1/2005−6/30/2015

	≥ 3 years				
	Exenatide (N= 11,613)		OADs (N= 12,392)		Standardized Difference
Characteristic	N	%	N	%	
Abdominal ultrasound	495	4.3	547	4.4	0.01
Biopsy of pancreas	0	0.0	0	0.0	−
Pancreatectomy	0	0.0	0	0.0	−
Endobronchial ultrasound	0	0.0	0	0.0	−
Magnetic resonance imaging (MRI), abdomen	56	0.5	60	0.5	0.00
Magnetic resonance cholangiopancreatography (MRCP)	0	0.0	0	0.0	−
Endoscopic retrograde cholangiopancreatography (ERCP)	6	0.1	5	0.0	0.00
Other operations on pancreas	0	0.0	0	0.0	−
X-ray for pancreas	17	0.1	27	0.2	0.01
Micro exam of pancreas	0	0.0	0	0.0	−
Malignant neoplasm of lip	0	0.0	0	0.0	−
Malignant neoplasm of tongue	2	0.0	1	0.0	0.01
Malignant neoplasm of major salivary glands	1	0.0	2	0.0	0.01
Malignant neoplasm of gum	0	0.0	0	0.0	−
Malignant neoplasm of floor of mouth	1	0.0	0	0.0	0.01
Malignant neoplasm of other and unspecified parts of mouth	2	0.0	0	0.0	0.02
Malignant neoplasm of oropharynx	1	0.0	2	0.0	0.01
Malignant neoplasm of nasopharynx	1	0.0	1	0.0	0.00
Malignant neoplasm of hypopharynx	0	0.0	0	0.0	−
Malignant neoplasm of other and ill-defined sites within the lip, oral cavity, and pharynx	0	0.0	0	0.0	−
Malignant neoplasm of esophagus	1	0.0	1	0.0	0.00
Malignant neoplasm of stomach	1	0.0	5	0.0	0.02
Malignant neoplasm of small intestine, including duodenum	1	0.0	1	0.0	0.00
Malignant neoplasm of colon	28	0.2	21	0.2	0.02
Malignant neoplasm of rectum, rectosigmoid junction, and anus	17	0.1	10	0.1	0.02
Malignant neoplasm of liver and intrahepatic bile ducts	3	0.0	3	0.0	0.00
Malignant neoplasm of gallbladder and extrahepatic bile ducts	1	0.0	2	0.0	0.01
Malignant neoplasm of retroperitoneum and peritoneum	0	0.0	5	0.0	0.03

Table 2.4a. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initiators by Duration of Follow-Up, Optum Research Database 6/1/2005−6/30/2015

	≥ 3 years				
	Exenatide (N= 11,613)		OADs (N= 12,392)		Standardized Difference
Characteristic	N	%	N	%	
Malignant neoplasm of other and ill-defined sites within the digestive organs and peritoneum	2	0.0	4	0.0	0.01
Malignant neoplasm of nasal cavities, middle ear, and accessory sinuses	1	0.0	0	0.0	0.01
Malignant neoplasm of larynx	0	0.0	0	0.0	−
Malignant neoplasm of trachea, bronchus, and lung Malignant	17	0.1	16	0.1	0.01
neoplasm of pleura	0	0.0	0	0.0	−
Malignant neoplasm of thymus, heart, and mediastinum	1	0.0	0	0.0	0.01
Malignant neoplasm of bone and articular cartilage Malignant	1	0.0	2	0.0	0.01
neoplasm of connective and other soft tissue Malignant	3	0.0	6	0.0	0.01
melanoma of skin	19	0.2	16	0.1	0.01
Other and unspecified malignant neoplasm of skin Malignant	121	1.0	134	1.1	0.00
neoplasm of female breast	137	1.2	147	1.2	0.00
Malignant neoplasm of male breast	2	0.0	0	0.0	0.02
Kaposi's sarcoma	1	0.0	2	0.0	0.01
Malignant neoplasm of uterus, part unspecified	2	0.0	4	0.0	0.01
Malignant neoplasm of cervix uteri	5	0.0	4	0.0	0.00
Malignant neoplasm of body of uterus	21	0.2	17	0.1	0.01
Malignant neoplasm of ovary and other uterine adnexa	8	0.1	11	0.1	0.01
Malignant neoplasm of other and unspecified female genital organs	0	0.0	2	0.0	0.02
Malignant neoplasm of prostate	73	0.6	90	0.7	0.01
Malignant neoplasm of testis	3	0.0	5	0.0	0.01
Malignant neoplasm of penis and other male genital organs	0	0.0	3	0.0	0.02
Malignant neoplasm of bladder	22	0.2	24	0.2	0.00
Malignant neoplasm of kidney and other and unspecified urinary organs	29	0.2	10	0.1	0.04
Malignant neoplasm of eye	1	0.0	2	0.0	0.01
Malignant neoplasm of brain	5	0.0	3	0.0	0.01
Malignant neoplasm of other and unspecified parts of nervous system	4	0.0	0	0.0	0.03
Malignant neoplasm of other endocrine glands and related structures	9	0.1	5	0.0	0.01

Table 2.4a. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initiators by Duration of Follow-Up, Optum Research Database 6/1/2005−6/30/2015

	≥ 3 years				
	Exenatide (N= 11,613)		OADs (N= 12,392)		Standardized Difference
Characteristic	N	%	N	%	
Malignant neoplasm of other and ill-defined sites	6	0.1	6	0.0	0.00
Secondary and unspecified malignant neoplasm of lymph nodes	8	0.1	18	0.1	0.02
Secondary malignant neoplasm of respiratory and digestive systems	5	0.0	13	0.1	0.03
Secondary malignant neoplasm of other specified sites	5	0.0	15	0.1	0.03
Malignant neoplasm without specification of site	9	0.1	10	0.1	0.00
Lymphosarcoma and reticulosarcoma and other specified malignant tumors of lymphatic tissue	20	0.2	13	0.1	0.02
Hodgkin's disease	9	0.1	8	0.1	0.00
Other malignant neoplasms of lymphoid and histiocytic tissue	28	0.2	32	0.3	0.00
Multiple myeloma and immunoproliferative neoplasms	2	0.0	13	0.1	0.03
Lymphoid leukemia	8	0.1	9	0.1	0.00
Myeloid leukemia	13	0.1	10	0.1	0.01
Monocytic leukemia	1	0.0	2	0.0	0.01
Other specified leukemia	0	0.0	1	0.0	0.01
Leukemia of unspecified cell type	1	0.0	3	0.0	0.01
Neuroendocrine tumors	2	0.0	0	0.0	0.02
Personal history of malignant neoplasm	323	2.8	345	2.8	0.00

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.
Standardized difference is calculated by the difference between the two proportions divided by the pooled standard deviation
Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 2.4b. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initatiors by Duration of Follow-Up, Impact National Benchmark Database 6/1/2005−3/31/2015

	1 to < 2 years					2 to < 3 years				
	Exenatide (N= 3,326)		OADs (N= 6,547)		Standardized Difference	Exenatide (N= 2,392)		OADs (N= 3,891)		Standardized Difference
Characteristic	N	%	N	%		N	%	N	%	
Age										
≤ 39	302	9.1	586	9.0	0.00	202	8.4	313	8.0	0.01
40-49	727	21.9	1,459	22.3	0.02	543	22.7	883	22.7	0.01
50-59	1,274	38.3	2,539	38.8	0.01	960	40.1	1,634	42.0	0.04
60-69	975	29.3	1,841	28.1	0.03	649	27.1	1,005	25.8	0.04
≥ 70	48	1.4	122	1.9	0.02	38	1.6	56	1.4	0.02
Number of Drugs Dispensed										
0-5 Unique drugs dispensed	178	5.4	535	8.2	0.08	131	5.5	292	7.5	0.05
6-10 Unique drugs dispensed	1,329	40.0	2,672	40.8	0.02	986	41.2	1,657	42.6	0.00
11-15 Unique drugs dispensed	1,147	34.5	2,065	31.5	0.04	856	35.8	1,255	32.3	0.06
≥16 Unique drugs dispensed	672	20.2	1,275	19.5	0.02	419	17.5	687	17.7	0.04
Gender										
Male	1,698	51.1	3,352	51.2	0.01	1,196	50.0	1,999	51.4	0.01
Geographic Area										
Northeast	2,300	69.2	4,332	66.2	0.06	1,495	62.5	2,454	63.1	0.01
Midwest	275	8.3	565	8.6	0.00	244	10.2	373	9.6	0.03
South	519	15.6	1,214	18.5	0.08	453	18.9	783	20.1	0.03
West	220	6.6	399	6.1	0.02	185	7.7	258	6.6	0.03
Unknown	12	0.4	37	0.6	0.02	15	0.6	23	0.6	0.01
Number of Physician Visits										
0-3 Physician visits	731	22.0	1,556	23.8	0.02	547	22.9	1,014	26.1	0.05
4-5 Physician visits	751	22.6	1,608	24.6	0.04	564	23.6	942	24.2	0.00
6-8 Physician visits	892	26.8	1,606	24.5	0.04	634	26.5	959	24.6	0.03
≥9 Physician visits	952	28.6	1,777	27.1	0.01	647	27.0	976	25.1	0.02
Number of Laboratory Tests										
0-4 Laboratory tests	1,088	32.7	2,059	31.4	0.04	640	26.8	1,157	29.7	0.06
5-9 Laboratory tests	626	18.8	1,259	19.2	0.01	474	19.8	780	20.0	0.00
10-15 Laboratory tests	654	19.7	1,330	20.3	0.01	494	20.7	859	22.1	0.04
>15 Laboratory tests	958	28.8	1,899	29.0	0.02	784	32.8	1,095	28.1	0.09
Stroke/transient ischemic attack	50	1.5	129	2.0	0.04	41	1.7	72	1.9	0.02
Ischemic heart disease	397	11.9	855	13.1	0.04	278	11.6	453	11.6	0.00
Myocardial infarction	50	1.5	77	1.2	0.03	26	1.1	56	1.4	0.03
Disorders of lipid metabolism	2,294	69.0	4,606	70.4	0.04	1,741	72.8	2,801	72.0	0.01
Other disorders of urethra and urinary tract	295	8.9	581	8.9	0.01	225	9.4	324	8.3	0.04
Osteoarthrosis and allied disorders	328	9.9	608	9.3	0.02	232	9.7	343	8.8	0.03

Table 2.4b. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initatiors by Duration of Follow-Up, Impact National Benchmark Database 6/1/2005−3/31/2015

	1 to < 2 years					2 to < 3 years				
	Exenatide (N= 3,326)		OADs (N= 6,547)		Standardized Difference	Exenatide (N= 2,392)		OADs (N= 3,891)		Standardized Difference
Characteristic	N	%	N	%		N	%	N	%	
Peripheral enthesopathies and allied syndromes	315	9.5	579	8.8	0.02	238	9.9	375	9.6	0.00
Other disorders of soft tissues	509	15.3	1,052	16.1	0.03	370	15.5	586	15.1	0.01
General symptoms	815	24.5	1,595	24.4	0.01	588	24.6	922	23.7	0.01
Symptoms involving skin and other integumentary tissue	349	10.5	578	8.8	0.05	245	10.2	348	8.9	0.04
Symptoms involving respiratory system and other chest symptoms	862	25.9	1,712	26.1	0.01	630	26.3	1,005	25.8	0.00
Symptoms involving digestive system	240	7.2	502	7.7	0.02	172	7.2	282	7.2	0.00
Nonspecific findings on examination of blood	300	9.0	620	9.5	0.01	219	9.2	374	9.6	0.01
Need for prophylactic vaccination and inoculation against certain viral diseases	751	22.6	1,315	20.1	0.06	423	17.7	693	17.8	0.01
Encounter for other and unspecified procedure and aftercare	458	13.8	974	14.9	0.03	352	14.7	595	15.3	0.03
General medical examination	706	21.2	1,374	21.0	0.01	526	22.0	896	23.0	0.02
Special investigations and examinations	809	24.3	1,651	25.2	0.02	597	25.0	900	23.1	0.04
Hypercholesterolemia	1,907	57.3	3,841	58.7	0.04	1,483	62.0	2,376	61.1	0.01
Chest x-ray	179	5.4	374	5.7	0.02	125	5.2	200	5.1	0.00
General health panel	423	12.7	846	12.9	0.00	296	12.4	480	12.3	0.01
Lipid panel	1,909	57.4	3,808	58.2	0.02	1,411	59.0	2,238	57.5	0.03
Urinalysis, automated, with microscopy	367	11.0	763	11.7	0.02	290	12.1	419	10.8	0.05
Albumin; urine, microalbumin, quantitative	1,099	33.0	2,146	32.8	0.00	900	37.6	1,352	34.7	0.05
Creatine kinase (CK), (CPK); total	288	8.7	560	8.6	0.00	243	10.2	310	8.0	0.08
Creatinine; other source	889	26.7	1,652	25.2	0.03	697	29.1	1,052	27.0	0.04
Glucose; quantitative, blood (except reagent strip)	498	15.0	1,049	16.0	0.04	463	19.4	707	18.2	0.02
Glucose, blood by glucose monitoring device(s) cleared by the FDA specifically for home use	433	13.0	911	13.9	0.03	358	15.0	533	13.7	0.04
Hemoglobin; glycosylated (A1C)	2,238	67.3	4,421	67.5	0.01	1,736	72.6	2,708	69.6	0.06
Prostate specific antigen (PSA); total	409	12.3	795	12.1	0.01	297	12.4	498	12.8	0.00
Transferase; aspartate amino (AST) (SGOT)	357	10.7	700	10.7	0.00	300	12.5	410	10.5	0.06
Automated hemogram	252	7.6	554	8.5	0.03	194	8.1	306	7.9	0.01
Level IV - Surgical pathology, gross and microscopic examination Abortion - spontaneous/missed Artery, biopsy Bone marrow, biopsy Bone exostosis Brain/meninges, other than for tumor resection Breast, biopsy, not requiring microscopic evaluation (truncated)	425	12.8	788	12.0	0.01	305	12.8	473	12.2	0.01

Table 2.4b. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initatiors by Duration of Follow-Up, Impact National Benchmark Database 6/1/2005−3/31/2015

Characteristic	1 to < 2 years					2 to < 3 years				
	Exenatide (N= 3,326)		OADs (N= 6,547)		Standardized Difference	Exenatide (N= 2,392)		OADs (N= 3,891)		Standardized Difference
	N	%	N	%		N	%	N	%	
Influenza virus vaccine, trivalent (IIV3), split virus, 0.5 mL dosage, for intramuscular use	825	24.8	1,456	22.2	0.06	489	20.4	786	20.2	0.01
Ophthalmological services: medical examination and evaluation, with initiation or continuation of diagnostic and treatment program; comprehensive, established patient, one or more visits.	734	22.1	1,430	21.8	0.01	567	23.7	878	22.6	0.02
Electrocardiogram, routine ECG with at least 12 leads; interpretation and report only	296	8.9	649	9.9	0.03	229	9.6	389	10.0	0.01
Doppler echocardiography color flow velocity mapping (List separately in addition to codes for echocardiography)	262	7.9	564	8.6	0.04	215	9.0	312	8.0	0.02
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A problem focused history; A problem focused examination; Straightforward medical decision making.	722	21.7	1,430	21.8	0.02	549	23.0	864	22.2	0.00
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: An expanded problem focused history; An expanded problem focused examination; Medical decision making of low complexity.	2,649	79.6	5,128	78.3	0.01	1,902	79.5	3,048	78.3	0.01
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A detailed history; A detailed examination; Medical decision making of moderate complexity.	2,695	81.0	5,271	80.5	0.00	1,937	81.0	3,089	79.4	0.03
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A comprehensive history; A comprehensive examination; Medical decision making of high complexity.	625	18.8	1,128	17.2	0.03	412	17.2	669	17.2	0.01
Subsequent hospital care, per day, for the evaluation and management of a patient, which requires at least 2 of these 3 key components: An expanded problem focused interval history; An expanded problem focused examination; Medical decision making of moderate complexity.	155	4.7	331	5.1	0.02	120	5.0	211	5.4	0.01

Table 2.4b. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initatiors by Duration of Follow-Up, Impact National Benchmark Database 6/1/2005−3/31/2015

	1 to < 2 years					2 to < 3 years				
	Exenatide (N= 3,326)		OADs (N= 6,547)		Standardized Difference	Exenatide (N= 2,392)		OADs (N= 3,891)		Standardized Difference
Characteristic	N	%	N	%		N	%	N	%	
Office consultation for a new or established patient, which requires these 3 key components: A detailed history; A detailed examination; and Medical decision making of low complexity.	440	13.2	852	13.0	0.01	302	12.6	494	12.7	0.01
Office consultation for a new or established patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical decision making of moderate complexity.	648	19.5	1,212	18.5	0.00	460	19.2	683	17.6	0.02
Periodic comprehensive preventive medicine reevaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, established patient; 40-64 years.	686	20.6	1,354	20.7	0.00	544	22.7	830	21.3	0.03
Computerized tomography (CT), abdomen	216	6.5	429	6.6	0.00	168	7.0	227	5.8	0.04
Routine chest x-ray	620	18.6	1,286	19.6	0.03	452	18.9	700	18.0	0.02
Echocardiogram	364	10.9	736	11.2	0.02	296	12.4	431	11.1	0.03
Other diagnostic ultrasound	403	12.1	814	12.4	0.02	282	11.8	448	11.5	0.00
Electrocardiogram	1,197	36.0	2,357	36.0	0.00	830	34.7	1,328	34.1	0.02
Microscopic exam (smear culture)	1,741	52.3	3,436	52.5	0.01	1,320	55.2	2,096	53.9	0.02
Radioisotope scan/function	309	9.3	604	9.2	0.01	215	9.0	359	9.2	0.01
Physical therapy exercises/manipulation	399	12.0	768	11.7	0.00	257	10.7	403	10.4	0.01
Other diagnostic radiology	1,143	34.4	2,240	34.2	0.00	824	34.4	1,295	33.3	0.02
Other therapeutic procedure	2,294	69.0	4,454	68.0	0.02	1,677	70.1	2,631	67.6	0.05
Other lab	2,687	80.8	5,284	80.7	0.01	2,027	84.7	3,193	82.1	0.07
Vaginal delivery	708	21.3	1,402	21.4	0.02	578	24.2	855	22.0	0.03
Miscellaneous medication administration	691	20.8	1,346	20.6	0.01	501	20.9	781	20.1	0.01
Durable medical equipment and supplies	907	27.3	1,731	26.4	0.00	669	28.0	1,031	26.5	0.02
Hypotensives, angiotensin receptor antagonist	821	24.7	1,461	22.3	0.03	541	22.6	892	22.9	0.03
Calcium channel blocking agents	527	15.8	993	15.2	0.02	365	15.3	620	15.9	0.02
Gastric acid secretion reducers	527	15.8	937	14.3	0.02	327	13.7	522	13.4	0.02
Analgesics, narcotics	915	27.5	1,789	27.3	0.00	643	26.9	1,030	26.5	0.01
Anticonvulsants	347	10.4	701	10.7	0.02	242	10.1	400	10.3	0.01
Skeletal muscle relaxants	286	8.6	545	8.3	0.01	193	8.1	325	8.4	0.02
Beta-adrenergic agents	330	9.9	679	10.4	0.02	216	9.0	387	9.9	0.03

Table 2.4b. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initatiors by Duration of Follow-Up, Impact National Benchmark Database 6/1/2005−3/31/2015

	1 to < 2 years					2 to < 3 years				
	Exenatide (N= 3,326)		OADs (N= 6,547)		Standardized Difference	Exenatide (N= 2,392)		OADs (N= 3,891)		Standardized Difference
Characteristic	N	%	N	%		N	%	N	%	
Beta-adrenergic blocking agents	790	23.8	1,578	24.1	0.01	540	22.6	958	24.6	0.05
Blood sugar diagnostics	1,891	56.9	3,618	55.3	0.00	1,397	58.4	2,204	56.6	0.01
Anti-hyperlipidemic - HMG CoA reductase inhibitors	703	21.1	1,530	23.4	0.02	559	23.4	892	22.9	0.05
Lipotropics	1,734	52.1	3,381	51.6	0.04	1,236	51.7	1,983	51.0	0.02
Thyroid hormones	395	11.9	825	12.6	0.04	305	12.8	459	11.8	0.02
Glucocorticoids	333	10.0	736	11.2	0.04	242	10.1	393	10.1	0.00
Topical anti-inflammatory steroidal	278	8.4	543	8.3	0.01	210	8.8	331	8.5	0.00
Nasal anti-inflammatory steroids	305	9.2	587	9.0	0.00	213	8.9	342	8.8	0.00
thiazide and related diuretics	451	13.6	850	13.0	0.02	311	13.0	495	12.7	0.01
Loop diuretics	374	11.2	680	10.4	0.01	246	10.3	354	9.1	0.02
Penicillins	609	18.3	1,129	17.2	0.02	409	17.1	669	17.2	0.01
Macrolides	582	17.5	1,154	17.6	0.01	377	15.8	657	16.9	0.04
Quinolones	495	14.9	1,023	15.6	0.04	340	14.2	564	14.5	0.02
Durable medical equipment, miscellaneous (Group 1)	778	23.4	1,547	23.6	0.02	579	24.2	889	22.8	0.03
Non-alcohol sedatives	538	16.2	1,026	15.7	0.00	365	15.3	600	15.4	0.01
Acid-suppressing drugs	682	20.5	1,301	19.9	0.01	450	18.8	722	18.6	0.00
Metformin	2,626	79.0	5,113	78.1	0.01	1,901	79.5	3,041	78.2	0.01
Sulfonylureas	1,532	46.1	2,933	44.8	0.00	1,105	46.2	1,706	43.8	0.01
Thiazolidinediones	1,199	36.0	2,260	34.5	0.02	860	36.0	1,421	36.5	0.06
Insulin glargine	453	13.6	728	11.1	0.05	328	13.7	507	13.0	0.01
Insulins	714	21.5	1,231	18.8	0.03	518	21.7	812	20.9	0.01
Ace Inhibitors	1,551	46.6	3,104	47.4	0.01	1,136	47.5	1,871	48.1	0.01
Obesity	538	16.2	937	14.3	0.03	381	15.9	589	15.1	0.00
Hospitalization within 45 days of Index	86	2.6	142	2.2	0.03	71	3.0	103	2.6	0.03
1 Anti-diabetic medication within 45 days of index	1,431	43.0	2,795	42.7	0.02	974	40.7	1,697	43.6	0.05
2 Anti-diabetic medications within 45 days of index	709	21.3	1,357	20.7	0.00	564	23.6	815	20.9	0.05
NSAIDs	667	20.1	1,287	19.7	0.01	521	21.8	771	19.8	0.04
Fibrates	368	11.1	764	11.7	0.03	300	12.5	443	11.4	0.03
Statins	2,031	61.1	4,075	62.2	0.04	1,486	62.1	2,396	61.6	0.01
Critical care procedure	30	0.9	61	0.9	0.00	15	0.6	29	0.7	0.01
Nephritis and nephropathy, not specified as acute or chronic	30	0.9	75	1.1	0.03	21	0.9	27	0.7	0.02
Retinopathy	178	5.4	353	5.4	0.01	126	5.3	201	5.2	0.00
Hypertension	2,046	61.5	3,977	60.7	0.02	1,496	62.5	2,364	60.8	0.03
Congestive heart failure	103	3.1	182	2.8	0.02	70	2.9	97	2.5	0.03

Table 2.4b. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initatiors by Duration of Follow-Up, Impact National Benchmark Database 6/1/2005−3/31/2015

	1 to < 2 years					2 to < 3 years				
	Exenatide (N= 3,326)		OADs (N= 6,547)		Standardized Difference	Exenatide (N= 2,392)		OADs (N= 3,891)		Standardized Difference
Characteristic	N	%	N	%		N	%	N	%	
Peripheral neuropathy	296	8.9	568	8.7	0.01	200	8.4	321	8.2	0.00
Hyperlipidemia	2,507	75.4	4,935	75.4	0.03	1,833	76.6	2,922	75.1	0.03
Thryotropin releasing hormone	884	26.6	1,758	26.9	0.02	711	29.7	1,029	26.4	0.05
T3, T4 testing	483	14.5	920	14.1	0.00	349	14.6	510	13.1	0.03
Computerized tomography (CT), soft tissue neck	17	0.5	20	0.3	0.03	9	0.4	14	0.4	0.00
Thyroid imaging	8	0.2	18	0.3	0.00	8	0.3	13	0.3	0.01
Ultrasound of head and neck	68	2.0	117	1.8	0.01	45	1.9	67	1.7	0.00
Biopsy thyroid	9	0.3	25	0.4	0.03	12	0.5	16	0.4	0.01
Thyroidectomy	0	0.0	3	0.0	0.03	0	0.0	0	0.0	−
Other operations on thyroid	0	0.0	0	0.0	−	0	0.0	0	0.0	−
Abdominal pain	337	10.1	672	10.3	0.00	254	10.6	396	10.2	0.01
Lipase	61	1.8	136	2.1	0.01	51	2.1	73	1.9	0.02
Amylase	54	1.6	138	2.1	0.04	55	2.3	75	1.9	0.03
Other nonspecific abnormal serum enzyme levels	22	0.7	41	0.6	0.01	9	0.4	25	0.6	0.04
Abdominal ultrasound	169	5.1	304	4.6	0.02	102	4.3	167	4.3	0.01
Biopsy of pancreas	0	0.0	0	0.0	−	0	0.0	0	0.0	−
Pancreatectomy	0	0.0	0	0.0	−	0	0.0	0	0.0	−
Endobronchial ultrasound	0	0.0	0	0.0	−	0	0.0	0	0.0	−
Magnetic resonance imaging (MRI), abdomen	8	0.2	41	0.6	0.05	19	0.8	17	0.4	0.05
Magnetic resonance cholangiopancreatography (MRCP)	0	0.0	0	0.0	−	0	0.0	0	0.0	−
Endoscopic retrograde cholangiopancreatography (ERCP)	2	0.1	2	0.0	0.02	1	0.0	3	0.1	0.01
Other operations on pancreas	0	0.0	0	0.0	−	0	0.0	0	0.0	−
X-ray for pancreas	3	0.1	5	0.1	0.00	2	0.1	5	0.1	0.01
Micro exam of pancreas	0	0.0	0	0.0	−	0	0.0	0	0.0	−
Malignant neoplasm of lip	1	0.0	1	0.0	0.01	0	0.0	0	0.0	−
Malignant neoplasm of tongue	1	0.0	0	0.0	0.02	0	0.0	0	0.0	−
Malignant neoplasm of major salivary glands	0	0.0	0	0.0	−	0	0.0	1	0.0	0.03
Malignant neoplasm of floor of mouth	1	0.0	1	0.0	0.01	0	0.0	1	0.0	0.02
Malignant neoplasm of other and unspecified parts of mouth	1	0.0	0	0.0	0.02	0	0.0	0	0.0	−
Malignant neoplasm of oropharynx	1	0.0	1	0.0	0.01	0	0.0	0	0.0	−
Malignant neoplasm of nasopharynx	1	0.0	0	0.0	0.02	0	0.0	0	0.0	−
Malignant neoplasm of other and ill-defined sites within the lip, oral cavity, and pharynx	0	0.0	0	0.0	−	0	0.0	0	0.0	−
Malignant neoplasm of esophagus	0	0.0	2	0.0	0.03	0	0.0	3	0.1	0.04

Table 2.4b. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initatiors by Duration of Follow-Up, Impact National Benchmark Database 6/1/2005−3/31/2015

	1 to < 2 years					2 to < 3 years				
	Exenatide (N= 3,326)		OADs (N= 6,547)		Standardized Difference	Exenatide (N= 2,392)		OADs (N= 3,891)		Standardized Difference
Characteristic	N	%	N	%		N	%	N	%	
Malignant neoplasm of stomach	0	0.0	2	0.0	0.02	0	0.0	0	0.0	.
Malignant neoplasm of small intestine, including duodenum	0	0.0	2	0.0	0.02	0	0.0	0	0.0	.
Malignant neoplasm of colon	8	0.2	15	0.2	0.00	6	0.3	13	0.3	0.01
Malignant neoplasm of rectum, rectosigmoid junction, and anus	4	0.1	10	0.2	0.01	3	0.1	11	0.3	0.03
Malignant neoplasm of liver and intrahepatic bile ducts	0	0.0	5	0.1	0.04	1	0.0	1	0.0	0.01
Malignant neoplasm of gallbladder and extrahepatic bile ducts	0	0.0	0	0.0	−	0	0.0	1	0.0	0.02
Malignant neoplasm of retroperitoneum and peritoneum	0	0.0	0	0.0	−	0	0.0	1	0.0	0.02
Malignant neoplasm of other and ill-defined sites within the digestive organs and peritoneum	0	0.0	1	0.0	0.02	0	0.0	1	0.0	0.02
Malignant neoplasm of nasal cavities, middle ear, and accessory sinuses	1	0.0	0	0.0	0.02	0	0.0	1	0.0	0.02
Malignant neoplasm of larynx	2	0.1	4	0.1	0.00	1	0.0	0	0.0	0.03
Malignant neoplasm of trachea, bronchus, and lung	3	0.1	13	0.2	0.03	6	0.3	12	0.3	0.01
Malignant neoplasm of pleura	0	0.0	0	0.0	−	0	0.0	1	0.0	0.02
Malignant neoplasm of thymus, heart, and mediastinum	0	0.0	2	0.0	0.02	1	0.0	0	0.0	0.03
Malignant neoplasm of bone and articular cartilage	1	0.0	2	0.0	0.00	0	0.0	1	0.0	0.03
Malignant neoplasm of connective and other soft tissue	1	0.0	7	0.1	0.03	0	0.0	3	0.1	0.04
Malignant melanoma of skin	5	0.2	9	0.1	0.00	3	0.1	8	0.2	0.02
Other and unspecified malignant neoplasm of skin	27	0.8	62	0.9	0.01	24	1.0	37	1.0	0.01
Malignant neoplasm of female breast	34	1.0	83	1.3	0.02	28	1.2	55	1.4	0.02
Malignant neoplasm of male breast	1	0.0	1	0.0	0.01	0	0.0	0	0.0	−
Kaposi's sarcoma	0	0.0	3	0.0	0.03	0	0.0	1	0.0	0.02
Malignant neoplasm of uterus, part unspecified	5	0.2	6	0.1	0.02	2	0.1	0	0.0	0.04
Malignant neoplasm of cervix uteri	2	0.1	1	0.0	0.02	0	0.0	3	0.1	0.04
Malignant neoplasm of body of uterus	9	0.3	13	0.2	0.02	4	0.2	8	0.2	0.01
Malignant neoplasm of ovary and other uterine adnexa	6	0.2	5	0.1	0.03	3	0.1	9	0.2	0.03
Malignant neoplasm of other and unspecified female genital organs	0	0.0	0	0.0	−	0	0.0	0	0.0	−
Malignant neoplasm of prostate	22	0.7	53	0.8	0.01	20	0.8	27	0.7	0.02
Malignant neoplasm of testis	1	0.0	2	0.0	0.01	1	0.0	1	0.0	0.01
Malignant neoplasm of bladder	9	0.3	13	0.2	0.01	11	0.5	11	0.3	0.02

Table 2.4b. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initatiors by Duration of Follow-Up, Impact National Benchmark Database 6/1/2005−3/31/2015

Characteristic	1 to < 2 years					2 to < 3 years				
	Exenatide (N= 3,326)		OADs (N= 6,547)		Standardized Difference	Exenatide (N= 2,392)		OADs (N= 3,891)		Standardized Difference
	N	%	N	%		N	%	N	%	
Malignant neoplasm of kidney and other and unspecified urinary organs	10	0.3	10	0.2	0.04	6	0.3	4	0.1	0.03
Malignant neoplasm of eye	0	0.0	1	0.0	0.02	0	0.0	2	0.1	0.03
Malignant neoplasm of brain	0	0.0	6	0.1	0.04	1	0.0	2	0.1	0.00
Malignant neoplasm of other and unspecified parts of nervous system	0	0.0	0	0.0	−	0	0.0	0	0.0	−
Malignant neoplasm of other endocrine glands and related structures	0	0.0	1	0.0	0.02	2	0.1	1	0.0	0.03
Malignant neoplasm of other and ill-defined sites	2	0.1	6	0.1	0.02	1	0.0	0	0.0	0.03
Secondary and unspecified malignant neoplasm of lymph nodes	4	0.1	4	0.1	0.02	1	0.0	8	0.2	0.04
Secondary malignant neoplasm of respiratory and digestive systems	3	0.1	11	0.2	0.02	1	0.0	7	0.2	0.04
Secondary malignant neoplasm of other specified sites	5	0.2	12	0.2	0.00	2	0.1	6	0.2	0.01
Malignant neoplasm without specification of site	4	0.1	14	0.2	0.02	2	0.1	4	0.1	0.00
Lymphosarcoma and reticulosarcoma and other specified malignant tumors of lymphatic tissue	5	0.2	10	0.2	0.01	1	0.0	4	0.1	0.02
Hodgkin's disease	4	0.1	2	0.0	0.03	0	0.0	3	0.1	0.04
Other malignant neoplasms of lymphoid and histiocytic tissue	10	0.3	22	0.3	0.01	3	0.1	10	0.3	0.03
Multiple myeloma and immunoproliferative neoplasms	1	0.0	6	0.1	0.03	3	0.1	5	0.1	0.01
Lymphoid leukemia	2	0.1	5	0.1	0.00	2	0.1	4	0.1	0.00
Myeloid leukemia	4	0.1	7	0.1	0.00	0	0.0	5	0.1	0.05
Monocytic leukemia	0	0.0	0	0.0	−	0	0.0	1	0.0	0.02
Other specified leukemia	0	0.0	1	0.0	0.02	0	0.0	0	0.0	−
Leukemia of unspecified cell type	1	0.0	2	0.0	0.00	0	0.0	0	0.0	−
Personal history of malignant neoplasm	74	2.2	148	2.3	0.00	65	2.7	100	2.6	0.01

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.
Standardized difference is calculated by the difference between the two proportions divided by the pooled standard deviation
Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 2.4b. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initiators by Duration of Follow-Up, Impact National Benchmark Database 6/1/2005−3/31/2015

	≥ 3 years				
	Exenatide (N= 5,348)		OADs (N= 5,819)		Standardized Difference
Characteristic	N	%	N	%	
Age					
≤ 39	427	8.0	421	7.2	0.03
40-49	1,268	23.7	1,298	22.3	0.03
50-59	2,352	44.0	2,647	45.5	0.04
60-69	1,217	22.8	1,356	23.3	0.00
≥ 70	84	1.6	97	1.7	0.00
Number of Drugs Dispensed					
0-5 Unique drugs dispensed	252	4.7	425	7.3	0.08
6-10 Unique drugs dispensed	2,103	39.3	2,470	42.4	0.03
11-15 Unique drugs dispensed	1,931	36.1	1,884	32.4	0.06
≥16 Unique drugs dispensed	1,062	19.9	1,040	17.9	0.01
Gender					
Male	2,649	49.5	3,031	52.1	0.04
Geographic Area					
Northeast	3,242	60.6	3,738	64.2	0.07
Midwest	600	11.2	686	11.8	0.02
South	1,313	24.6	1,201	20.6	0.09
West	121	2.3	120	2.1	0.01
Unknown	72	1.3	74	1.3	0.01
Number of Physician Visits					
0-3 Physician visits	1,220	22.8	1,565	26.9	0.07
4-5 Physician visits	1,313	24.6	1,429	24.6	0.01
6-8 Physician visits	1,418	26.5	1,397	24.0	0.05
≥9 Physician visits	1,397	26.1	1,428	24.5	0.01
Number of Laboratory Tests					
0-4 Laboratory tests	1,691	31.6	1,870	32.1	0.00
5-9 Laboratory tests	1,090	20.4	1,178	20.2	0.01
10-15 Laboratory tests	1,079	20.2	1,190	20.5	0.00
>15 Laboratory tests	1,488	27.8	1,581	27.2	0.01
Stroke/transient ischemic attack	78	1.5	88	1.5	0.00
Ischemic heart disease	645	12.1	680	11.7	0.00
Myocardial infarction	58	1.1	54	0.9	0.02
Disorders of lipid metabolism	3,809	71.2	4,023	69.1	0.03
Other disorders of urethra and urinary tract	486	9.1	492	8.5	0.02

Table 2.4b. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initiators by Duration of Follow-Up, Impact National Benchmark Database 6/1/2005−3/31/2015

	≥ 3 years				
	Exenatide (N= 5,348)		OADs (N= 5,819)		Standardized Difference
Characteristic	N	%	N	%	
Osteoarthritis and allied disorders	529	9.9	551	9.5	0.01
Peripheral enthesopathies and allied synromes	481	9.0	497	8.5	0.01
Other disorders of soft tissues	826	15.4	872	15.0	0.00
General symptoms	1,282	24.0	1,286	22.1	0.03
Symptoms involving skin and other integumentary tissue	511	9.6	478	8.2	0.04
Symptoms involving respiratory system and other chest symptoms	1,329	24.9	1,381	23.7	0.02
Symptoms involving digestive system	355	6.6	360	6.2	0.01
Nonspecific findings on examination of blood	502	9.4	496	8.5	0.03
Need for prophylactic vaccination and inoculation against certain viral diseases	1,065	19.9	1,129	19.4	0.00
Encounter for other and unspecified procedure and aftercare	830	15.5	798	13.7	0.04
General medical examination	1,068	20.0	1,284	22.1	0.04
Special investigations and examinations	1,392	26.0	1,437	24.7	0.02
Hypercholesterolemia	3,148	58.9	3,313	56.9	0.02
Chest x-ray	258	4.8	283	4.9	0.00
General health panel	708	13.2	672	11.5	0.05
Lipid panel	3,104	58.0	3,359	57.7	0.00
Urinalysis, automated, with microscopy	635	11.9	635	10.9	0.03
Albumin; urine, microalbumin, quantitative	1,742	32.6	1,920	33.0	0.02
Creatine kinase (CK), (CPK); total	484	9.1	487	8.4	0.02
Creatinine; other source	1,394	26.1	1,600	27.5	0.05
Glucose; quantitative, blood (except reagent strip)	794	14.8	924	15.9	0.04
Glucose, blood by glucose monitoring device(s) cleared by the FDA specifically for home use	779	14.6	812	14.0	0.01
Hemoglobin; glycosylated (A1C)	3,623	67.7	3,907	67.1	0.00
Prostate specific antigen (PSA); total	613	11.5	705	12.1	0.01
Transferase; aspartate amino (AST) (SGOT)	644	12.0	702	12.1	0.01
Automated hemogram	437	8.2	553	9.5	0.05

Table 2.4b. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initiators by Duration of Follow-Up, Impact National Benchmark Database 6/1/2005−3/31/2015

	≥ 3 years				
	Exenatide (N= 5,348)		OADs (N= 5,819)		Standardized Difference
Characteristic	N	%	N	%	
Level IV - Surgical pathology, gross and microscopic examination abortion - spontaneous/missed artery, biopsy bone marrow, biopsy bone exostosis brain/meninges, other than for tumor resection breast biopsy, not requiring micropscopic evaluation.	632	11.8	666	11.4	0.01
Influenza virus vaccine, trivalent (IIV3), split virus, 0.5 mL dosage, for intramuscular use	1,127	21.1	1,210	20.8	0.00
Ophthalmological services: medical examination and evaluaiton, with initiation or continuation of diagnostic and treatment program; comprehensive, established patient, one or more visits.	1,261	23.6	1,426	24.5	0.03
Electrocardiogram, routine ECG with at least 12 leads; interpretation and report only	535	10.0	617	10.6	0.02
Doppler echocardiography color flow velocity mapping (List separately in addition to codes for echocardiography)	490	9.2	464	8.0	0.02
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A problem focused history; A problem focused examination; Straightforward medical decision making.	1,271	23.8	1,352	23.2	0.00
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: An expanded problem focused history; An expanded problem focused examination; Medical decision making of low complexity.	4,216	78.8	4,531	77.9	0.02
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A detailed history; A detailed examination; Medical decision making of moderate complexity.	4,254	79.5	4,576	78.6	0.01

Table 2.4b. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initiators by Duration of Follow-Up, Impact National Benchmark Database 6/1/2005−3/31/2015

	≥ 3 years				
	Exenatide (N= 5,348)		OADs (N= 5,819)		Standardized Difference
Characteristic	N	%	N	%	
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A comprehensive history; A comprehensive examination; Medical decision making of high complexity.	995	18.6	996	17.1	0.03
Subsequent hospital care, per day, for the evaluation and management of a patient, which requires at least 2 of these 3 key components: An expanded problem focused interval history; An expanded problem focused examination; Medical decision making of moderate complexity.	230	4.3	279	4.8	0.03
Office consultation for a new or established patient, which requires these 3 key components: A detailed history; A detailed examination; and Medical decision making of low complexity.	775	14.5	756	13.0	0.03
Office consultation for a new or established patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical decision making of moderate complexity.	1,089	20.4	1,062	18.3	0.03
Periodic comprehensive preventive medicine reevaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, established patient; 40-64 years.	1,150	21.5	1,317	22.6	0.02
Computerized tomography (CT), abdomen	359	6.7	323	5.6	0.05
Routine chest x-ray	967	18.1	1,069	18.4	0.01
Echocardiogram	599	11.2	612	10.5	0.01
Other diagnostic ultrasound	611	11.4	611	10.5	0.03
Electrocardiogram	1,825	34.1	1,930	33.2	0.01
Microscopic exam (smear culture)	2,753	51.5	3,028	52.0	0.02
Radioisotope scan/function	475	8.9	479	8.2	0.01
Physical therapy exercises/manipulation	598	11.2	575	9.9	0.03
Other diagnostic radiology	1,832	34.3	1,868	32.1	0.04
Other therapeutic procedure	3,654	68.3	4,039	69.4	0.03

Table 2.4b. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initiators by Duration of Follow-Up, Impact National Benchmark Database 6/1/2005−3/31/2015

	≥ 3 years				
	Exenatide (N= 5,348)		OADs (N= 5,819)		Standardized Difference
Characteristic	N	%	N	%	
Other lab	4,361	81.5	4,669	80.2	0.01
Vaginal delivery	1,197	22.4	1,183	20.3	0.03
Miscellaneous medication administration	1,105	20.7	1,097	18.9	0.04
Durable medical equipment and supplies	1,338	25.0	1,389	23.9	0.01
Hypotensives, angiotensin receptor antagonist	1,215	22.7	1,243	21.4	0.01
Calcium channel blocking agents	769	14.4	923	15.9	0.04
Gastric acid secretion reducers	911	17.0	905	15.6	0.02
Analgesics, narcotics	1,481	27.7	1,502	25.8	0.03
Anticonvulsants	550	10.3	559	9.6	0.01
Skeletal muscle relaxants	453	8.5	461	7.9	0.02
Beta-adrenergic agents	500	9.3	503	8.6	0.02
Beta-adrenergic blocking agents	1,255	23.5	1,392	23.9	0.02
Blood sugar diagnostics	3,094	57.9	3,324	57.1	0.01
Anti-hyperlipidemic - HMG CoA reductase inhibitors	1,145	21.4	1,409	24.2	0.04
Lipotropics	2,932	54.8	3,018	51.9	0.02
Thyroid hormones	691	12.9	669	11.5	0.03
Glucocorticoids	560	10.5	558	9.6	0.03
Topical anti-inflammatory steroidal	491	9.2	511	8.8	0.01
Nasal anti-inflammatory steroids	455	8.5	537	9.2	0.04
Thiazide and related diuretics	655	12.2	800	13.7	0.05
Loop diuretics	578	10.8	556	9.6	0.03
Penicillins	973	18.2	1,029	17.7	0.01
Macrolides	921	17.2	976	16.8	0.01
Quinolones	841	15.7	835	14.3	0.03
Durable medical equipment, miscellaneous (Group 1)	1,293	24.2	1,353	23.3	0.02
Non-alcohol sedatives	830	15.5	839	14.4	0.02
Acid-suppressing drugs	1,116	20.9	1,145	19.7	0.02
Metformin	4,263	79.7	4,529	77.8	0.02
Sulfonylureas	2,486	46.5	2,626	45.1	0.00
Thiazolidinediones	2,082	38.9	2,077	35.7	0.02
Insulin glargine	563	10.5	717	12.3	0.09
Insulins	982	18.4	1,167	20.1	0.08
Ace inhibitors	2,558	47.8	2,898	49.8	0.03
Obesity	772	14.4	821	14.1	0.00

Table 2.4b. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initiators by Duration of Follow-Up, Impact National Benchmark Database 6/1/2005−3/31/2015

	≥ 3 years				
	Exenatide (N= 5,348)		OADs (N= 5,819)		Standardized Difference
Characteristic	N	%	N	%	
Hospitalization within 45 days of index	92	1.7	144	2.5	0.05
1 Anti-diabetic medication within 45 days of index	2,268	42.4	2,462	42.3	0.02
2 Anti-diabetic medications within 45 days of index	1,187	22.2	1,294	22.2	0.02
NSAIDs	1,082	20.2	1,139	19.6	0.02
Fibrates	612	11.4	660	11.3	0.01
Statins	3,306	61.8	3,596	61.8	0.01
Critical care procedure	34	0.6	38	0.7	0.00
Nephritis and nephropathy, not specified as acute or chronic	48	0.9	50	0.9	0.00
Retinopathy	278	5.2	342	5.9	0.04
Hypertension	3,205	59.9	3,454	59.4	0.01
Congestive heart failure	128	2.4	127	2.2	0.01
Peripheral neuropathy	481	9.0	490	8.4	0.01
Hyperlipidemia	4,080	76.3	4,268	73.3	0.04
Thryotropin releasing hormone	1,436	26.9	1,504	25.8	0.01
T3, T4 testing	797	14.9	769	13.2	0.04
Computerized tomography (CT), soft tissue neck	13	0.2	19	0.3	0.02
Thyroid imaging	12	0.2	8	0.1	0.01
Ultrasound of head and neck	102	1.9	92	1.6	0.01
Biopsy thyroid	20	0.4	19	0.3	0.01
Thyroidectomy	0	0.0	0	0.0	−
Other operations on thyroid	0	0.0	0	0.0	−
Abdominal pain	549	10.3	531	9.1	0.04
Lipase	97	1.8	84	1.4	0.03
Amylase	103	1.9	100	1.7	0.01
Other nonspecific abnormal serum enzyme levels	37	0.7	25	0.4	0.04
Abdominal ultrasound	249	4.7	235	4.0	0.03
Biopsy of pancreas	0	0.0	0	0.0	−
Pancreatectomy	0	0.0	0	0.0	−
Endobronchial ultrasound	0	0.0	0	0.0	−
Magnetic resonance imaging (MRI), abdomen	25	0.5	32	0.5	0.02
Magnetic resonance cholangiopancreatography (MRCP)	0	0.0	0	0.0	−
Endoscopic retrograde cholangiopancreatography (ERCP)	3	0.1	1	0.0	0.02
Other operations on pancreas	0	0.0	0	0.0	−

Table 2.4b. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initiators by Duration of Follow-Up, Impact National Benchmark Database 6/1/2005−3/31/2015

	≥ 3 years				
	Exenatide (N= 5,348)		OADs (N= 5,819)		Standardized Difference
Characteristic	N	%	N	%	
X-ray for pancreas	2	0.0	5	0.1	0.02
Micro exam of pancreas	0	0.0	0	0.0	−
Malignant neoplasm of lip	1	0.0	0	0.0	0.02
Malignant neoplasm of tongue	0	0.0	0	0.0	−
Malignant neoplasm of major salivary glands	1	0.0	2	0.0	0.01
Malignant neoplasm of floor of mouth	0	0.0	0	0.0	−
Malignant neoplasm of other and unspecified parts of mouth	0	0.0	0	0.0	−
Malignant neoplasm of oropharynx	0	0.0	0	0.0	−
Malignant neoplasm of nasopharynx	0	0.0	1	0.0	0.02
Malignant neoplasm of other and ill-defined sites within the lip, oral cavity, and pharynx	0	0.0	1	0.0	0.02
Malignant neoplasm of esophagus	0	0.0	0	0.0	−
Malignant neoplasm of stomach	0	0.0	0	0.0	−
Malignant neoplasm of small intestine, including duodenum	0	0.0	1	0.0	0.02
Malignant neoplasm of colon	15	0.3	14	0.2	0.01
Malignant neoplasm of rectum, rectosigmoid junction, and anus	8	0.1	9	0.2	0.00
Malignant neoplasm of liver and intrahepatic bile ducts	1	0.0	2	0.0	0.01
Malignant neoplasm of gallbladder and extrahepatic bile ducts	0	0.0	2	0.0	0.03
Malignant neoplasm of retroperitoneum and peritoneum	1	0.0	0	0.0	0.02
Malignant neoplasm of other and ill-defined sites within the digestive organs and peritoneum	0	0.0	0	0.0	−
Malignant neoplasm of nasal cavities, middle ear, and accessory sinuses	1	0.0	2	0.0	0.01
Malignant neoplasm of larynx	2	0.0	2	0.0	0.00
Malignant neoplasm of trachea, bronchus, and lung	3	0.1	6	0.1	0.01
Malignant neoplasm of pleura	0	0.0	0	0.0	−
Malignant neoplasm of thymus, heart, and mediastinum	1	0.0	1	0.0	0.00
Malignant neoplasm of bone and articular cartilage	3	0.1	2	0.0	0.01
Malignant neoplasm of connective and other soft tissue	1	0.0	6	0.1	0.03
Malignant melanoma of skin	10	0.2	13	0.2	0.00

Table 2.4b. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initiators by Duration of Follow-Up, Impact National Benchmark Database 6/1/2005−3/31/2015

	≥ 3 years				
	Exenatide (N= 5,348)		OADs (N= 5,819)		Standardized Difference
Characteristic	N	%	N	%	
Other and unspecified malignant neoplasm of skin	55	1.0	64	1.1	0.01
Malignant neoplasm of female breast	56	1.0	83	1.4	0.03
Malignant neoplasm of male breast	1	0.0	0	0.0	0.02
Kaposi's sarcoma	0	0.0	1	0.0	0.02
Malignant neoplasm of uterus, part unspecified	4	0.1	1	0.0	0.03
Malignant neoplasm of cervix uteri	3	0.1	4	0.1	0.00
Malignant neoplasm of body of uterus	13	0.2	6	0.1	0.03
Malignant neoplasm of ovary and other uterine adnexa	2	0.0	4	0.1	0.02
Malignant neoplasm of other and unspecified female genital organs	1	0.0	0	0.0	0.02
Malignant neoplasm of prostate	35	0.7	39	0.7	0.00
Malignant neoplasm of testis	1	0.0	2	0.0	0.01
Malignant neoplasm of bladder	9	0.2	12	0.2	0.01
Malignant neoplasm of kidney and other and unspecified urinary organs	11	0.2	7	0.1	0.02
Malignant neoplasm of eye	1	0.0	0	0.0	0.02
Malignant neoplasm of brain	1	0.0	2	0.0	0.01
Malignant neoplasm of other and unspecified parts of nervous system	0	0.0	1	0.0	0.02
Malignant neoplasm of other endocrine glands and related structures	1	0.0	1	0.0	0.00
Malignant neoplasm of other and ill-defined sites	3	0.1	3	0.1	0.01
Secondary and unspecified malignant neoplasm of lymph nodes	2	0.0	8	0.1	0.03
Secondary malignant neoplasm of respiratory and digestive systems	0	0.0	1	0.0	0.02
Secondary malignant neoplasm of other specified sites	1	0.0	8	0.1	0.04
Malignant neoplasm without specification of site	2	0.0	1	0.0	0.01
Lymphosarcoma and reticulosarcoma and other specified malignant tumors of lymphatic tissue	4	0.1	3	0.1	0.01
Hodgkin's disease	4	0.1	4	0.1	0.00
Other malignant neoplasms of lymphoid and histiocytic tissue	15	0.3	12	0.2	0.02
Multiple myeloma and immunoproliferative neoplasms	5	0.1	1	0.0	0.03

Table 2.4b. Selected Baseline Characteristics of Matched Exenatide Initiators and Other Antidiabetic Drug Initiators by Duration of Follow-Up, Impact National Benchmark Database 6/1/2005−3/31/2015

	≥ 3 years				
	Exenatide (N= 5,348)		OADs (N= 5,819)		Standardized Difference
Characteristic	N	%	N	%	
Lymphoid leukemia	4	0.1	2	0.0	0.02
Myeloid leukemia	3	0.1	6	0.1	0.03
Monocytic leukemia	1	0.0	0	0.0	0.02
Other specified leukemia	0	0.0	0	0.0	–
Leukemia of unspecified cell type	3	0.1	3	0.1	0.01
Personal history of malignant neoplasm	122	2.3	140	2.4	0.01

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.

Standardized difference is calculated by the difference between the two proportions divided by the pooled standard deviation

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 3.1a.The Top 200* Most Frequently Recorded Baseline Diagnoses Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Optum Research Database 6/1/2005−6/30/2015**

ICD-9-CM Code	Descriptions	Exenatide			OADs		
		Rank	Count	Percent	Rank	Count	Percent
250	Diabetes mellitus	1	45,791	100.00	1	311,047	100.00
272	Disorders of lipoid metabolism	2	36,785	80.33	2	223,154	71.74
401	Essential hypertension	3	34,526	75.40	3	221,128	71.09
780	General symptoms	4	14,960	32.67	4	89,470	28.76
V58	Encounter for other and unspecified procedure and aftercare	5	12,882	28.13	6	81,432	26.18
786	Symptoms involving respiratory system and other chest symptoms	6	12,518	27.34	5	86,121	27.69
V76	Special screening for malignant neoplasms	7	12,479	27.25	7	73,724	23.70
278	Overweight, obesity and other hyperalimentation	8	11,628	25.39	13	49,773	16.00
V72	Special investigations and examinations	9	11,143	24.33	8	62,256	20.02
719	Other and unspecified disorders of joint	10	9,106	19.89	10	54,496	17.52
V04	Need for prophylactic vaccination and inoculation against certain viral diseases	11	9,058	19.78	9	54,940	17.66
729	Other disorders of soft tissues	12	8,898	19.43	11	54,235	17.44
724	Other and unspecified disorders of back	13	7,709	16.84	15	46,593	14.98
244	Acquired hypothyroidism	14	7,178	15.68	21	34,125	10.97
V70	General medical examination	15	6,722	14.68	12	53,824	17.30
414	Other forms of chronic ischemic heart disease	16	6,137	13.40	17	42,487	13.66
782	Symptoms involving skin and other integumentary tissue	17	6,035	13.18	18	35,815	11.51
789	Other symptoms involving abdomen and pelvis	18	5,998	13.10	16	43,045	13.84
790	Nonspecific findings on examination of blood	19	5,627	12.29	14	49,111	15.79
530	Diseases of esophagus	20	5,539	12.10	19	35,415	11.39
715	Osteoarthrosis and allied disorders	21	5,403	11.80	22	32,000	10.29
461	Acute sinusitis	22	5,159	11.27	28	26,497	8.52
599	Other disorders of urethra and urinary tract	23	4,685	10.23	23	31,984	10.28
726	Peripheral enthesopathies and allied syndromes	24	4,429	9.67	37	22,255	7.16
787	Symptoms involving digestive system	25	4,382	9.57	20	34,462	11.08
362	Other retinal disorders	26	4,334	9.47	32	24,659	7.93
466	Acute bronchitis and bronchiolitis	27	4,318	9.43	31	24,719	7.95
366	Cataract	28	4,087	8.93	24	27,531	8.85
465	Acute upper respiratory infections of multiple or unspecified sites	29	3,961	8.65	36	22,819	7.34
477	Allergic rhinitis	30	3,957	8.64	40	21,268	6.84
794	Nonspecific abnormal results of function studies	31	3,855	8.42	27	26,735	8.60

Table 3.1a.The Top 200* Most Frequently Recorded Baseline Diagnoses Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Optum Research Database 6/1/2005−6/30/2015**

ICD-9-CM Code	Descriptions	Exenatide			OADs		
		Rank	Count	Percent	Rank	Count	Percent
327	Organic sleep disorders	32	3,696	8.07	48	18,456	5.93
722	Intervertebral disc disorders	33	3,637	7.94	39	21,476	6.90
788	Symptoms involving urinary system	34	3,503	7.65	29	26,460	8.51
784	Symptoms involving head and neck	35	3,468	7.57	30	25,519	8.20
493	Asthma	36	3,435	7.50	43	18,913	6.08
285	Other and unspecified anemias	37	3,367	7.35	26	27,023	8.69
785	Symptoms involving cardiovascular system	38	3,334	7.28	33	24,606	7.91
311	Depressive disorder, not elsewhere classified	39	3,314	7.24	45	18,785	6.04
723	Other disorders of cervical region	40	3,215	7.02	47	18,548	5.96
300	Anxiety, dissociative and somatoform disorders	41	3,210	7.01	41	20,319	6.53
728	Disorders of muscle, ligament, and fascia	42	3,172	6.93	44	18,796	6.04
V45	Other postprocedural status	43	3,154	6.89	34	24,185	7.78
365	Glaucoma	44	3,129	6.83	46	18,730	6.02
367	Disorders of refraction and accommodation	45	3,059	6.68	51	17,280	5.56
110	Dermatophytosis	46	2,939	6.42	49	18,453	5.93
682	Other cellulitis and abscess	47	2,792	6.10	42	19,989	6.43
427	Cardiac dysrhythmias	48	2,596	5.67	35	23,230	7.47
702	Other dermatoses	49	2,427	5.30	58	13,934	4.48
793	Nonspecific (abnormal) findings on radiological and other examination of body structure	50	2,381	5.20	50	18,395	5.91
783	Symptoms concerning nutrition, metabolism, and development	51	2,376	5.19	62	13,351	4.29
462	Acute pharyngitis	52	2,324	5.08	65	13,068	4.20
733	Other disorders of bone and cartilage	53	2,318	5.06	57	14,131	4.54
627	Menopausal and postmenopausal disorders	54	2,282	4.98	95	9,354	3.01
277	Other and unspecified disorders of metabolism	55	2,270	4.96	143	6,105	1.96
296	Episodic mood disorders	56	2,247	4.91	78	11,355	3.65
276	Disorders of fluid, electrolyte, and acid-base balance	57	2,222	4.85	25	27,105	8.71
727	Other disorders of synovium, tendon, and bursa	58	2,180	4.76	80	10,987	3.53
692	Contact dermatitis and other eczema	59	2,149	4.69	71	12,543	4.03
268	Vitamin D deficiency	60	2,074	4.53	61	13,373	4.30
739	Nonallopathic lesions, not elsewhere classified	61	2,071	4.52	86	10,287	3.31
357	Inflammatory and toxic neuropathy	62	2,052	4.48	77	11,369	3.66
V03	Need for prophylactic vaccination and inoculation against bacterial diseases	63	2,015	4.40	64	13,069	4.20

Table 3.1a.The Top 200* Most Frequently Recorded Baseline Diagnoses Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Optum Research Database 6/1/2005−6/30/2015**

ICD-9-CM Code	Descriptions	Exenatide			OADs		
		Rank	Count	Percent	Rank	Count	Percent
791	Nonspecific findings on examination of urine	64	1,977	4.32	66	13,039	4.19
402	Hypertensive heart disease	65	1,967	4.30	73	12,195	3.92
305	Nondependent abuse of drugs	66	1,955	4.27	38	21,802	7.01
211	Benign neoplasm of other parts of digestive system	67	1,917	4.19	75	11,804	3.80
424	Other diseases of endocardium	68	1,895	4.14	55	14,934	4.80
V65	Other persons seeking consultation	69	1,882	4.11	89	9,870	3.17
721	Spondylosis and allied disorders	70	1,868	4.08	72	12,370	3.98
473	Chronic sinusitis	71	1,855	4.05	90	9,752	3.14
562	Diverticula of intestine	72	1,810	3.95	74	12,087	3.89
216	Benign neoplasm of skin	73	1,788	3.91	109	8,641	2.78
428	Heart failure	74	1,755	3.83	54	15,426	4.96
372	Disorders of conjunctiva	75	1,670	3.65	92	9,539	3.07
607	Disorders of penis	76	1,664	3.63	67	12,972	4.17
611	Other disorders of breast	77	1,659	3.62	121	7,684	2.47
600	Hyperplasia of prostate	78	1,651	3.61	56	14,449	4.65
429	Ill-defined descriptions and complications of heart disease	79	1,648	3.60	59	13,906	4.47
796	Other nonspecific abnormal findings	80	1,639	3.58	69	12,731	4.09
238	Neoplasm of uncertain behavior of other and unspecified sites and tissues	81	1,633	3.57	93	9,535	3.07
703	Diseases of nail	82	1,624	3.55	111	8,537	2.75
571	Chronic liver disease and cirrhosis	83	1,604	3.50	76	11,389	3.66
626	Disorders of menstruation and other abnormal bleeding from female genital tract	84	1,600	3.49	119	7,823	2.52
V15	Other personal history presenting hazards to health	85	1,594	3.48	53	15,555	5.00
V12	Personal history of certain other diseases	86	1,572	3.43	70	12,586	4.05
455	Hemorrhoids	87	1,561	3.41	94	9,510	3.06
585	Chronic kidney disease (CKD)	88	1,557	3.40	60	13,800	4.44
257	Testicular dysfunction	89	1,540	3.36	131	7,017	2.26
518	Other diseases of lung	90	1,538	3.36	52	16,710	5.37
593	Other disorders of kidney and ureter	91	1,537	3.36	63	13,109	4.21
564	Functional digestive disorders, not elsewhere classified	92	1,528	3.34	81	10,888	3.50
716	Other and unspecified arthropathies	93	1,487	3.25	96	9,352	3.01

Table 3.1a.The Top 200* Most Frequently Recorded Baseline Diagnoses Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Optum Research Database 6/1/2005−6/30/2015**

ICD-9-CM Code	Descriptions	Exenatide			OADs		
		Rank	Count	Percent	Rank	Count	Percent
280	Iron deficiency anemias	94	1,459	3.19	87	10,226	3.29
847	Sprains and strains of other and unspecified parts of back	95	1,450	3.17	101	8,987	2.89
V06	Need for prophylactic vaccination and inoculation against combinations of diseases	96	1,435	3.13	82	10,799	3.47
356	Hereditary and idiopathic peripheral neuropathy	97	1,421	3.10	110	8,561	2.75
496	Chronic airway obstruction, not elsewhere classified	98	1,409	3.08	68	12,909	4.15
V67	Follow-up examination	99	1,395	3.05	97	9,256	2.98
379	Other disorders of eye	100	1,387	3.03	99	9,050	2.91
959	Injury, other and unspecified	101	1378	3.01	84	10,496	3.37
535	Gastritis and duodenitis	102	1,371	2.99	88	10,091	3.24
709	Other disorders of skin and subcutaneous tissue	103	1,371	2.99	115	8,149	2.62
443	Other peripheral vascular disease	104	1,346	2.94	85	10,383	3.34
616	Inflammatory disease of cervix, vagina, and vulva	106	1,332	2.91	118	7,831	2.52
706	Diseases of sebaceous glands	107	1,332	2.91	130	7,076	2.28
V10	Personal history of malignant neoplasm	108	1,327	2.90	83	10,549	3.39
490	Bronchitis, not specified as acute or chronic	109	1,323	2.89	116	8,103	2.61
625	Pain and other symptoms associated with female genital organs	110	1,300	2.84	137	6,478	2.08
701	Other hypertrophic and atrophic conditions of skin	111	1,284	2.80	135	6,632	2.13
355	Mononeuritis of lower limb and unspecified site	112	1,263	2.76	132	6,994	2.25
380	Disorders of external ear	113	1,256	2.74	106	8,729	2.81
569	Other disorders of intestine	114	1,250	2.73	108	8,701	2.80
799	Other ill-defined and unknown causes of morbidity and mortality	115	1,239	2.71	79	11,269	3.62
413	Angina pectoris	116	1,237	2.70	117	7,979	2.57
354	Mononeuritis of upper limb and mononeuritis multiplex	117	1,223	2.67	146	5,887	1.89
V57	Care involving use of rehabilitation procedures	118	1,214	2.65	103	8,878	2.85
V43	Organ or tissue replaced by other means	119	1,140	2.49	105	8,786	2.83
241	Nontoxic nodular goiter	120	1,134	2.48	181	3,932	1.26
995	Certain adverse effects not elsewhere classified	121	1,133	2.47	104	8,834	2.84
553	Other hernia of abdominal cavity without mention of obstruction or gangrene	122	1,125	2.46	122	7,548	2.43

Table 3.1a.The Top 200* Most Frequently Recorded Baseline Diagnoses Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Optum Research Database 6/1/2005−6/30/2015**

ICD-9-CM Code	Descriptions	Exenatide			OADs		
		Rank	Count	Percent	Rank	Count	Percent
274	Gout	123	1,114	2.43	102	8,901	2.86
592	Calculus of kidney and ureter	124	1,103	2.41	126	7,301	2.35
707	Chronic ulcer of skin	125	1,101	2.40	114	8,285	2.66
V16	Family history of malignant neoplasm	126	1,087	2.37	152	5,463	1.76
681	Cellulitis and abscess of finger and toe	127	1,081	2.36	140	6,373	2.05
382	Suppurative and unspecified otitis media	128	1,078	2.35	147	5,730	1.84
440	Atherosclerosis	129	1,045	2.28	107	8,717	2.80
112	Candidiasis	130	1,039	2.27	120	7,696	2.47
V85	Body mass index [BMI]	131	999	2.18	100	9,039	2.91
V99	Unknown diagosis	132	998	2.18	149	5,582	1.80
346	Migraine	133	982	2.15	159	4,906	1.58
433	Occlusion and stenosis of precerebral arteries	134	972	2.12	113	8,388	2.70
368	Visual disturbances	135	969	2.12	123	7,474	2.40
781	Symptoms involving nervous and musculoskeletal systems	136	964	2.11	98	9,092	2.92
388	Other disorders of ear	137	961	2.10	150	5,542	1.78
381	Nonsuppurative otitis media and Eustachian tube disorders	138	955	2.09	164	4,812	1.55
309	Adjustment reaction	139	943	2.06	156	5,080	1.63
486	Pneumonia, organism unspecified	140	943	2.06	91	9,567	3.08
558	Other noninfectious gastroenteritis and colitis	141	936	2.04	136	6,630	2.13
478	Other diseases of upper respiratory tract	142	902	1.97	155	5,212	1.68
375	Disorders of lacrimal system	143	899	1.96	151	5,540	1.78
389	Hearing loss	144	893	1.95	153	5,461	1.76
425	Cardiomyopathy	145	876	1.91	128	7,092	2.28
V77	Special screening for endocrine, nutritional, metabolic, and immunity disorders	146	875	1.91	125	7,323	2.35
459	Other disorders of circulatory system	147	870	1.90	148	5,656	1.82
717	Internal derangement of knee	148	865	1.89	184	3,855	1.24
704	Diseases of hair and hair follicles	149	848	1.85	190	3,705	1.19
240	Simple and unspecified goiter	150	843	1.84	227	2,934	0.94
256	Ovarian dysfunction	151	836	1.83	248	2,507	0.81
735	Acquired deformities of toe	152	829	1.81	166	4,715	1.52
924	Contusion of lower limb and of other and unspecified sites	153	829	1.81	168	4,702	1.51
840	Sprains and strains of shoulder and upper arm	154	824	1.80	165	4,782	1.54

Table 3.1a.The Top 200* Most Frequently Recorded Baseline Diagnoses Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Optum Research Database 6/1/2005−6/30/2015**

ICD-9-CM Code	Descriptions	Exenatide			OADs		
		Rank	Count	Percent	Rank	Count	Percent
411	Other acute and subacute forms of ischemic heart disease	155	796	1.74	141	6,343	2.04
578	Gastrointestinal hemorrhage	156	773	1.69	144	6,050	1.95
412	Old myocardial infarction	157	765	1.67	138	6,396	2.06
695	Erythematous conditions	158	756	1.65	185	3,771	1.21
275	Disorders of mineral metabolism	159	755	1.65	142	6,192	1.99
795	Other and nonspecific abnormal cytological, histological, immunological and DNA test findings	160	736	1.61	179	4,056	1.30
845	Sprains and strains of ankle and foot	161	715	1.56	197	3,534	1.14
836	Dislocation of knee	162	704	1.54	209	3,292	1.06
078	Other diseases due to viruses and Chlamydiae	163	694	1.52	186	3,768	1.21
403	Hypertensive chronic kidney disease	164	687	1.50	127	7,267	2.34
491	Chronic bronchitis	165	683	1.49	145	6,049	1.95
610	Benign mammary dysplasias	166	678	1.48	225	2,970	0.96
373	Inflammation of eyelids	167	676	1.48	175	4,170	1.34
V82	Special screening for other condition	168	671	1.47	171	4,593	1.48
333	Other extrapyramidal disease and abnormal movement disorders	169	669	1.46	198	3,445	1.11
288	Diseases of white blood cells	170	657	1.44	124	7,465	2.40
714	Rheumatoid arthritis and other inflammatory polyarthropathies	171	655	1.43	178	4,074	1.31
536	Disorders of function of stomach	172	646	1.41	158	5,007	1.61
281	Other deficiency anemias	173	644	1.41	187	3,760	1.21
041	Bacterial infection in conditions classified elsewhere and of unspecified site	174	640	1.40	134	6,933	2.23
338	Pain, not elsewhere classified	175	636	1.39	133	6,963	2.24
V17	Family history of certain chronic disabling diseases	176	636	1.39	169	4,653	1.50
573	Other disorders of liver	177	631	1.38	154	5,223	1.68
583	Nephritis and nephropathy, not specified as acute or chronic	178	622	1.36	207	3,299	1.06
472	Chronic pharyngitis and nasopharyngitis	179	615	1.34	224	3,020	0.97
251	Other disorders of pancreatic internal secretion	180	608	1.33	174	4,235	1.36
696	Psoriasis and similar disorders	181	597	1.30	200	3,419	1.10

Table 3.1a.The Top 200* Most Frequently Recorded Baseline Diagnoses Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Optum Research Database 6/1/2005−6/30/2015**

ICD-9-CM Code	Descriptions	Exenatide			OADs		
		Rank	Count	Percent	Rank	Count	Percent
V71	Observation and evaluation for suspected conditions not found	182	577	1.26	160	4,898	1.58
079	Viral and chlamydial infection in conditions classified elsewhere and of unspecified site	183	576	1.26	188	3,736	1.20
595	Cystitis	184	573	1.25	211	3,273	1.05
239	Neoplasms of unspecified nature	185	569	1.24	177	4,083	1.31
454	Varicose veins of lower extremities	186	567	1.24	233	2,798	0.90
574	Cholelithiasis	187	559	1.22	167	4,710	1.51
620	Noninflammatory disorders of ovary, fallopian tube, and broad ligament	188	553	1.21	240	2,619	0.84
686	Other local infection of skin and subcutaneous tissue	189	552	1.21	192	3,668	1.18
V49	Problems with limbs and other problems	190	552	1.21	176	4,094	1.32
242	Thyrotoxicosis with or without goiter	191	550	1.20	231	2,840	0.91
698	Pruritus and related conditions	192	544	1.19	208	3,296	1.06
218	Uterine leiomyoma	193	543	1.19	223	3,021	0.97
307	Special symptoms or syndromes, not elsewhere classified	194	526	1.15	229	2,908	0.94
V25	Contraceptive management	195	515	1.13	237	2,711	0.87
V14	Personal history of allergy to medicinal agents	196	506	1.11	183	3,876	1.25
844	Sprains and strains of knee and leg	197	502	1.10	236	2,714	0.87
998	Other complications of procedures, not elsewhere classified	198	502	1.10	173	4,385	1.41
E849	Place of occurrence	199	500	1.09	204	3,355	1.08
173	Other and unspecified malignant neoplasm of skin	200	495	1.08	191	3,675	1.18

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and

* Only a proportion of diagnoses in the top 200 list were retained in the propensity score model via stepwise selection.

** Baseline includes 9-month period prior to drug initiation.

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 3.1b.The Top 200* Most Frequently Recorded Baseline Diagnoses Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Impact National Benchmark Database 6/1/2005−3/31/2015**

		Exenatide			OADs		
ICD-9-CM Code	Descriptions	Rank	Count	Percent	Rank	Count	Percent
250	Diabetes mellitus	1	24,287	100.00	1	142,616	100.00
272	Disorders of lipoid metabolism	2	17,544	72.24	3	89,989	63.10
401	Essential hypertension	3	16,292	67.08	2	90,299	63.32
786	Symptoms involving respiratory system and other chest symptoms	4	6,718	27.66	4	38,398	26.92
V76	Special screening for malignant neoplasms	5	6,470	26.64	5	33,277	23.33
780	General symptoms	6	6,466	26.62	6	33,027	23.16
V72	Special investigations and examinations	7	6,224	25.63	7	31,937	22.39
278	Overweight, obesity and other hyperalimentation	8	5,479	22.56	17	17,295	12.13
V04	Need for prophylactic vaccination and inoculation against certain viral diseases	9	5,007	20.62	9	24,585	17.24
V70	General medical examination	10	4,874	20.07	8	31,855	22.34
719	Other and unspecified disorders of joint	11	4,490	18.49	10	22,503	15.78
729	Other disorders of soft tissues	12	4,167	17.16	12	21,302	14.94
V58	Encounter for other and unspecified procedure and aftercare	13	3,976	16.37	11	22,068	15.47
724	Other and unspecified disorders of back	14	3,550	14.62	14	18,286	12.82
414	Other forms of chronic ischemic heart disease	15	3,529	14.53	13	19,694	13.81
244	Acquired hypothyroidism	16	2,977	12.26	25	11,627	8.15
362	Other retinal disorders	17	2,931	12.07	19	12,568	8.81
789	Other symptoms involving abdomen and pelvis	18	2,794	11.50	16	17,549	12.31
715	Osteoarthrosis and allied disorders	19	2,691	11.08	20	12,547	8.80
782	Symptoms involving skin and other integumentary tissue	20	2,639	10.87	18	13,114	9.20
726	Peripheral enthesopathies and allied syndromes	21	2,498	10.29	27	10,724	7.52
366	Cataract	22	2,349	9.67	21	12,454	8.73
599	Other disorders of urethra and urinary tract	23	2,206	9.08	23	12,118	8.50
790	Nonspecific findings on examination of blood	24	2,160	8.89	15	17,599	12.34
530	Diseases of esophagus	25	2,156	8.88	24	11,938	8.37
461	Acute sinusitis	26	2,084	8.58	34	9,235	6.48
365	Glaucoma	27	2,038	8.39	30	9,993	7.01
466	Acute bronchitis and bronchiolitis	28	1,914	7.88	35	9,219	6.46
787	Symptoms involving digestive system	29	1,816	7.48	22	12,220	8.57
465	Acute upper respiratory infections of multiple or unspecified sites	30	1,776	7.31	36	8,941	6.27
785	Symptoms involving cardiovascular system	31	1,726	7.11	26	10,967	7.69

Table 3.1b.The Top 200* Most Frequently Recorded Baseline Diagnoses Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Impact National Benchmark Database 6/1/2005−3/31/2015**

		Exenatide			OADs		
ICD-9-CM Code	**Descriptions**	**Rank**	**Count**	**Percent**	**Rank**	**Count**	**Percent**
493	Asthma	32	1,707	7.03	40	8,107	5.68
722	Intervertebral disc disorders	33	1,648	6.79	38	8,520	5.97
788	Symptoms involving urinary system	34	1,627	6.70	28	10,048	7.05
794	Nonspecific abnormal results of function studies	35	1,617	6.66	32	9,860	6.91
110	Dermatophytosis	36	1,564	6.44	44	7,322	5.13
477	Allergic rhinitis	37	1,533	6.31	48	6,876	4.82
300	Anxiety, dissociative and somatoform disorders	38	1,525	6.28	43	7,564	5.30
784	Symptoms involving head and neck	39	1,522	6.27	33	9,548	6.70
728	Disorders of muscle, ligament, and fascia	40	1,486	6.12	49	6,701	4.70
285	Other and unspecified anemias	41	1,485	6.11	31	9,906	6.95
723	Other disorders of cervical region	42	1,484	6.11	47	7,082	4.97
327	Organic sleep disorders	43	1,429	5.88	58	5,645	3.96
427	Cardiac dysrhythmias	44	1,427	5.88	29	10,037	7.04
682	Other cellulitis and abscess	45	1,401	5.77	39	8,146	5.71
367	Disorders of refraction and accommodation	46	1,400	5.76	42	7,704	5.40
311	Depressive disorder, not elsewhere classified	47	1,292	5.32	50	6,188	4.34
296	Episodic mood disorders	48	1,278	5.26	59	5,642	3.96
727	Other disorders of synovium, tendon, and bursa	49	1,250	5.15	65	5,202	3.65
V65	Other persons seeking consultation	50	1,226	5.05	71	4,633	3.25
793	Nonspecific (abnormal) findings on radiological and other examination of body structure	51	1,215	5.00	41	8,105	5.68
702	Other dermatoses	52	1,189	4.90	57	5,680	3.98
733	Other disorders of bone and cartilage	53	1,186	4.88	53	5,986	4.20
211	Benign neoplasm of other parts of digestive system	54	1,163	4.79	51	6,187	4.34
216	Benign neoplasm of skin	55	1,128	4.64	74	4,506	3.16
V45	Other postprocedural status	56	1,126	4.64	45	7,315	5.13
277	Other and unspecified disorders of metabolism	57	1,110	4.57	148	2,130	1.49
692	Contact dermatitis and other eczema	58	1,108	4.56	61	5,444	3.82
627	Menopausal and postmenopausal disorders	59	1,084	4.46	84	4,149	2.91
703	Diseases of nail	60	1,083	4.46	80	4,303	3.02
462	Acute pharyngitis	61	1,075	4.43	64	5,294	3.71
402	Hypertensive heart disease	62	1,043	4.29	66	5,189	3.64
424	Other diseases of endocardium	63	995	4.10	54	5,984	4.20
562	Diverticula of intestine	64	967	3.98	63	5,349	3.75
739	Nonallopathic lesions, not elsewhere classified	65	961	3.96	79	4,309	3.02

Table 3.1b.The Top 200* Most Frequently Recorded Baseline Diagnoses Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Impact National Benchmark Database 6/1/2005−3/31/2015**

		Exenatide			OADs		
ICD-9-CM Code	Descriptions	Rank	Count	Percent	Rank	Count	Percent
473	Chronic sinusitis	66	935	3.85	85	4,127	2.89
357	Inflammatory and toxic neuropathy	67	926	3.81	103	3,520	2.47
611	Other disorders of breast	68	925	3.81	94	3,746	2.63
783	Symptoms concerning nutrition, metabolism, and development	69	925	3.81	75	4,487	3.15
V03	Need for prophylactic vaccination and inoculation against bacterial diseases	70	913	3.76	68	4,950	3.47
428	Heart failure	71	906	3.73	52	6,071	4.26
600	Hyperplasia of prostate	72	885	3.64	55	5,931	4.16
429	Ill-defined descriptions and complications of heart disease	73	870	3.58	60	5,562	3.90
721	Spondylosis and allied disorders	74	869	3.58	70	4,774	3.35
791	Nonspecific findings on examination of urine	75	853	3.51	78	4,339	3.04
276	Disorders of fluid, electrolyte, and acid-base balance	76	831	3.42	37	8,622	6.05
518	Other diseases of lung	77	801	3.30	46	7,268	5.10
238	Neoplasm of uncertain behavior of other and unspecified sites and tissues	78	796	3.28	97	3,714	2.60
455	Hemorrhoids	79	786	3.24	86	4,122	2.89
372	Disorders of conjunctiva	80	778	3.20	89	3,993	2.80
571	Chronic liver disease and cirrhosis	81	775	3.19	69	4,813	3.38
496	Chronic airway obstruction, not elsewhere classified	82	766	3.15	62	5,353	3.75
593	Other disorders of kidney and ureter	83	764	3.15	67	5,042	3.54
379	Other disorders of eye	84	758	3.12	82	4,180	2.93
709	Other disorders of skin and subcutaneous tissue	85	756	3.11	110	3,406	2.39
799	Other ill-defined and unknown causes of morbidity and mortality	86	752	3.10	73	4,589	3.22
626	Disorders of menstruation and other abnormal bleeding from female genital tract	87	745	3.07	117	3,044	2.13
701	Other hypertrophic and atrophic conditions of skin	88	741	3.05	130	2,782	1.95
716	Other and unspecified arthropathies	89	737	3.04	108	3,451	2.42
585	Chronic kidney disease (CKD)	90	724	2.98	72	4,597	3.22
535	Gastritis and duodenitis	91	723	2.98	81	4,213	2.95
681	Cellulitis and abscess of finger and toe	92	717	2.95	122	2,935	2.06

Table 3.1b.The Top 200* Most Frequently Recorded Baseline Diagnoses Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Impact National Benchmark Database 6/1/2005−3/31/2015**

		Exenatide			OADs		
ICD-9-CM Code	Descriptions	Rank	Count	Percent	Rank	Count	Percent
847	Sprains and strains of other and unspecified parts of back	93	711	2.93	100	3,580	2.51
380	Disorders of external ear	94	705	2.90	96	3,731	2.62
413	Angina pectoris	95	704	2.90	93	3,811	2.67
268	Vitamin D deficiency	96	690	2.84	98	3,701	2.60
569	Other disorders of intestine	97	687	2.83	91	3,906	2.74
607	Disorders of penis	98	686	2.83	77	4,401	3.09
564	Functional digestive disorders, not elsewhere classified	99	685	2.82	90	3,915	2.75
706	Diseases of sebaceous glands	100	680	2.80	113	3,235	2.27
490	Bronchitis, not specified as acute or chronic	101	677	2.79	107	3,487	2.45
443	Other peripheral vascular disease	102	673	2.77	83	4,172	2.93
354	Mononeuritis of upper limb and mononeuritis multiplex	103	664	2.73	134	2,605	1.83
796	Other nonspecific abnormal findings	104	657	2.71	76	4,442	3.12
707	Chronic ulcer of skin	105	648	2.67	102	3,522	2.47
959	Injury, other and unspecified	106	644	2.65	88	4,026	2.82
616	Inflammatory disease of cervix, vagina, and vulva	107	634	2.61	119	3,013	2.11
241	Nontoxic nodular goiter	108	632	2.60	171	1,774	1.24
V06	Need for prophylactic vaccination and inoculation against combinations of diseases	109	629	2.59	99	3,699	2.59
592	Calculus of kidney and ureter	110	626	2.58	111	3,391	2.38
280	Iron deficiency anemias	111	621	2.56	106	3,507	2.46
309	Adjustment reaction	112	606	2.50	129	2,784	1.95
433	Occlusion and stenosis of precerebral arteries	113	602	2.48	92	3,861	2.71
305	Nondependent abuse of drugs	114	593	2.44	56	5,922	4.15
356	Hereditary and idiopathic peripheral neuropathy	115	592	2.44	124	2,899	2.03
625	Pain and other symptoms associated with female genital organs	116	592	2.44	135	2,513	1.76
V10	Personal history of malignant neoplasm	117	587	2.42	95	3,739	2.62
355	Mononeuritis of lower limb and unspecified site	118	582	2.40	133	2,616	1.83
440	Atherosclerosis	119	582	2.40	101	3,573	2.51
V12	Personal history of certain other diseases	120	567	2.34	105	3,510	2.46
V67	Follow-up examination	121	541	2.23	109	3,428	2.40
389	Hearing loss	122	538	2.22	132	2,684	1.88
V57	Care involving use of rehabilitation procedures	123	538	2.22	104	3,514	2.46

Table 3.1b.The Top 200* Most Frequently Recorded Baseline Diagnoses Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Impact National Benchmark Database 6/1/2005−3/31/2015**

		Exenatide			OADs		
ICD-9-CM Code	Descriptions	Rank	Count	Percent	Rank	Count	Percent
553	Other hernia of abdominal cavity without mention of obstruction or gangrene	124	529	2.18	123	2,925	2.05
257	Testicular dysfunction	125	527	2.17	165	1,838	1.29
368	Visual disturbances	126	512	2.11	116	3,047	2.14
V16	Family history of malignant neoplasm	127	487	2.01	147	2,142	1.50
425	Cardiomyopathy	128	485	2.00	121	2,936	2.06
486	Pneumonia, organism unspecified	129	477	1.96	87	4,031	2.83
459	Other disorders of circulatory system	130	472	1.94	141	2,222	1.56
717	Internal derangement of knee	131	470	1.94	166	1,820	1.28
V43	Organ or tissue replaced by other means	132	465	1.92	125	2,868	2.01
478	Other diseases of upper respiratory tract	133	464	1.91	149	2,108	1.48
995	Certain adverse effects not elsewhere classified	134	461	1.90	115	3,060	2.15
388	Other disorders of ear	135	458	1.89	144	2,186	1.53
375	Disorders of lacrimal system	136	456	1.88	145	2,174	1.52
840	Sprains and strains of shoulder and upper arm	137	452	1.86	143	2,191	1.54
735	Acquired deformities of toe	138	442	1.82	152	2,020	1.42
382	Suppurative and unspecified otitis media	139	439	1.81	146	2,171	1.52
078	Other diseases due to viruses and Chlamydiae	140	433	1.78	164	1,839	1.29
274	Gout	141	431	1.78	114	3,135	2.20
558	Other noninfectious gastroenteritis and colitis	142	430	1.77	128	2,815	1.97
112	Candidiasis	143	429	1.77	138	2,421	1.70
381	Nonsuppurative otitis media and Eustachian tube disorders	144	426	1.75	159	1,909	1.34
V15	Other personal history presenting hazards to health	145	426	1.75	120	2,996	2.10
781	Symptoms involving nervous and musculoskeletal systems	146	425	1.75	112	3,247	2.28
836	Dislocation of knee	147	424	1.75	182	1,625	1.14
695	Erythematous conditions	148	416	1.71	177	1,670	1.17
411	Other acute and subacute forms of ischemic heart disease	149	415	1.71	127	2,851	2.00
373	Inflammation of eyelids	150	405	1.67	151	2,045	1.43
795	Other and nonspecific abnormal cytological, histological, immunological and DNA test findings	151	394	1.62	157	1,930	1.35
696	Psoriasis and similar disorders	152	388	1.60	163	1,845	1.29

Table 3.1b.The Top 200* Most Frequently Recorded Baseline Diagnoses Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Impact National Benchmark Database 6/1/2005−3/31/2015**

		Exenatide			OADs		
ICD-9-CM Code	Descriptions	Rank	Count	Percent	Rank	Count	Percent
573	Other disorders of liver	153	387	1.59	136	2,482	1.74
924	Contusion of lower limb and of other and unspecified sites	154	386	1.59	179	1,658	1.16
845	Sprains and strains of ankle and foot	155	383	1.58	194	1,455	1.02
240	Simple and unspecified goiter	156	378	1.56	223	1,091	0.77
578	Gastrointestinal hemorrhage	157	361	1.49	126	2,857	2.00
V71	Observation and evaluation for suspected conditions not found	158	358	1.47	139	2,316	1.62
704	Diseases of hair and hair follicles	159	357	1.47	195	1,453	1.02
275	Disorders of mineral metabolism	160	354	1.46	156	1,936	1.36
256	Ovarian dysfunction	161	352	1.45	251	836	0.59
491	Chronic bronchitis	162	347	1.43	137	2,472	1.73
346	Migraine	163	345	1.42	180	1,650	1.16
V82	Special screening for other condition	164	333	1.37	174	1,729	1.21
079	Viral and chlamydial infection in conditions classified elsewhere and of unspecified site	165	320	1.32	172	1,768	1.24
472	Chronic pharyngitis and nasopharyngitis	166	317	1.31	201	1,332	0.93
218	Uterine leiomyoma	167	315	1.30	190	1,531	1.07
574	Cholelithiasis	168	306	1.26	154	2,000	1.40
686	Other local infection of skin and subcutaneous tissue	169	301	1.24	192	1,501	1.05
610	Benign mammary dysplasias	170	299	1.23	204	1,263	0.89
583	Nephritis and nephropathy, not specified as acute or chronic	171	297	1.22	215	1,164	0.82
V85	Body mass index [BMI]	172	290	1.19	175	1,694	1.19
V54	Other orthopedic aftercare	173	289	1.19	176	1,672	1.17
536	Disorders of function of stomach	174	287	1.18	169	1,780	1.25
242	Thyrotoxicosis with or without goiter	175	286	1.18	206	1,239	0.87
307	Special symptoms or syndromes, not elsewhere classified	176	284	1.17	222	1,096	0.77
844	Sprains and strains of knee and leg	177	283	1.17	218	1,130	0.79
174	Malignant neoplasm of female breast	178	274	1.13	181	1,629	1.14
239	Neoplasms of unspecified nature	179	274	1.13	161	1,878	1.32
714	Rheumatoid arthritis and other inflammatory polyarthropathies	180	273	1.12	183	1,617	1.13
251	Other disorders of pancreatic internal secretion	181	270	1.11	184	1,610	1.13

Table 3.1b.The Top 200* Most Frequently Recorded Baseline Diagnoses Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Impact National Benchmark Database 6/1/2005−3/31/2015**

		Exenatide			OADs		
ICD-9-CM Code	Descriptions	Rank	Count	Percent	Rank	Count	Percent
412	Old myocardial infarction	182	267	1.10	153	2,010	1.41
620	Noninflammatory disorders of ovary, fallopian tube, and broad ligament	183	267	1.10	216	1,157	0.81
839	Other, multiple, and ill-defined dislocations	184	262	1.079	236	968	0.68
454	Varicose veins of lower extremities	185	260	1.07	205	1,240	0.87
173	Other and unspecified malignant neoplasm of skin	186	259	1.07	188	1,536	1.08
386	Vertiginous syndromes and other disorders of vestibular system	187	253	1.04	208	1,211	0.85
281	Other deficiency anemias	188	252	1.04	203	1,315	0.92
403	Hypertensive chronic kidney disease	189	251	1.03	155	1,985	1.39
333	Other extrapyramidal disease and abnormal movement disorders	190	248	1.02	225	1,077	0.76
426	Conduction disorders	191	246	1.01	170	1,778	1.25
998	Other complications of procedures, not elsewhere classified	192	241	0.99	167	1,807	1.27
V77	Special screening for endocrine, nutritional, metabolic, and immunity disorders	193	240	0.99	158	1,925	1.35
374	Other disorders of eyelids	194	238	0.98	228	1,052	0.74
245	Thyroiditis	195	236	0.97	337	501	0.35
410	Acute myocardial infarction	196	230	0.95	140	2,294	1.61
V05	Need for other prophylactic vaccination and inoculation against single diseases	197	229	0.94	196	1,434	1.01
V49	Problems with limbs and other problems	198	229	0.94	202	1,321	0.93
041	Bacterial infection in conditions classified elsewhere and of unspecified site	199	227	0.94	150	2,067	1.45
718	Other derangement of joint	200	224	0.92	231	1,020	0.72

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and

* Only a proportion of diagnoses in the top 200 list were retained in the propensity score model via stepwise selection.

** Baseline includes 9-month period prior to drug initiation.

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 3.2a.The Top 200* Most Frequently Recorded Baseline Procedures Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Optum Research Database 6/1/2005−6/30/2015**

CPT or HCPC Code	Descriptions	Exenatide			OADs		
		Rank	Count	Percent	Rank	Count	Percent
99214	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A detailed history; A detailed examination; Medical decision making of moderate complexity.	1	38,518	84.12	1	234,654	75.44
83036	Hemoglobin; glycosylated (A1C)	2	37,567	82.04	2	227,227	73.05
99213	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: An expanded problem focused history; An expanded problem focused examination; Medical decision making of low complexity.	3	35,227	76.93	3	218,492	70.24
80061	Lipid panel; This panel must include the following: Cholesterol, serum, total (82465) Lipoprotein, direct measurement, high density cholesterol (HDL cholesterol) (83718) Triglycerides (84478)	4	33,225	72.56	4	199,544	64.15
36415	Collection of venous blood by venipuncture	5	29,276	63.93	5	183,609	59.03
80053	Comprehensive metabolic panel; This panel must include the following: Albumin (82040) Bilirubin, total (82247) Calcium, total (82310) Carbon dioxide (bicarbonate) (82374) Chloride (82435) Creatinine (82565) Glucose (82947) Phosphatase, alkaline (84075) Potassium (84132) Protein, total (84155) Sodium (84295) Transferase, alanine amino (ALT) (SGPT) (84460) Transferase, aspartate amino (AST) (SGOT) (84450) Urea nitrogen (BUN) (84520)	6	25,768	56.27	6	151,935	48.85
82043	Albumin; urine, microalbumin, quantitative	7	17,246	37.66	8	93,763	30.14
85025	Blood count; complete (CBC), automated (Hgb, Hct, RBC, WBC and platelet count) and automated differential WBC count	8	15,208	33.21	7	101,732	32.71
82570	Creatinine; other source	9	13,948	30.46	10	71,898	23.11
84443	Thyroid stimulating hormone (TSH)	10	13,695	29.91	14	62,088	19.96
80050	General health panel This panel must include the following: Comprehensive metabolic panel (80053) Blood count, complete (CBC), automated and automated differential WBC count (85025 or 85027 and 85004) OR Blood count, complete (CBC), automated (85027) and appropriate manual differential WBC count (85007 or 85009) Thyroid stimulating hormone (TSH) (84443)	11	11,477	25.06	9	71,907	23.12
93000	Electrocardiogram, routine ECG with at least 12 leads; with interpretation and report	12	10,218	22.31	12	66,411	21.35

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CPT or HCPC Code	Descriptions	Exenatide			OADs		
		Rank	Count	Percent	Rank	Count	Percent
99212	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A problem focused history; A problem focused examination; Straightforward medical decision making	13	10,183	22.24	17	56,082	18.03
76499	Unlisted diagnostic radiographic procedure	14	10,083	22.02	13	62,443	20.08
89240	Unlisted miscellaneous pathology test	15	9,914	21.65	11	68,488	22.02
99215	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A comprehensive history; A comprehensive examination; Medical decision making of high complexity.	16	9,768	21.33	20	50,439	16.22
80048	Basic metabolic panel (Calcium, total) This panel must include the following: Calcium (82310) Carbon dioxide (82374) Chloride (82435) Creatinine (82565) Glucose (82947) Potassium (84132) Sodium (84295) Urea nitrogen (BUN) (84520)	17	9,291	20.29	15	57,988	18.64
99244	Office consultation for a new or established patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical decision making of moderate complexity.	18	8,793	19.20	32	37,676	12.11
90471	Immunization administration (includes percutaneous, intradermal, subcutaneous, or intramuscular injections); one vaccine (single or combination vaccine/toxoid)	19	8,516	18.60	21	50,152	16.12
90658	Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use	20	8,166	17.83	24	43,357	13.94
99203	Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: A detailed history; A detailed examination; Medical decision making of low complexity.	21	8,012	17.50	18	52,213	16.79
71020	Radiologic examination, chest, two views, frontal and lateral	22	7,711	16.84	16	57,172	18.38
99396	Periodic comprehensive preventive medicine reevaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, established patient; 40-64 years	23	7,270	15.88	28	40,471	13.01
92014	Ophthalmological services: medical examination and evaluation, with initiation or continuation of diagnostic and treatment program; comprehensive, established patient, one or more visits	24	7,244	15.82	31	38,673	12.43
82962	Glucose, blood by glucose monitoring device(s) cleared by the FDA specifically for home use	25	6,853	14.97	30	39,148	12.59

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CPT or HCPC Code	Descriptions	Exenatide			OADs		
		Rank	Count	Percent	Rank	Count	Percent
81001	Urinalysis, by dip stick or tablet reagent for bilirubin, glucose, hemoglobin, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen, any number of these constituents; automated, with microscopy	26	6,545	14.29	23	45,605	14.66
84439	Thyroxine; free	27	6,515	14.23	40	26,896	8.65
84153	Prostate specific antigen (PSA); total	28	6,411	14.00	19	52,176	16.77
99204	Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; Medical decision making of moderate complexity.	29	6,403	13.98	26	42,282	13.59
82947	Glucose; quantitative, blood (except reagent strip)	30	6,301	13.76	33	36,932	11.87
81003	Urinalysis, by dip stick or tablet reagent for bilirubin, glucose, hemoglobin, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen, any number of these constituents; automated, without microscopy	31	6,129	13.38	27	41,578	13.37
88305	Level IV - Surgical pathology, gross and microscopic examination Abortion - spontaneous/missed Artery, biopsy Bone marrow, biopsy Bone exostosis Brain/meninges, other than for tumor resection Breast, biopsy, not requiring microscopic evaluation (truncated)	32	5,868	12.81	34	36,605	11.77
81002	Urinalysis, by dip stick or tablet reagent for bilirubin, glucose, hemoglobin, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen, any number of these constituents; non-automated, without microscopy	33	5,574	12.17	35	35,881	11.54
92015	Determination of refractive state	34	5,268	11.50	39	27,854	8.95
93010	Electrocardiogram, routine ECG with at least 12 leads; interpretation and report only	35	5,217	11.39	22	49,019	15.76
99243	Office consultation for a new or established patient, which requires these 3 key components: A detailed history; A detailed examination; and Medical decision making of low complexity.	36	5,201	11.36	41	26,413	8.49
99245	Office consultation for a new or established patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical decision making of high complexity.	37	4,763	10.40	65	17,998	5.79
99000	Handling and/or conveyance of specimen for transfer from the physician's office to a laboratory	38	4,741	10.35	43	25,527	8.21

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CPT or HCPC Code	Descriptions	Exenatide			OADs		
		Rank	Count	Percent	Rank	Count	Percent
80076	Hepatic function panel This panel must include the following: Albumin (82040) Bilirubin, total (82247) Bilirubin, direct (82248) Phosphatase, alkaline (84075) Protein, total (84155) Transferase, alanine amino (ALT) (SGPT) (84460) Transferase, aspartate amino (AST) (SGOT) (84450)	39	4,316	9.43	45	24,102	7.75
84460	Transferase; alanine amino (ALT) (SGPT)	40	4,268	9.32	55	20,257	6.51
82550	Creatine kinase (CK), (CPK); total	41	4,220	9.22	46	22,832	7.34
99211	Office or other outpatient visit for the evaluation and management of an established patient, that may not require the presence of a physician. Usually, the presenting problem(s) are minimal. Typically, 5 minutes are spent performing or supervising these services	42	3,818	8.34	59	19,199	6.17
99285	Emergency department visit for the evaluation and management of a patient, which requires these 3 key components within the constraints imposed by the urgency of the patient's clinical condition and/or mental status: A comprehensive history; A comprehensive examination; and Medical decision making of high complexity.	43	3,669	8.01	29	40,079	12.89
84436	Thyroxine; total	44	3,662	8.00	63	18,528	5.96
82306	Calcifediol (25-OH Vitamin D-3)	45	3,626	7.92	47	22,286	7.16
93325	Doppler echocardiography color flow velocity mapping (List separately in addition to codes for echocardiography)	46	3,593	7.85	54	20,837	6.70
93320	Doppler echocardiography, pulsed wave and/or continuous wave with spectral display (List separately in addition to codes for echocardiographic imaging); complete	47	3,537	7.72	56	19,958	6.42
81000	Urinalysis, by dip stick or tablet reagent for bilirubin, glucose, hemoglobin, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen, any number of these constituents; non-automated, with microscopy	48	3,527	7.70	53	20,980	6.75
82948	Glucose; blood, reagent strip	49	3,520	7.69	57	19,432	6.25
82044	Albumin; urine, microalbumin, semiquantitative (eg, reagent strip assay)	50	3,442	7.52	67	17,215	5.53
93015	Cardiovascular stress test using maximal or submaximal treadmill or bicycle exercise, continuous electrocardiographic monitoring, and/or pharmacological stress; with physician supervision, with interpretation and report	51	3,384	7.39	76	15,855	5.10
84550	Uric acid; blood	52	3,361	7.34	58	19,308	6.21
93307	Echocardiography, transthoracic, real-time with image documentation (2D) with or without M-mode recording; complete	53	3,352	7.32	64	18,113	5.82
87086	Culture, bacterial; quantitative colony count, urine	54	3,281	7.17	51	21,358	6.87

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CPT or HCPC Code	Descriptions	Exenatide			OADs		
		Rank	Count	Percent	Rank	Count	Percent
78465	Myocardial perfusion imaging; tomographic (SPECT), multiple studies (including attenuation correction when performed), at rest and/or stress (exercise and/or pharmacologic) and redistribution and/or rest injection, with or without quantification	55	3,275	7.15	84	14,375	4.62
78478	Myocardial perfusion study with wall motion, qualitative or quantitative study (List separately in addition to code for primary procedure) Myocardial	56	3,270	7.14	88	14,118	4.54
78480	perfusion study with ejection fraction (List separately in addition to code for primary procedure)	57	3,243	7.08	89	14,067	4.52
A7035	Headgear used with positive airway pressure device	58	3,185	6.96	108	11,367	3.65
77052	Computer-aided detection (computer algorithm analysis of digital image data for lesion detection) with further review for interpretation, with or without digitization of film radiographic images; screening mammography (List separately in addition to code for primary procedure)	59	3,160	6.90	61	18,870	6.07
99202	Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: An expanded problem focused history; An expanded problem focused examination; Straightforward medical decision making.	60	3,150	6.88	60	19,160	6.16
82248	Bilirubin; direct	61	3,148	6.87	73	16,341	5.25
97110	Therapeutic procedure, one or more areas, each 15 minutes; therapeutic exercises to develop strength and endurance, range of motion and flexibility	62	3,106	6.78	79	15,325	4.93
0000000	Unknown procedure	63	3,081	6.73	25	42,954	13.81
71010	Radiologic examination, chest; single view, frontal	64	3,068	6.70	37	34,689	11.15
83721	Lipoprotein, direct measurement; LDL cholesterol	65	3,045	6.65	82	14,621	4.70
85027	Blood count; complete (CBC), automated (Hgb, Hct, RBC, WBC and platelet count)	66	3,041	6.64	50	21,738	6.99
99284	Emergency department visit for the evaluation and management of a patient, which requires these 3 key components: A detailed history; A detailed examination; and Medical decision making of moderate complexity	67	3,038	6.63	42	26,202	8.42
85610	Prothrombin time	68	3,005	6.56	48	21,794	7.01
84403	Testosterone; total	69	2,986	6.52	93	13,391	4.31
82607	Cyanocobalamin (Vitamin B-12)	70	2,959	6.46	70	16,584	5.33
84450	Transferase; aspartate amino (AST) (SGOT)	71	2,923	6.38	85	14,364	4.62
82565	Creatinine; blood	72	2,913	6.36	72	16,410	5.28

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CPT or HCPC Code	Descriptions	Exenatide			OADs		
		Rank	Count	Percent	Rank	Count	Percent
88142	Cytopathology, cervical or vaginal (any reporting system), collected in preservative fluid, automated thin layer preparation; manual screening under physician supervision	73	2,895	6.32	109	11,041	3.55
88175	Cytopathology, cervical or vaginal (any reporting system), collected in preservative fluid, automated thin layer preparation; with screening by automated system and manual rescreening or review, under physician supervision	74	2,888	6.31	83	14,421	4.64
99205	Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; Medical decision making of high complexity.	75	2,804	6.12	78	15,367	4.94
36416	Collection of capillary blood specimen (eg, finger, heel, ear stick)	76	2,773	6.06	98	12,465	4.01
91000	Esophageal intubation and collection of washings for cytology, including preparation of specimens (separate procedure)	77	2,773	6.06	52	21,302	6.85
83540	Iron	78	2,709	5.92	77	15,388	4.95
A7034	Nasal interface (mask or cannula type) used with positive airway pressure device, with or without head strap	79	2,645	5.78	131	9,017	2.90
99232	Subsequent hospital care, per day, for the evaluation and management of a patient, which requires at least 2 of these 3 key components: An expanded problem focused interval history; An expanded problem focused examination; Medical decision making of moderate complexity.	80	2,629	5.74	36	34,943	11.23
92250	Fundus photography with interpretation and report	81	2,598	5.67	81	14,770	4.75
G0202	Screening mammography, producing direct digital image, bilateral, all views	82	2,559	5.59	75	15,979	5.14
99283	Emergency department visit for the evaluation and management of a patient, which requires these 3 key components: An expanded problem focused history; An expanded problem focused examination; and Medical decision making of moderate complexity.	83	2,528	5.52	62	18,663	6.00
20610	Arthrocentesis, aspiration and/or injection; major joint or bursa (eg, shoulder, hip, knee joint, subacromial bursa)	84	2,527	5.52	99	12,423	3.99
A7037	Tubing used with positive airway pressure device	85	2,509	5.48	126	9,208	2.96
76092	Screening mammography, bilateral (two view film study of each breast)	86	2,461	5.37	157	7,665	2.46
97140	Manual therapy techniques (eg, mobilization/ manipulation, manual lymphatic drainage, manual traction), one or more regions, each 15 minutes	87	2,401	5.24	107	11,591	3.73

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CPT or HCPC Code	Descriptions	Exenatide			OADs		
		Rank	Count	Percent	Rank	Count	Percent
92012	Ophthalmological services: medical examination and evaluation, with initiation or continuation of diagnostic and treatment program; intermediate, established patient	88	2,388	5.22	92	13,438	4.32
97001	Physical therapy evaluation	89	2,263	4.94	111	10,973	3.53
82270	Blood, occult, by peroxidase activity (eg, guaiac), qualitative; feces, consecutive collected specimens with single determination, for colorectal neoplasm screening (ie, patient was provided 3 cards or single triple card for consecutive collection)	90	2,261	4.94	97	12,490	4.02
84479	Thyroid hormone (T3 or T4) uptake or thyroid hormone binding ratio (THBR)	91	2,201	4.81	113	10,495	3.37
G0108	Diabetes outpatient self-management training services, individual, per 30 minutes	92	2,156	4.71	212	5,641	1.81
90732	Pneumococcal polysaccharide vaccine, 23-valent, adult or immunosuppressed patient dosage, when administered to individuals 2 years or older, for subcutaneous or intramuscular use	93	2,153	4.70	96	12,778	4.11
92004	Ophthalmological services: medical examination and evaluation with initiation of diagnostic and treatment program; comprehensive, new patient, one or more visits	94	2,150	4.70	87	14,191	4.56
73630	Radiologic examination, foot; complete, minimum of three views	95	2,143	4.68	103	11,893	3.82
99223	Initial hospital care, per day, for the evaluation and management of a patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical decision making of high complexity.	96	2,142	4.68	38	28,711	9.23
97100	Physical therapy treatment	97	2,125	4.64	110	10,985	3.53
82728	Ferritin	98	2,111	4.61	105	11,867	3.82
E0601	Continuous airway pressure (CPAP) device	99	2,082	4.55	175	6,931	2.23
84681	C-peptide	100	2,063	4.51	179	6,758	2.17
A7038	Filter, disposable, used with positive airway pressure device Sedimentation	101	2,060	4.50	150	8,049	2.59
85652	rate, erythrocyte; automated	102	2,037	4.45	102	11,965	3.85
84100	Phosphorus inorganic (phosphate)	103	1,954	4.27	100	12,332	3.96
99199	Unlisted special service, procedure or report	104	1,949	4.26	127	9,195	2.96
83735	Magnesium	105	1,944	4.25	90	13,669	4.39
90772	Therapeutic, prophylactic or diagnostic injection (specify substance or drug); subcutaneous or intramuscular	106	1,937	4.23	149	8,086	2.60
98941	Chiropractic manipulative treatment (CMT); spinal, three to four regions	107	1,924	4.20	129	9,036	2.91

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CPT or HCPC Code	Descriptions	Exenatide			OADs		
		Rank	Count	Percent	Rank	Count	Percent
94760	Noninvasive ear or pulse oximetry for oxygen saturation; single determination	108	1,909	4.17	94	13,010	4.18
99238	Hospital discharge day management; 30 minutes or less	109	1,843	4.02	49	21,774	7.00
J3301	Injection, triamcinolone acetonide, per 10 mg	110	1,834	4.01	125	9,262	2.98
85730	Thromboplastin time, partial (PTT); plasma or whole blood	111	1,826	3.99	91	13,560	4.36
92083	Visual field examination, unilateral or bilateral, with interpretation and report; extended examination (eg, Goldmann visual fields with at least 3 isopters plotted and static determination within the central 30 degrees or quantitative, automated threshold perimetry, Octopus program G-1, 32 or 42, Humphrey visual field analyzer full threshold programs 30-2, 24-2, or 30/60-2)	112	1,799	3.93	117	10,154	3.26
83550	Iron binding capacity	113	1,769	3.86	114	10,356	3.33
92135	Scanning computerized ophthalmic diagnostic imaging, posterior segment, (eg, scanning laser) with interpretation and report, unilateral	114	1,758	3.84	133	9,005	2.90
82977	Glutamyltransferase, gamma (GGT)	115	1,738	3.80	124	9,441	3.04
77057	Screening mammography, bilateral (2-view film study of each breast)	116	1,695	3.70	161	7,564	2.43
76083	Computer aided detection (computer algorithm analysis of digital image data for lesion detection) with further physician review for interpretation, with or without digitization of film radiographic images; screening mammography (List separately in addition to code for primary procedure)	117	1,661	3.63	241	4,872	1.57
98940	Chiropractic manipulative treatment (CMT); spinal, one to two regions	118	1,653	3.61	152	7,979	2.57
A9500	Technetium Tc-99m sestamibi, diagnostic, per study dose, up to 40 millicuries	119	1,645	3.59	165	7,296	2.35
83615	Lactate dehydrogenase (LD), (LDH)	120	1,638	3.58	120	9,813	3.15
99233	Subsequent hospital care, per day, for the evaluation and management of a patient, which requires at least 2 of these 3 key components: A detailed interval history; A detailed examination; Medical decision making of high complexity.	121	1,618	3.53	44	24,290	7.81
87070	Culture, bacterial; any other source except urine, blood or stool, aerobic, with isolation and presumptive identification of isolates	122	1,607	3.51	112	10,812	3.48
82746	Folic acid; serum	123	1,583	3.46	122	9,707	3.12
86038	Antinuclear antibodies (ANA)	124	1,568	3.42	143	8,474	2.72
86141	C-reactive protein; high sensitivity (hsCRP)	125	1,554	3.39	197	6,083	1.96
93880	Duplex scan of extracranial arteries; complete bilateral study	126	1,536	3.35	101	12,182	3.92
86140	C-reactive protein	127	1,516	3.31	142	8,546	2.75

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CPT or HCPC Code	Descriptions	Exenatide			OADs		
		Rank	Count	Percent	Rank	Count	Percent
17000	Destruction (eg, laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), premalignant lesions (eg, actinic keratoses); first lesion	128	1,515	3.31	138	8,686	2.79
73030	Radiologic examination, shoulder; complete, minimum of two views	129	1,510	3.30	130	9,018	2.90
99254	Inpatient consultation for a new or established patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical decision making of moderate complexity.	130	1,503	3.28	66	17,966	5.78
72100	Radiologic examination, spine, lumbosacral; two or three views	131	1,500	3.28	128	9,041	2.91
87088	Culture, bacterial; with isolation and presumptive identification of each isolate, urine	132	1,493	3.26	135	8,877	2.85
83001	Gonadotropin; follicle stimulating hormone (FSH)	133	1,482	3.24	253	4,657	1.50
E0562	Humidifier, heated, used with positive airway pressure device	134	1,480	3.23	230	5,057	1.63
84520	Urea nitrogen; quantitative	135	1,470	3.21	134	8,915	2.87
85018	Blood count; hemoglobin (Hgb)	136	1,467	3.20	139	8,671	2.79
97014	Application of a modality to one or more areas; electrical stimulation (unattended)	137	1,464	3.20	209	5,698	1.83
93018	Cardiovascular stress test using maximal or submaximal treadmill or bicycle exercise, continuous electrocardiographic monitoring, and/or pharmacological stress; interpretation and report only	138	1,448	3.16	121	9,749	3.13
90806	Individual psychotherapy, insight oriented, behavior modifying and/or supportive, in an office or outpatient facility, approximately 45 to 50 minutes face-to-face with the patient	139	1,428	3.12	224	5,289	1.70
99242	Office consultation for a new or established patient, which requires these 3 key components: An expanded problem focused history; An expanded problem focused examination; and Straightforward medical decision making.	140	1,420	3.10	158	7,593	2.44
84132	Potassium; serum	141	1,401	3.06	144	8,447	2.72
97035	Application of a modality to one or more areas; ultrasound, each 15 minutes	142	1,367	2.99	200	5,997	1.93
70450	Computed tomography, head or brain; without contrast material	143	1,362	2.97	80	15,303	4.92
45378	Colonoscopy, flexible, proximal to splenic flexure; diagnostic, with or without collection of specimen(s) by brushing or washing, with or without colon decompression (separate procedure)	144	1,360	2.97	159	7,580	2.44
87186	Susceptibility studies, antimicrobial agent; microdilution or agar dilution (minimum inhibitory concentration (MIC) or breakpoint), each multi-antimicrobial, per plate	145	1,346	2.94	123	9,446	3.04

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		Rank	Count	Percent	Rank	Count	Percent
95904	Nerve conduction, amplitude and latency/velocity study, each nerve; sensory	146	1,336	2.92	208	5,744	1.85
84481	Triiodothyronine T3; free	147	1,333	2.91	237	4,975	1.60
95811	Polysomnography; sleep staging with 4 or more additional parameters of sleep, with initiation of continuous positive airway pressure therapy or bilevel ventilation, attended by a technologist	148	1,321	2.88	266	4,339	1.40
11100	Biopsy of skin, subcutaneous tissue and/or mucous membrane (including simple closure), unless otherwise listed; single lesion	149	1,313	2.87	169	7,174	2.31
J1030	Injection, methylprednisolone acetate, 40 mg	150	1,313	2.87	184	6,528	2.10
A0425	Ground mileage, per statute mile	151	1,311	2.86	69	16,872	5.42
84402	Testosterone; free	152	1,306	2.85	242	4,856	1.56
93016	Cardiovascular stress test using maximal or submaximal treadmill or bicycle exercise, continuous electrocardiographic monitoring, and/or pharmacological stress; physician supervision only, without interpretation and report	153	1,306	2.85	137	8,733	2.81
73560	Radiologic examination, knee; one or two views	154	1,304	2.85	177	6,781	2.18
84480	Triiodothyronine T3; total (TT-3)	155	1,302	2.84	205	5,862	1.88
G0008	Administration of influenza virus vaccine	156	1,265	2.76	148	8,115	2.61
97010	Application of a modality to one or more areas; hot or cold packs Infectious	157	1,245	2.72	221	5,339	1.72
87880	agent detection by immunoassay with direct optical observation; Streptococcus, group A	158	1,240	2.71	178	6,765	2.17
76830	Ultrasound, transvaginal	159	1,236	2.70	203	5,878	1.89
94010	Spirometry, including graphic record, total and timed vital capacity, expiratory flow rate measurement(s), with or without maximal voluntary ventilation	160	1,230	2.69	181	6,719	2.16
43239	Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; with biopsy, single or multiple	161	1,223	2.67	147	8,187	2.63
73562	Radiologic examination, knee; three views	162	1,220	2.66	189	6,391	2.05
96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular	163	1,215	2.65	95	12,865	4.14
A4253	Blood glucose test or reagent strips for home blood glucose monitor, per 50 strips	164	1,209	2.64	119	9,845	3.17
87077	Culture, bacterial; aerobic isolate, additional methods required for definitive identification, each isolate	165	1,202	2.63	155	7,774	2.50

Table 3.2a.The Top 200* Most Frequently Recorded Baseline Procedures Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Optum Research Database 6/1/2005−6/30/2015**

CPT or HCPC Code	Descriptions	Exenatide			OADs		
		Rank	Count	Percent	Rank	Count	Percent
87621	Infectious agent detection by nucleic acid (DNA or RNA); papillomavirus, human, amplified probe technique	166	1,202	2.63	186	6,472	2.08
93545	Injection procedure during cardiac catheterization; for selective coronary angiography (injection of radiopaque material may be by hand)	167	1,188	2.59	151	8,027	2.58
83002	Gonadotropin; luteinizing hormone (LH)	168	1,187	2.59	298	3,697	1.19
72193	Computed tomography, pelvis; with contrast material(s)	169	1,181	2.58	132	9,015	2.90
93556	Imaging supervision, interpretation and report for injection procedure(s) during cardiac catheterization; pulmonary angiography, aortography, and/or selective coronary angiography including venous bypass grafts and arterial conduits (whether native or used in bypass)	170	1,175	2.57	154	7,922	2.55
99231	Subsequent hospital care, per day, for the evaluation and management of a patient, which requires at least 2 of these 3 key components: A problem focused interval history; A problem focused examination; Medical decision making that is straightforward or of low complexity.	171	1,174	2.56	71	16,443	5.29
A9502	Technetium Tc-99m tetrofosmin, diagnostic, per study dose, up to 40 millicuries	172	1,172	2.56	207	5,756	1.85
84484	Troponin, quantitative	173	1,166	2.55	118	9,850	3.17
85651	Sedimentation rate, erythrocyte; non-automated	174	1,156	2.52	183	6,648	2.14
A7039	Filter, nondisposable, used with positive airway pressure device Psychiatric	175	1,143	2.50	263	4,437	1.43
90801	diagnostic interview examination	176	1,142	2.49	218	5,431	1.75
83690	Lipase	177	1,137	2.48	136	8,876	2.85
72148	Magnetic resonance (eg, proton) imaging, spinal canal and contents, lumbar; without contrast material	178	1,133	2.47	187	6,442	2.07
84156	Protein, total, except by refractometry; urine	179	1,132	2.47	199	6,039	1.94
82150	Amylase	180	1,122	2.45	153	7,950	2.56
83525	Insulin; total	181	1,122	2.45	281	3,975	1.28
76705	Ultrasound, abdominal, real time with image documentation; limited (eg, single organ, quadrant, follow-up)	182	1,118	2.44	141	8,556	2.75
74160	Computed tomography, abdomen; with contrast material(s)	183	1,114	2.43	140	8,621	2.77
73620	Radiologic examination, foot; two views	184	1,109	2.42	239	4,945	1.59
J1100	Injection, dexamethasone sodium phosphate, 1 mg	185	1,109	2.42	164	7,400	2.38
93306	Echocardiography, transthoracic, real-time with image documentation (2D), includes M-mode recording, when performed, complete, with spectral Doppler echocardiography, and with color flow Doppler echocardiography	186	1,107	2.42	74	16,183	5.20
99239	Hospital discharge day management; more than 30 minutes	187	1,104	2.41	68	17,156	5.52

Table 3.2a.The Top 200* Most Frequently Recorded Baseline Procedures Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Optum Research Database 6/1/2005−6/30/2015**

CPT or HCPC Code	Descriptions	Exenatide			OADs		
		Rank	Count	Percent	Rank	Count	Percent
88304	Level III - Surgical pathology, gross and microscopic examination Abortion, induced Abscess Aneurysm - arterial/ventricular Anus, tag Appendix, other than incidental Artery, atheromatous plaque Bartholin's gland cyst Bone fragment(s), (truncated)	188	1,097	2.40	162	7,426	2.39
93555	Imaging supervision, interpretation and report for injection procedure(s) during cardiac catheterization; ventricular and/or atrial angiography	189	1,097	2.40	167	7,220	2.32
93543	Injection procedure during cardiac catheterization; for selective left ventricular or left atrial angiography	190	1,095	2.39	168	7,194	2.31
99395	Periodic comprehensive preventive medicine reevaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, established patient; 18-39 years	191	1,093	2.39	215	5,543	1.78
76700	Ultrasound, abdominal, real time with image documentation; complete Left	192	1,082	2.36	146	8,193	2.63
93510	heart catheterization, retrograde, from the brachial artery, axillary artery or femoral artery; percutaneous	193	1,082	2.36	170	7,089	2.28
74150	Computed tomography, abdomen; without contrast material	194	1,079	2.36	180	6,733	2.16
95810	Polysomnography; sleep staging with 4 or more additional parameters of sleep, attended by a technologist	195	1,077	2.35	309	3,627	1.17
83090	Homocysteine	196	1,064	2.32	294	3,745	1.20
77080	Dual-energy x-ray absorptiometry (DXA), bone density study, 1 or more sites; axial skeleton (eg, hips, pelvis, spine)	197	1,062	2.32	198	6,060	1.95
76536	Ultrasound, soft tissues of head and neck (eg, thyroid, parathyroid, parotid), real time with image documentation	198	1,058	2.31	303	3,660	1.18
J0696	Injection, ceftriaxone sodium, per 250 mg	199	1,055	2.30	182	6,705	2.16
99222	Initial hospital care, per day, for the evaluation and management of a patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical decision making of moderate complexity.	200	1,047	2.29	86	14,310	4.60

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.

* Only a proportion of procedures in the top 200 list were retained in the propensity score model via stepwise selection.

** Baseline includes 9-month period prior to drug initiation.

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 3.2b.The Top 200* Most Frequently Recorded Baseline Procedures Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Impact National Benchmark Database 6/1/2005−3/31/2015**

CPT or HCPC Code	Descriptions	Exenatide			OADs		
		Rank	Count	Percent	Rank	Count	Percent
99214	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A detailed history; A detailed examination; Medical decision making of moderate complexity.	1	20,156	82.99	2	104,528	73.29
99213	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: An expanded problem focused history; An expanded problem focused examination; Medical decision making of low complexity.	2	19,586	80.64	1	105,695	74.11
83036	Hemoglobin; glycosylated (A1C)	3	16,748	68.96	3	89,482	62.74
36415	Collection of venous blood by venipuncture	4	15,393	63.38	4	87,837	61.59
80061	Lipid panel; This panel must include the following: Cholesterol, serum, total (82465) Lipoprotein, direct measurement, high density cholesterol (HDL cholesterol) (83718) Triglycerides (84478)	5	14,299	58.88	5	76,108	53.37
80053	Comprehensive metabolic panel; This panel must include the following: Albumin (82040) Bilirubin, total (82247) Calcium, total (82310) Carbon dioxide (bicarbonate) (82374) Chloride (82435) Creatinine (82565) Glucose (82947) Phosphatase, alkaline (84075) Potassium (84132) Protein, total (84155) Sodium (84295) Transferase, alanine amino (ALT) (SGPT) (84460) Transferase, aspartate amino (AST) (SGOT) (84450) Urea nitrogen (BUN) (84520)	6	9,842	40.52	6	53,512	37.52
82043	Albumin; urine, microalbumin, quantitative	7	8,410	34.63	8	41,498	29.10
85025	Blood count; complete (CBC), automated (Hgb, Hct, RBC, WBC and platelet count) and automated differential WBC count	8	7,481	30.80	7	44,275	31.04
84443	Thyroid stimulating hormone (TSH)	9	7,197	29.63	11	30,989	21.73
82570	Creatinine; other source	10	6,847	28.19	10	32,737	22.95
93000	Electrocardiogram, routine ECG with at least 12 leads; with interpretation and report	11	6,802	28.01	9	38,096	26.71
99212	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A problem focused history; A problem focused examination; Straightforward medical decision making.	12	6,130	25.24	13	28,390	19.91
92014	Ophthalmological services: medical examination and evaluation, with initiation or continuation of diagnostic and treatment program; comprehensive, established patient, one or more visits	13	5,843	24.06	16	26,457	18.55

Table 3.2b.The Top 200* Most Frequently Recorded Baseline Procedures Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Impact National Benchmark Database 6/1/2005−3/31/2015**

CPT or HCPC Code	Descriptions	Exenatide			OADs		
		Rank	Count	Percent	Rank	Count	Percent
99244	Office consultation for a new or established patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical decision making of moderate complexity.	14	5,410	22.28	22	20,398	14.30
90658	Influenza virus vaccine, trivalent (IIV3), split virus, 0.5 mL dosage, for intramuscular use	15	5,391	22.20	17	25,051	17.57
80048	Basic metabolic panel (Calcium, total) This panel must include the following: Calcium (82310) Carbon dioxide (82374) Chloride (82435) Creatinine (82565) Glucose (82947) Potassium (84132) Sodium (84295) Urea nitrogen (BUN) (84520)	16	5,231	21.54	12	30,351	21.28
99396	Periodic comprehensive preventive medicine reevaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, established patient; 40-64 years	17	5,113	21.05	14	27,045	18.96
99215	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A comprehensive history; A comprehensive examination; Medical decision making of high complexity.	18	4,982	20.51	19	21,712	15.22
90471	Immunization administration (includes percutaneous, intradermal, subcutaneous, or intramuscular injections); one vaccine (single or combination vaccine/toxoid)	19	4,925	20.28	18	24,777	17.37
71020	Radiologic examination, chest, two views, frontal and lateral	20	4,086	16.82	15	26,927	18.88
82947	Glucose; quantitative, blood (except reagent strip)	21	3,873	15.95	21	21,059	14.77
82962	Glucose, blood by glucose monitoring device(s) cleared by the FDA specifically for home use	22	3,701	15.24	25	18,171	12.74
99203	Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: A detailed history; A detailed examination; Medical decision making of low complexity.	23	3,647	15.02	24	19,957	13.99
84460	Transferase; alanine amino (ALT) (SGPT)	24	3,616	14.89	29	16,838	11.81
99243	Office consultation for a new or established patient, which requires these 3 key components: A detailed history; A detailed examination; and Medical decision making of low complexity.	25	3,560	14.66	31	15,331	10.75
88305	Level IV - Surgical pathology, gross and microscopic examination Abortion - spontaneous/missed Artery, biopsy Bone marrow, biopsy Bone exostosis Brain/meninges, other than for tumor resection Breast, biopsy, not requiring microscopic evaluation (truncated)	26	3,229	13.30	28	17,209	12.07

Table 3.2b.The Top 200* Most Frequently Recorded Baseline Procedures Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Impact National Benchmark Database 6/1/2005−3/31/2015**

CPT or HCPC Code	Descriptions	Exenatide			OADs		
		Rank	Count	Percent	Rank	Count	Percent
80050	General health panel This panel must include the following: Comprehensive metabolic panel (80053) Blood count, complete (CBC), automated and automated differential WBC count (85025 or 85027 and 85004) OR Blood count, complete (CBC), automated (85027) and appropriate manual differential WBC count (85007 or 85009) Thyroid stimulating hormone (TSH) (84443)	27	3,154	12.99	26	17,948	12.58
84439	Thyroxine; free	28	3,006	12.38	47	10,427	7.31
99204	Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; Medical decision making of moderate complexity.	29	2,998	12.34	30	16,572	11.62
99245	Office consultation for a new or established patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical decision making of high complexity.	30	2,931	12.07	53	9,200	6.45
81002	Urinalysis, by dip stick or tablet reagent for bilirubin, glucose, hemoglobin, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen, any number of these constituents; non-automated, without microscopy	31	2,922	12.03	33	14,028	9.84
84450	Transferase; aspartate amino (AST) (SGOT)	32	2,859	11.77	38	13,161	9.23
81001	Urinalysis, by dip stick or tablet reagent for bilirubin, glucose, hemoglobin, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen, any number of these constituents; automated, with microscopy	33	2,761	11.37	27	17,825	12.50
G0108	Diabetes outpatient self-management training services, individual, per 30 minutes	34	2,725	11.22	91	5,873	4.12
84153	Prostate specific antigen (PSA); total	35	2,724	11.22	23	20,292	14.23
82565	Creatinine; blood	36	2,676	11.02	35	13,677	9.59
93010	Electrocardiogram, routine ECG with at least 12 leads; interpretation and report only	37	2,568	10.57	20	21,126	14.81
80076	Hepatic function panel This panel must include the following: Albumin (82040) Bilirubin, total (82247) Bilirubin, direct (82248) Phosphatase, alkaline (84075) Protein, total (84155) Transferase, alanine amino (ALT) (SGPT) (84460) Transferase, aspartate amino (AST) (SGOT) (84450)	38	2,500	10.29	36	13,476	9.45
93325	Doppler echocardiography color flow velocity mapping (List separately in addition to codes for echocardiography)	39	2,366	9.74	40	11,668	8.18

Table 3.2b.The Top 200* Most Frequently Recorded Baseline Procedures Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Impact National Benchmark Database 6/1/2005−3/31/2015**

CPT or HCPC Code	Descriptions	Exenatide			OADs		
		Rank	Count	Percent	Rank	Count	Percent
99211	Office or other outpatient visit for the evaluation and management of an established patient, that may not require the presence of a physician. Usually, the presenting problem(s) are minimal. Typically, 5 minutes are spent performing or supervising these services.	40	2,358	9.71	49	9,987	7.00
93320	Doppler echocardiography, pulsed wave and/or continuous wave with spectral display (List separately in addition to codes for echocardiographic imaging); complete	41	2,343	9.65	41	11,392	7.99
82550	Creatine kinase (CK), (CPK); total	42	2,304	9.49	42	11,387	7.98
99000	Handling and/or conveyance of specimen for transfer from the physician's office to a laboratory	43	2,282	9.40	48	10,043	7.04
93307	Echocardiography, transthoracic, real-time with image documentation (2D), includes M-mode recording, when performed, complete, without spectral or color Doppler echocardiography	44	2,212	9.11	45	10,577	7.42
81000	Urinalysis, by dip stick or tablet reagent for bilirubin, glucose, hemoglobin, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen, any number of these constituents; non-automated, with microscopy	45	2,132	8.78	46	10,497	7.36
97110	Therapeutic procedure, one or more areas, each 15 minutes; therapeutic exercises to develop strength and endurance, range of motion and flexibility	46	2,096	8.63	63	8,432	5.91
82948	Glucose; blood, reagent strip	47	2,056	8.47	54	9,141	6.41
81003	Urinalysis, by dip stick or tablet reagent for bilirubin, glucose, hemoglobin, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen, any number of these constituents; automated, without microscopy	48	2,030	8.36	39	12,574	8.82
93015	Cardiovascular stress test using maximal or submaximal treadmill or bicycle exercise, continuous electrocardiographic monitoring, and/or pharmacological stress; with physician supervision, with interpretation and report	49	1,978	8.14	68	7,878	5.52
78478	Myocardial perfusion study with wall motion, qualitative or quantitative study (List separately in addition to code for primary procedure)	50	1,930	7.95	70	7,782	5.46
78465	Myocardial perfusion imaging; tomographic (SPECT), multiple studies (including attenuation correction when performed), at rest and/or stress (exercise and/or pharmacologic) and redistribution and/or rest injection, with or without quantification	51	1,921	7.91	69	7,830	5.49

Table 3.2b.The Top 200* Most Frequently Recorded Baseline Procedures Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Impact National Benchmark Database 6/1/2005−3/31/2015**

CPT or HCPC Code	Descriptions	Exenatide			OADs		
		Rank	Count	Percent	Rank	Count	Percent
85027	Blood count; complete (CBC), automated (Hgb, Hct, RBC, WBC and platelet count)	52	1,921	7.91	34	13,857	9.72
92015	Determination of refractive state	53	1,887	7.77	56	8,821	6.19
83721	Lipoprotein, direct measurement; LDL cholesterol	54	1,832	7.54	59	8,625	6.05
92012	Ophthalmological services: medical examination and evaluation, with initiation or continuation of diagnostic and treatment program; intermediate, established patient	55	1,831	7.54	62	8,579	6.02
84520	Urea nitrogen; quantitative	56	1,802	7.42	52	9,219	6.46
82270	Blood, occult, by peroxidase activity (eg, guaiac), qualitative; feces, consecutive collected specimens with single determination, for colorectal neoplasm screening (ie, patient was provided 3 cards or single triple card for consecutive collection)	57	1,785	7.35	51	9,231	6.47
78480	Myocardial perfusion study with ejection fraction (List separately in addition to code for primary procedure)	58	1,757	7.23	77	7,293	5.11
76092	Screening mammography, bilateral (two view film study of each breast)	59	1,733	7.14	93	5,812	4.08
92250	Fundus photography with interpretation and report	60	1,700	7.00	73	7,643	5.36
97001	Physical therapy evaluation	61	1,687	6.95	81	6,777	4.75
85610	Prothrombin time	62	1,622	6.68	44	10,659	7.47
77052	Computer-aided detection (computer algorithm analysis of digital image data for lesion detection) with further review for interpretation, with or without digitization of film radiographic images; screening mammography (List separately in addition to code for primary procedure)	63	1,621	6.67	57	8,792	6.16
G0202	Screening mammography, bilateral (2-view study of each breast), including computer-aided detection (CAD) when performed	64	1,597	6.58	64	8,406	5.89
A7035	Headgear used with positive airway pressure device	65	1,527	6.29	110	4,886	3.43
88142	Cytopathology, cervical or vaginal (any reporting system), collected in preservative fluid, automated thin layer preparation; manual screening under physician supervision	66	1,521	6.26	92	5,870	4.12
84550	Uric acid; blood	67	1,518	6.25	60	8,610	6.04
99202	Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: An expanded problem focused history; An expanded problem focused examination; Straightforward medical decision making.	68	1,511	6.22	76	7,377	5.17

Table 3.2b.The Top 200* Most Frequently Recorded Baseline Procedures Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Impact National Benchmark Database 6/1/2005−3/31/2015**

CPT or HCPC Code	Descriptions	Exenatide			OADs		
		Rank	Count	Percent	Rank	Count	Percent
97140	Manual therapy techniques (eg, mobilization/ manipulation, manual lymphatic drainage, manual traction), one or more regions, each 15 minutes	69	1,508	6.21	90	5,883	4.13
87086	Culture, bacterial; quantitative colony count, urine	70	1,475	6.07	67	7,983	5.60
82248	Bilirubin; direct	71	1,473	6.07	75	7,418	5.20
92004	Ophthalmological services: medical examination and evaluation with initiation of diagnostic and treatment program; comprehensive, new patient, one or more visits	72	1,428	5.88	58	8,707	6.11
99205	Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; Medical decision making of high complexity.	73	1,410	5.81	84	6,322	4.43
83540	Iron	74	1,402	5.77	74	7,432	5.21
82306	Calcifediol (25-OH Vitamin D-3)	75	1,396	5.75	72	7,774	5.45
71010	Radiologic examination, chest; single view, frontal	76	1,359	5.60	37	13,164	9.23
20610	Arthrocentesis, aspiration and/or injection; major joint or bursa (eg, shoulder, hip, knee joint, subacromial bursa)	77	1,344	5.53	96	5,675	3.98
A7034	Nasal interface (mask or cannula type) used with positive airway pressure device, with or without head strap	78	1,319	5.43	134	3,925	2.75
99232	Subsequent hospital care, per day, for the evaluation and management of a patient, which requires at least 2 of these 3 key components: An expanded problem focused interval history; An expanded problem focused examination; Medical decision making of moderate complexity.	79	1,316	5.42	32	14,669	10.29
84436	Thyroxine; total	80	1,285	5.29	88	5,894	4.13
93005	Electrocardiogram, routine ECG with at least 12 leads; tracing only, without interpretation and report	81	1,272	5.24	65	8,122	5.70
76083	Computer aided detection (computer algorithm analysis of digital image data for lesion detection) with further physician review for interpretation, with or without digitization of film radiographic images; screening mammography (List separately in addition to code for primary procedure)	82	1,254	5.16	143	3,787	2.66
A7037	Tubing used with positive airway pressure device	83	1,253	5.16	133	3,930	2.76
80051	Electrolyte panel This panel must include the following: Carbon dioxide (82374) Chloride (82435) Potassium (84132) Sodium (84295)	84	1,248	5.14	89	5,888	4.13
82607	Cyanocobalamin (Vitamin B-12)	85	1,218	5.02	82	6,447	4.52
92083	Visual field examination, unilateral or bilateral, with interpretation and report; extended examination (eg, Goldmann visual fields with at least 3 isopters plotted and static determination within the central 30 degrees or quantitative, automated threshold perimetry, Octopus program G-1, 32 or 42, Humphrey visual field analyzer full threshold programs 30-2, 24-2, or 30/60-2)	86	1,163	4.79	99	5,521	3.87

Table 3.2b.The Top 200* Most Frequently Recorded Baseline Procedures Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Impact National Benchmark Database 6/1/2005−3/31/2015**

CPT or HCPC Code	Descriptions	Exenatide			OADs		
		Rank	Count	Percent	Rank	Count	Percent
92135	Scanning computerized ophthalmic diagnostic imaging, posterior segment, (eg, scanning laser) with interpretation and report, unilateral	87	1,159	4.77	111	4,740	3.32
73630	Radiologic examination, foot; complete, minimum of three views Individual	88	1,126	4.64	107	5,075	3.56
90806	psychotherapy, insight oriented, behavior modifying and/or supportive, in an office or outpatient facility, approximately 45 to 50 minutes face-to-face with the patient	89	1,108	4.56	130	4,036	2.83
90732	Pneumococcal polysaccharide vaccine, 23-valent, adult or immunosuppressed patient dosage, when administered to individuals 2 years or older, for subcutaneous or intramuscular use	90	1,085	4.47	86	6,019	4.22
84403	Testosterone; total	91	1,051	4.33	138	3,852	2.70
82728	Ferritin	92	1,030	4.24	100	5,411	3.79
A9500	Technetium Tc-99m sestamibi, diagnostic, per study dose, up to 40 millicuries	93	1,007	4.15	132	3,942	2.76
82465	Cholesterol, serum or whole blood, total	94	1,001	4.12	102	5,176	3.63
93880	Duplex scan of extracranial arteries; complete bilateral study	95	997	4.11	95	5,719	4.01
84681	C-peptide	96	980	4.04	245	2,191	1.54
E0601	Continuous airway pressure (CPAP) device	97	980	4.04	183	3,053	2.14
85730	Thromboplastin time, partial (PTT); plasma or whole blood	98	977	4.02	79	7,103	4.98
84100	Phosphorus inorganic (phosphate)	99	975	4.01	87	5,952	4.17
99223	Initial hospital care, per day, for the evaluation and management of a patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical decision making of high complexity.	100	972	4.00	43	10,792	7.57
99242	Office consultation for a new or established patient, which requires these 3 key components: An expanded problem focused history; An expanded problem focused examination; and Straightforward medical decision making.	101	957	3.94	125	4,212	2.95
92226	Ophthalmoscopy, extended, with retinal drawing (eg, for retinal detachment, melanoma), with interpretation and report; subsequent	102	954	3.93	139	3,850	2.70
82044	Albumin; urine, microalbumin, semiquantitative (eg, reagent strip assay)	103	944	3.89	113	4,607	3.23

Table 3.2b.The Top 200* Most Frequently Recorded Baseline Procedures Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Impact National Benchmark Database 6/1/2005−3/31/2015**

CPT or HCPC Code	Descriptions	Exenatide			OADs		
		Rank	Count	Percent	Rank	Count	Percent
93018	Cardiovascular stress test using maximal or submaximal treadmill or bicycle exercise, continuous electrocardiographic monitoring, and/or pharmacological stress; interpretation and report only	104	941	3.87	101	5,268	3.69
99238	Hospital discharge day management; 30 minutes or less	105	933	3.84	55	8,969	6.29
A7038	Filter, disposable, used with positive airway pressure device	106	930	3.83	184	3,020	2.12
98940	Chiropractic manipulative treatment (CMT); spinal, one to two regions	107	922	3.80	136	3,913	2.74
83735	Magnesium	108	920	3.79	85	6,149	4.31
84478	Triglycerides	109	911	3.75	120	4,301	3.02
94010	Spirometry, including graphic record, total and timed vital capacity, expiratory flow rate measurement(s), with or without maximal voluntary ventilation	110	900	3.71	116	4,455	3.12
88175	Cytopathology, cervical or vaginal (any reporting system), collected in preservative fluid, automated thin layer preparation; with screening by automated system and manual rescreening or review, under physician supervision	111	881	3.63	126	4,193	2.94
97035	Application of a modality to one or more areas; ultrasound, each 15 minutes	112	879	3.62	186	3,002	2.11
77057	Screening mammography, bilateral (2-view film study of each breast)	113	876	3.61	154	3,586	2.51
83550	Iron binding capacity	114	863	3.55	112	4,627	3.24
98941	Chiropractic manipulative treatment (CMT); spinal, three to four regions	115	862	3.55	146	3,690	2.59
11721	Debridement of nail(s) by any method(s); six or more	116	850	3.50	171	3,188	2.24
73030	Radiologic examination, shoulder; complete, minimum of two views	117	845	3.48	122	4,290	3.01
85652	Sedimentation rate, erythrocyte; automated	118	844	3.48	115	4,484	3.14
G0008	Administration of influenza virus vaccine	119	844	3.48	127	4,124	2.89
85651	Sedimentation rate, erythrocyte; non-automated	120	836	3.44	121	4,295	3.01
76830	Ultrasound, transvaginal	121	831	3.42	177	3,136	2.20
84132	Potassium; serum	122	828	3.41	103	5,158	3.62
17000	Destruction (eg, laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), premalignant lesions (eg, actinic keratoses); first lesion	123	816	3.36	140	3,842	2.69
J3301	Injection, triamcinolone acetonide, not otherwise specified, 10 mg	124	812	3.34	151	3,635	2.55
36416	Collection of capillary blood specimen (eg, finger, heel, ear stick)	125	811	3.34	157	3,502	2.46
45378	Colonoscopy, flexible, proximal to splenic flexure; diagnostic, with or without collection of specimen(s) by brushing or washing, with or without colon decompression (separate procedure)	126	805	3.31	131	4,021	2.82
83615	Lactate dehydrogenase (LD), (LDH)	127	803	3.31	105	5,140	3.60

Table 3.2b.The Top 200* Most Frequently Recorded Baseline Procedures Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Impact National Benchmark Database 6/1/2005−3/31/2015**

CPT or HCPC Code	Descriptions	Exenatide			OADs		
		Rank	Count	Percent	Rank	Count	Percent
A0425	Ground mileage, per statute mile	128	803	3.31	61	8,591	6.02
97802	Medical nutrition therapy; initial assessment and intervention, individual, face-to-face with the patient, each 15 minutes	129	797	3.28	200	2,763	1.94
97014	Application of a modality to one or more areas; electrical stimulation (unattended)	130	793	3.27	196	2,857	2.00
86141	C-reactive protein; high sensitivity (hsCRP)	131	787	3.24	197	2,813	1.97
83718	Lipoprotein, direct measurement; high density cholesterol (HDL cholesterol)	132	785	3.23	128	4,041	2.83
93016	Cardiovascular stress test using maximal or submaximal treadmill or bicycle exercise, continuous electrocardiographic monitoring, and/or pharmacological stress; physician supervision only, without interpretation and report	133	768	3.16	118	4,325	3.03
99254	Inpatient consultation for a new or established patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical decision making of moderate complexity.	134	760	3.13	66	8,091	5.67
76700	Ultrasound, abdominal, real time with image documentation; complete	135	751	3.09	108	4,940	3.46
90772	Therapeutic, prophylactic or diagnostic injection (specify substance or drug); subcutaneous or intramuscular	136	742	3.06	191	2,945	2.07
95904	Nerve conduction, amplitude and latency/velocity study, each nerve; sensory	137	742	3.06	193	2,919	2.05
90801	Psychiatric diagnostic interview examination	138	738	3.04	167	3,212	2.25
84480	Triiodothyronine T3; total (TT-3)	139	733	3.02	219	2,461	1.73
87070	Culture, bacterial; any other source except urine, blood or stool, aerobic, with isolation and presumptive identification of isolates	140	728	3.00	117	4,342	3.04
43239	Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; with biopsy, single or multiple	141	726	2.99	137	3,864	2.71
94060	Bronchodilation responsiveness, spirometry as in 94010, pre- and post-bronchodilator administration	142	719	2.96	153	3,594	2.52
11100	Biopsy of skin, subcutaneous tissue and/or mucous membrane (including simple closure), unless otherwise listed; single lesion	143	714	2.94	168	3,202	2.25
72100	Radiologic examination, spine, lumbosacral; two or three views	144	707	2.91	149	3,648	2.56
95811	Polysomnography; sleep staging with 4 or more additional parameters of sleep, with initiation of continuous positive airway pressure therapy or bilevel ventilation, attended by a technologist	145	707	2.91	275	1,924	1.35
82977	Glutamyltransferase, gamma (GGT)	146	699	2.88	147	3,676	2.58

Table 3.2b.The Top 200* Most Frequently Recorded Baseline Procedures Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Impact National Benchmark Database 6/1/2005−3/31/2015**

CPT or HCPC Code	Descriptions	Exenatide			OADs		
		Rank	Count	Percent	Rank	Count	Percent
99233	Subsequent hospital care, per day, for the evaluation and management of a patient, which requires at least 2 of these 3 key components: A detailed interval history; A detailed examination; Medical decision making of high complexity.	147	699	2.88	50	9,449	6.63
73560	Radiologic examination, knee; one or two views	148	692	2.85	190	2,954	2.07
73562	Radiologic examination, knee; three views	149	692	2.85	176	3,142	2.20
88304	Level III - Surgical pathology, gross and microscopic examination Abortion, induced Abscess Aneurysm - arterial/ventricular Anus, tag Appendix, other than incidental Artery, atheromatous plaque Bartholin's gland cyst Bone fragment(s), (truncated)	150	692	2.85	144	3,787	2.66
E0562	Humidifier, heated, used with positive airway pressure device	151	683	2.81	257	2,100	1.47
82746	Folic acid; serum	152	678	2.79	135	3,924	2.75
86038	Antinuclear antibodies (ANA)	153	669	2.75	163	3,290	2.31
86140	C-reactive protein	154	669	2.75	160	3,341	2.34
73620	Radiologic examination, foot; two views	155	667	2.75	237	2,253	1.58
76856	Ultrasound, pelvic (nonobstetric), real time with image documentation; complete	156	665	2.74	198	2,789	1.96
84479	Thyroid hormone (T3 or T4) uptake or thyroid hormone binding ratio (THBR)	157	661	2.72	170	3,190	2.24
A4253	Blood glucose test or reagent strips for home blood glucose monitor, per 50 strips	158	658	2.71	156	3,526	2.47
97010	Application of a modality to one or more areas; hot or cold packs Magnetic	159	645	2.66	220	2,424	1.70
72148	resonance (eg, proton) imaging, spinal canal and contents, lumbar; without contrast material	160	644	2.65	180	3,103	2.18
87088	Culture, bacterial; with isolation and presumptive identification of each isolate, urine	161	642	2.64	164	3,290	2.31
00810	Anesthesia for lower intestinal endoscopic procedures, endoscope introduced distal to duodenum	162	636	2.62	166	3,218	2.26
99231	Subsequent hospital care, per day, for the evaluation and management of a patient, which requires at least 2 of these 3 key components: A problem focused interval history; A problem focused examination; Medical decision making that is straightforward or of low complexity.	163	633	2.61	71	7,776	5.45
87186	Susceptibility studies, antimicrobial agent; microdilution or agar dilution (minimum inhibitory concentration (MIC) or breakpoint), each multi-antimicrobial, per plate	164	632	2.60	148	3,656	2.56
72193	Computed tomography, pelvis; with contrast material(s)	165	628	2.59	114	4,496	3.15

Table 3.2b.The Top 200* Most Frequently Recorded Baseline Procedures Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Impact National Benchmark Database 6/1/2005−3/31/2015**

CPT or HCPC Code	Descriptions	Exenatide			OADs		
		Rank	Count	Percent	Rank	Count	Percent
93545	Injection procedure during cardiac catheterization; for selective coronary angiography (injection of radiopaque material may be by hand)	166	625	2.57	142	3,801	2.67
99222	Initial hospital care, per day, for the evaluation and management of a patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical decision making of moderate complexity.	167	625	2.57	80	6,854	4.81
73721	Magnetic resonance (eg, proton) imaging, any joint of lower extremity; without contrast material	168	619	2.55	224	2,378	1.67
90862	Pharmacologic management, including prescription, use, and review of medication with no more than minimal medical psychotherapy	169	617	2.54	210	2,640	1.85
93556	Imaging supervision, interpretation and report for injection procedure(s) during cardiac catheterization; pulmonary angiography, aortography, and/or selective coronary angiography including venous bypass grafts and arterial conduits (whether native or used in bypass)	170	613	2.52	145	3,729	2.61
J1030	Injection, methylprednisolone acetate, 40 mg	171	608	2.50	202	2,714	1.90
76075	Dual energy X-ray absorptiometry (DXA), bone density study, one or more sites; axial skeleton (eg, hips, pelvis, spine)	172	607	2.50	262	2,065	1.45
76536	Ultrasound, soft tissues of head and neck (eg, thyroid, parathyroid, parotid), real time with image documentation	173	602	2.48	295	1,729	1.21
84484	Troponin, quantitative	174	600	2.47	119	4,313	3.02
94760	Noninvasive ear or pulse oximetry for oxygen saturation; single determination	175	594	2.45	152	3,601	2.53
	Computed tomography, abdomen; with contrast material(s)						
74160	Phosphatase, alkaline	176	589	2.43	124	4,239	2.97
84075	Infectious agent detection by immunoassay with direct optical observation;	177	589	2.43	161	3,329	2.33
87880	Streptococcus, group A	178	580	2.39	189	2,956	2.07
	Gonadotropin; follicle stimulating hormone (FSH)						
83001	Computed tomography, abdomen; without contrast material	179	576	2.37	301	1,679	1.18
74150	Periodic comprehensive preventive medicine reevaluation and management	180	575	2.37	162	3,322	2.33
99395	of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, established patient; 18-39 years	181	572	2.36	205	2,690	1.89
45380	Colonoscopy, flexible, proximal to splenic flexure; with biopsy, single or multiple	182	568	2.34	185	3,005	2.11

Table 3.2b.The Top 200* Most Frequently Recorded Baseline Procedures Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Impact National Benchmark Database 6/1/2005−3/31/2015**

CPT or HCPC Code	Descriptions	Exenatide			OADs		
		Rank	Count	Percent	Rank	Count	Percent
76645	Ultrasound, breast(s) (unilateral or bilateral), real time with image documentation	183	564	2.32	231	2,315	1.62
92225	Ophthalmoscopy, extended, with retinal drawing (eg, for retinal detachment, melanoma), with interpretation and report; initial	184	561	2.31	195	2,897	2.03
82040	Albumin; serum	185	558	2.30	214	2,552	1.79
93971	Duplex scan of extremity veins including responses to compression and other maneuvers; unilateral or limited study	186	555	2.29	182	3,076	2.16
A9502	Technetium Tc-99m tetrofosmin, diagnostic, per study dose, up to 40 millicuries	187	554	2.28	221	2,411	1.69
95903	Nerve conduction, amplitude and latency/velocity study, each nerve; motor, with F-wave study	188	550	2.26	260	2,067	1.45
20550	Injection(s); single tendon sheath, or ligament, aponeurosis (eg, plantar "fascia")	189	547	2.25	274	1,928	1.35
J2250	Injection, midazolam HCl, per 1 mg	190	543	2.24	158	3,470	2.43
84155	Protein, total, except by refractometry; serum	191	534	2.20	192	2,940	2.06
93510	Left heart catheterization, retrograde, from the brachial artery, axillary artery or femoral artery; percutaneous	192	533	2.19	181	3,098	2.17
G0109	Diabetes outpatient self-management training services, group session (2 or more), per 30 minutes	193	529	2.18	327	1,442	1.01
72192	Computed tomography, pelvis; without contrast material	194	528	2.17	175	3,143	2.20
97112	Therapeutic procedure, one or more areas, each 15 minutes; neuromuscular reeducation of movement, balance, coordination, kinesthetic sense, posture, and/or proprioception for sitting and/or standing activities	195	528	2.17	242	2,210	1.55
95810	Polysomnography; sleep staging with 4 or more additional parameters of sleep, attended by a technologist	196	524	2.16	318	1,516	1.06
93543	Injection procedure during cardiac catheterization; for selective left ventricular or left atrial angiography	197	520	2.14	172	3,178	2.23
93555	Imaging supervision, interpretation and report for injection procedure(s) during cardiac catheterization; ventricular and/or atrial angiography	198	519	2.14	169	3,198	2.24
70450	Computed tomography, head or brain; without contrast material	199	512	2.11	98	5,541	3.89
84481	Triiodothyronine T3; free	200	512	2.11	322	1,478	1.04

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.
* Only a proportion of diagnoses in the top 200 list were retained in the propensity score model via stepwise selection.
** Baseline includes 9-month period prior to drug initiation.
Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 3.3a.The Top 200* Most Frequently Recorded Baseline Drug Dispensings Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Optum Research Database 6/1/2005−6/30/2015**

Therapeutic Drug Class Description	Exenatide			OADs		
	Rank	Count	Percent	Rank	Count	Percent
HYPOGLYCEMICS, BIGUANIDE TYPE (NON-SULFONYLUREAS)	1	30,846	67.36	1	151,929	48.84
NEEDLES/NEEDLELESS DEVICES	2	30,155	65.85	19	35,231	11.33
BLOOD SUGAR DIAGNOSTICS	3	26,076	56.95	2	136,428	43.86
HYPOGLYCEMICS, INSULIN-RELEASE STIMULANT TYPE	4	22,293	48.68	5	98,730	31.74
LIPOTROPICS	5	21,876	47.77	6	94,068	30.24
HYPOTENSIVES, ACE INHIBITORS	6	18,900	41.27	3	123,203	39.61
HYPOGLYCEMICS, INSULIN-RESPONSE ENHANCER (N-S)	7	18,506	40.41	11	55,075	17.71
ANALGESICS,NARCOTICS	8	14,575	31.83	7	91,601	29.45
INSULINS	9	13,012	28.42	17	45,559	14.65
ANTI-HYPERLIPIDEMIC - HMG COA REDUCTASE INHIBITORS	10	11,872	25.93	4	105,381	33.88
HYPOTENSIVES, ANGIOTENSIN RECEPTOR ANTAGONIST	11	10,874	23.75	16	45,582	14.65
DURABLE MEDICAL EQUIPMENT, MISCELLANEOUS (GROUP 1)	12	9,982	21.80	8	63,094	20.28
NSAIDS, CYCLOOXYGENASE INHIBITOR - TYPE	13	9,870	21.55	10	57,558	18.50
BETA-ADRENERGIC BLOCKING AGENTS	14	9,301	20.31	9	62,857	20.21
PENICILLINS	15	8,613	18.81	12	52,125	16.76
MACROLIDES	16	8,326	18.18	15	45,623	14.67
SEROTONIN SPECIFIC REUPTAKE INHIBITOR (SSRIS)	17	8,118	17.73	18	39,050	12.55
QUINOLONES	18	8,030	17.54	14	46,025	14.80
CALCIUM CHANNEL BLOCKING AGENTS THYROID	19	7,026	15.34	13	49,741	15.99
HORMONES	20	6,415	14.01	24	29,365	9.44
SYRINGES AND ACCESSORIES	21	6,005	13.11	21	32,550	10.46
LOOP DIURETICS	22	5,737	12.53	25	28,187	9.06
GASTRIC ACID SECRETION REDUCERS	23	5,689	12.42	33	21,184	6.81
ANTICONVULSANTS	24	5,507	12.03	23	30,974	9.96
THIAZIDE AND RELATED DIURETICS	25	5,288	11.55	22	31,292	10.06
GLUCOCORTICOIDS	26	5,114	11.17	20	34,384	11.05
SKELETAL MUSCLE RELAXANTS	27	4,826	10.54	26	27,505	8.84

Table 3.3a.The Top 200* Most Frequently Recorded Baseline Drug Dispensings Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Optum Research Database 6/1/2005−6/30/2015**

Therapeutic Drug Class Description	Exenatide			OADs		
	Rank	Count	Percent	Rank	Count	Percent
ANTI-ANXIETY DRUGS	28	4,720	10.31	27	27,404	8.81
NASAL ANTI-INFLAMMATORY STEROIDS	29	4,507	9.84	31	22,298	7.17
BETA-ADRENERGIC AGENTS	30	4,442	9.70	30	24,450	7.86
ANTIFUNGAL AGENTS	31	3,869	8.45	34	21,050	6.77
CEPHALOSPORINS - 1ST GENERATION	32	3,754	8.20	32	21,938	7.05
SEDATIVE-HYPNOTICS, NON-BARBITURATE	33	3,748	8.19	39	18,891	6.07
TOPICAL ANTI-INFLAMMATORY STEROIDAL	34	3,603	7.87	36	20,278	6.52
ANTIHISTAMINES - 2ND GENERATION	35	3,513	7.67	49	12,157	3.91
SEROTONIN-NOREPINEPHRINE REUPTAKE-INHIB (SNRIS)	36	3,444	7.52	48	12,575	4.04
POTASSIUM REPLACEMENT	37	3,434	7.50	37	19,589	6.30
TOPICAL ANTIFUNGALS	38	3,244	7.08	40	18,563	5.97
PLATELET AGGREGATION INHIBITORS	39	2,867	6.26	35	20,323	6.53
ABSORBABLE SULFONAMIDES	40	2,764	6.04	38	19,236	6.18
PROTON-PUMP INHIBITORS	41	2,744	5.99	28	26,327	8.46
DIABETIC SUPPLIES	42	2,648	5.78	29	25,464	8.19
DRUGS TO TREAT IMPOTENCY	43	2,629	5.74	42	17,199	5.53
ANGIOTENSIN RECEPTOR ANTAGONIST/THIAZIDE AND RELATED COMBINATION	44	2,500	5.46	43	16,121	5.18
ALPHA/BETA-ADRENERGIC BLOCKING AGENTS	45	2,335	5.10	44	15,477	4.98
ANTIHISTAMINES - 1ST GENERATION	46	2,270	4.96	46	13,548	4.36
NOREPINEPHRINE AND DOPAMINE REUPTAKE INHIB (NDRIS)	47	2,261	4.94	66	8,254	2.65
LAXATIVES AND CATHARTICS	48	2,201	4.81	47	13,327	4.28
TETRACYCLINES	49	2,088	4.56	45	13,583	4.37
HYPOGLY, INSULIN-REL STIM. & BIGUANIDE (N-S) COMBINATION	50	2,087	4.56	73	6,922	2.23
ACE INHIBITOR/THIAZIDE & THIAZIDE-LIKE	51	2,066	4.51	41	17,377	5.59
ESTROGENIC AGENTS	52	1,973	4.31	72	7,175	2.31
POTASSIUM SPARING DIURETICS IN COMBINATION	53	1,958	4.28	52	10,153	3.26
LEUKOTRIENE RECEPTOR ANTAGONISTS	54	1,929	4.21	68	7,915	2.54
VASODILATORS, CORONARY	55	1,796	3.92	50	12,092	3.89
BETA-ADRENERGICS AND GLUCOCORTICOIDS COMBINATION	56	1,794	3.92	58	9,238	2.97

Table 3.3a.The Top 200* Most Frequently Recorded Baseline Drug Dispensings Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Optum Research Database 6/1/2005−6/30/2015**

Therapeutic Drug Class Description	Exenatide			OADs		
	Rank	Count	Percent	Rank	Count	Percent
ANTIVIRALS, GENERAL	57	1,759	3.84	53	10,108	3.25
NARCOTIC ANTITUSSIVE-EXPECTORANT COMBINATION	58	1,755	3.83	57	9,246	2.97
TRICYCLIC ANTIDEPRESSANTS & RELATED NON-SELECTIVE REUPTAKE INHIBITORS	59	1,655	3.61	62	8,873	2.85
NARCOTIC ANTITUSSIVE-1ST GENERATION ANTIHISTAMINE	60	1,649	3.60	63	8,609	2.77
ACE INHIBITOR/CALCIUM CHANNEL BLOCKER COMBINATION	61	1,627	3.55	64	8,594	2.76
VITAMIN D PREPARATIONS	62	1,521	3.32	60	9,156	2.94
LINCOSAMIDES	63	1,511	3.30	56	9,368	3.01
OPHTHALMIC ANTIBIOTICS	64	1,508	3.29	59	9,204	2.96
ANTITUSSIVES, NON-NARCOTIC	65	1,470	3.21	65	8,550	2.75
PURINE INHIBITORS	66	1,460	3.19	61	9,010	2.90
TOPICAL ANTIBIOTICS	67	1,331	2.91	71	7,415	2.38
ORAL ANTICOAGULANTS, COUMARIN TYPE	68	1,305	2.85	51	10,167	3.27
POTASSIUM SPARING DIURETICS	69	1,301	2.84	75	6,317	2.03
ANTI-HYPERLIPIDEMIC - HMG COA REDUCTASE INHIBITORS & CHOLESTEROL ABSORPTION INHIBITOR	70	1,216	2.66	74	6,701	2.15
ANTIEMETIC/ANTIVERTIGO AGENTS	71	1,199	2.62	55	9,438	3.03
MIOTICS/OTHER INTRAOCULAR PRESSURE REDUCERS	72	1,183	2.58	69	7,828	2.52
HYPOTENSIVES, SYMPATHOLYTIC	73	1,138	2.49	67	7953	2.56
BENIGN PROSTATIC HYPERTROPHY/ MICTURITION AGENTS	74	1,127	2.46	54	9,695	3.12
CONTRACEPTIVES, ORAL	75	1,111	2.43	87	4,170	1.34
ANDROGENIC AGENTS	76	1,085	2.37	86	4,547	1.46
HYPOGLY, INSUL-RESP. ENHANCER & BIGUANIDE COMBINATION	77	1,071	2.34	108	2,635	0.85
ANAEROBIC ANTIPROTOZOAL-ANTIBACTERIAL AGENTS	78	1,036	2.26	70	7,429	2.39
SEROTONIN-2 ANTAGONIST/REUPTAKE INHIBITORS (SARIS)	79	1,021	2.23	76	5,914	1.90

Table 3.3a.The Top 200* Most Frequently Recorded Baseline Drug Dispensings Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Optum Research Database 6/1/2005−6/30/2015**

Therapeutic Drug Class Description	Exenatide			OADs		
	Rank	Count	Percent	Rank	Count	Percent
CEPHALOSPORINS - 3RD GENERATION	80	1,018	2.22	85	4,710	1.51
DECONGESTANT-EXPECTORANT COMBINATIONS	81	1,008	2.20	96	3,200	1.03
BONE RESORPTION SUPPRESSION AGENTS	82	944	2.06	77	5,814	1.87
NITROFURAN DERIVATIVES	83	933	2.04	81	5,324	1.71
CEPHALOSPORINS - 2ND GENERATION	84	843	1.84	84	4,754	1.53
ANTIPARKINSONISM DRUGS, OTHER	85	803	1.75	92	3,783	1.22
EYE ANTIINFLAMMATORY AGENTS	86	797	1.74	78	5,441	1.75
ALPHA-ADRENERGIC BLOCKING AGENTS	87	774	1.69	80	5407	1.74
INTESTINAL MOTILITY STIMULANTS	88	770	1.68	83	4,879	1.57
URINARY TRACT ANTISPASMODIC/ANTIINCONTINENCE AGENT	89	768	1.68	88	3,987	1.28
NARCOTIC ANTITUSS-1ST GEN. ANTIHISTAMINE-DECONGESTANT	90	754	1.65	101	2,883	0.93
DIGITALIS GLYCOSIDES	91	668	1.46	79	5,414	1.74
ANTIMIGRAINE PREPARATIONS	92	660	1.44	103	2,815	0.91
VITAMIN B PREPARATIONS	93	632	1.38	109	2,612	0.84
EYE ANTIBIOTIC-CORTICOID COMBINATIONS	94	631	1.38	95	3,224	1.04
DENTAL AIDS AND PREPARATIONS	95	620	1.35	90	3,950	1.27
2ND GEN ANTIHISTAMINE & DECONGESTANT COMBINATIONS	96	615	1.34	120	2,211	0.71
NASAL ANTIHISTAMINE	97	610	1.33	118	2,238	0.72
FOLIC ACID PREPARATIONS	98	604	1.32	89	3,958	1.27
PROGESTATIONAL AGENTS	99	592	1.29	115	2,332	0.75
TOPICAL LOCAL ANESTHETICS	100	584	1.28	94	3,322	1.07
BILE SALT SEQUESTRANTS	101	564	1.23	102	2,827	0.91
EYE ANTIHISTAMINES	102	564	1.23	116	2,304	0.74
ANTIMALARIAL DRUGS	103	563	1.23	111	2,567	0.83
URINARY TRACT ANESTHETIC/ANALGESIC AGENT (AZO-DYE)	104	563	1.23	97	3,017	0.97
ANTI-NARCOLEPSY/ANTI-HYPERKINESIS AGENTS	105	541	1.18	135	1,580	0.51
NARCOTIC ANALGESIC & NON-SALICYLATE ANALGESIC COMB	106	534	1.17	82	4,992	1.60
ANTIPSYCHOTICS, ATYPICAL, DOPAMINE, & SEROTONIN ANTAGONIST	107	531	1.16	93	3,522	1.13

Table 3.3a.The Top 200* Most Frequently Recorded Baseline Drug Dispensings Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Optum Research Database 6/1/2005−6/30/2015**

Therapeutic Drug Class Description	Exenatide			OADs		
	Rank	Count	Percent	Rank	Count	Percent
GENERAL BRONCHODILATOR AGENTS	108	515	1.12	91	3,862	1.24
EAR PREPARATIONS, ANTIBIOTICS	109	503	1.10	99	2,975	0.96
VAGINAL ESTROGEN PREPARATIONS	110	488	1.07	123	1,974	0.63
HYPOTENSIVES, MISCELLANEOUS	111	473	1.03	112	2,423	0.78
ANTIDIARRHEALS	112	471	1.03	110	2,604	0.84
BELLADONNA ALKALOIDS	113	468	1.02	117	2,267	0.73
NARCOTIC ANTITUSSIVE-ANTICHOLINERGIC COMBINATION	114	461	1.01	100	2,914	0.94
HYPOGLY, INSULIN-RESPONSE & INSULIN RELEASE COMBINATION	115	459	1.00	154	1,202	0.39
ROSACEA AGENTS, TOPICAL	116	452	0.99	132	1,672	0.54
VAGINAL ANTIFUNGALS	117	442	0.97	114	2,341	0.75
ANTI-HYPERLIPIDEMIC (HMGCOA) & CALCIUM CHANNEL BLOCKER COMBINATION	118	439	0.96	130	1,686	0.54
KETOLIDES	119	427	0.93	156	1,176	0.38
COLCHICINE	120	414	0.90	98	2,990	0.96
HYPOGLYCEMICS, ALPHA-GLUCOSIDASE INHIB TYPE (N-S)	121	412	0.90	163	1,004	0.32
RECTAL PREPARATIONS	122	410	0.90	107	2,677	0.86
TOPICAL SULFONAMIDES	123	400	0.87	122	2,032	0.65
ANTIFUNGAL ANTIBIOTICS	124	350	0.76	106	2,695	0.87
ANTIHISTAMINE AND DECONGESTANT COMBINATIONS	125	335	0.73	129	1,718	0.55
HEPARIN AND RELATED PREPARATIONS	126	330	0.72	113	2,386	0.77
KERATOLYTICS	127	329	0.72	150	1,319	0.42
ANTICHOLINERGICS/ANTISPASMODICS	128	320	0.70	119	2,219	0.71
ANTIMETABOLITES	129	304	0.66	125	1,902	0.61
NON-NARCOTIC ANTITUSSIVE AND EXPECTORANT COMBINATION	130	295	0.64	162	1,020	0.33
ADRENERGICS, AROMATIC, NON-CATECHOLAMINE	131	294	0.64	145	1,379	0.44
ANALGESICS, NARCOTIC AGONIST AND NSAID COMBINATION	132	293	0.64	134	1,620	0.52
OTIC PREPARATIONS, ANTI-INFLAMMATORY - ANTIBIOTICS	133	292	0.64	138	1,513	0.49

Table 3.3a.The Top 200* Most Frequently Recorded Baseline Drug Dispensings Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Optum Research Database 6/1/2005−6/30/2015**

Therapeutic Drug Class Description	Exenatide			OADs		
	Rank	Count	Percent	Rank	Count	Percent
NON-NARCOTIC ANTITUSSIVE - 1ST GENERATION	134	290	0.63	127	1,837	0.59
HYPOTENSIVES, VASODILATORS	135	286	0.62	104	2,800	0.90
ANAPHYLAXIS THERAPY AGENTS	136	286	0.62	155	1,182	0.38
ANTIARRHYTHMICS	137	283	0.62	105	2,793	0.90
ANTI-HYPERGLYCEMC-SOD/GLUC COTRANSPORT2(SGLT2)INHIB	138	275	0.60	153	1,237	0.40
BULK CHEMICALS	139	267	0.58	137	1,574	0.51
URINARY TRACT ANTISPASMODIC, M(3) SELECTIVE ANTAGONIST	140	266	0.58	143	1,416	0.46
ANTI-HYPERGLYCEMIC, AMYLIN ANALOG-TYPE	141	259	0.57	210	467	0.15
1ST GEN ANTIHIST-DECONGESTANT-ANTICHOLINERGIC COMBINATION	142	257	0.56	169	855	0.27
VAGINAL ANTIBIOTICS	143	253	0.55	151	1,285	0.41
ESTROGEN/ANDROGEN COMBINATIONS	144	251	0.55	186	648	0.21
ANTI-ULCER PREPARATIONS	145	248	0.54	126	1,896	0.61
ANTI-INFLAMMATORY TUMOR NECROSIS FACTOR INHIBITOR	146	216	0.47	158	1,107	0.36
TOPICAL ANTIVIRALS	147	215	0.47	164	964	0.31
NON-NARCOTIC ANTITUSS-DECONGESTANT-EXPECTORANT COMBINATION	148	206	0.45	170	843	0.27
UNKNOWN	149	204	0.45	159	1,075	0.35
IRON REPLACEMENT	150	203	0.44	167	891	0.29
FLUORIDE PREPARATIONS	151	195	0.43	166	936	0.30
IMMUNOSUPPRESSIVES	152	194	0.42	124	1,940	0.62
BETA-ADRENERGIC AND ANTICHOLINERGIC COMBINATIONS	153	194	0.42	121	2,193	0.71
LOCAL ANESTHETICS	154	193	0.42	149	1,338	0.43
ANTIPSYCHOTICS, ATYP, D2 PARTIAL AGONIS	155	188	0.41	161	1,039	0.33
NON-NARC ANTITUSSIVE - 1ST GENERATION ANTIHISTAMINE COMBINATION	156	188	0.41	140	1,471	0.47
ANGIOTENSIN RECEPTR ANTAGONIST & CALCIUM CHANNEL BLOCKER	157	184	0.40	136	1,577	0.51
PRENATAL VITAMIN PREPARATIONS	158	182	0.40	128	1,829	0.59

Table 3.3a.The Top 200* Most Frequently Recorded Baseline Drug Dispensings Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Optum Research Database 6/1/2005−6/30/2015**

Therapeutic Drug Class Description	Exenatide			OADs		
	Rank	Count	Percent	Rank	Count	Percent
ANALGESIC, NON-SALICYLATE, BARBITURATE, & XANTHINE COMBINATION	159	178	0.39	147	1,347	0.43
SMOKING DETERRENT-NICOTINIC RECEPTOR PARTIAL AGONIST	160	177	0.39	152	1,239	0.40
ANALGESIC/ANTIPYRETICS, SALICYLATES	161	177	0.39	144	1,411	0.45
ANALGESIC/ANTIPYRETICS, NON-SALICYLATE	162	174	0.38	193	585	0.19
ALPHA-2 RECEPTOR ANTAGONIST	163	168	0.37	142	1,421	0.46
ANTIDEPRESSANTS						
URINARY PH MODIFIERS	164	165	0.36	168	881	0.28
TOPICAL ANTI-INFLAMMATORY, NSAIDS	165	165	0.36	146	1,374	0.44
DRUG TX - CHRONIC INFLAMMATORY COLON DX, 5-AMINOSALICYLAT	166	158	0.35	160	1,057	0.34
HYPERGLYCEMICS	167	155	0.34	139	1,499	0.48
TOPICAL IMMUNOSUPPRESSIVE AGENTS	168	153	0.33	185	655	0.21
OPHTHALMIC ANTI-INFLAMMATORY	169	150	0.33	178	741	0.24
IMMUNOMODULATOR-TYPE						
ANTIHYPERLIPIDEMIC-HMG COA REDUCTASE INHIBITOR & NIACIN	170	146	0.32	165	939	0.30
NARCOTIC ANTITUSSIVE - DECONGESTANT - EXPECTORANT COMBINATION	171	142	0.31	188	625	0.20
HYPNOTICS, MELATONIN MT1/MT2 RECEPTOR AGONISTS	172	142	0.31	220	355	0.11
XANTHINES	173	142	0.31	174	753	0.24
ANTIPSORIATICS AGENTS	174	141	0.31	192	589	0.19
BETA-ADRENERGIC BLOCKING AGENTS/THIAZIDE & RELATED	175	141	0.31	131	1,679	0.54
ANTICHOLINERGICS,QUATERNARY AMMONIUM	176	131	0.29	183	666	0.21
EYE SULFONAMIDES	177	131	0.29	181	686	0.22
HISTAMINE H2-RECEPTOR INHIBITORS	178	129	0.28	148	1,346	0.43
CHEMOTHERAPEUTICS, ANTIBACTERIAL, MISC.	179	129	0.28	187	626	0.20
TOPICAL ANTINEOPLASTIC & PREMALIGNANT LESION AGNTS	180	129	0.28	179	729	0.23
ANTI-ULCER-H.PYLORI AGENTS	181	124	0.27	172	813	0.26
ANTINEOPLASTICS, MISCELLANEOUS	182	121	0.26	195	561	0.18

Table 3.3a.The Top 200* Most Frequently Recorded Baseline Drug Dispensings Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Optum Research Database 6/1/2005−6/30/2015**

Therapeutic Drug Class Description	Exenatide			OADs		
	Rank	Count	Percent	Rank	Count	Percent
EAR PREPARATIONS, LOCAL ANESTHETICS	183	120	0.26	184	666	0.21
IRRITABLE BOWEL SYNDROME AGENT, 5HT-4 PARTIAL AGONIST	184	118	0.26	224	336	0.11
NOSE PREPARATIONS, MISCELLANEOUS (RX)	185	117	0.26	189	618	0.20
TOPICAL	186	117	0.26	141	1,423	0.46
EAR PREPARATIONS, MISC. ANTI-INFECTIVES	187	111	0.24	197	552	0.18
RENIN INHIBITOR, DIRECT	188	105	0.23	190	607	0.20
CONTRACEPTIVES, INJECTABLE	189	102	0.22	215	387	0.12
ANTINEOPLASTIC - AROMATASE INHIBITORS	190	100	0.22	176	747	0.24
ANTI-MANIA DRUGS	191	98	0.21	191	603	0.19
EMOLLIENTS	192	96	0.21	211	454	0.15
SELECTIVE ESTROGEN RECEPTOR MODULATORS	193	93	0.20	207	483	0.16
ANTITHYROID PREPARATIONS	194	89	0.19	203	491	0.16
GLUCOCORTICOIDS, ORALLY INHALED	195	89	0.19	171	831	0.27
TOPICAL ANTIPARASITICS	196	88	0.19	180	721	0.23
TOPICAL PREPARATIONS, ANTIBACTERIALS	197	87	0.19	221	347	0.11
IMMUNOMODULATORS	198	85	0.19	208	483	0.16
CHOLINESTERASE INHIBITORS	199	84	0.18	133	1,655	0.53
ANTITUBERCULAR ANTIBIOTICS	200	83	0.18	194	583	0.19

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.

* Exposure drug and comparators were removed from the top 200 list. Only a proportion of drugs in the top 200 list were retained in the propensity score model via stepwise selection.

** Baseline includes 9-month period prior to drug initiation

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 3.3b.The Top 200* Most Frequently Recorded Baseline Drug Dispensings Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Impact National Benchmark Database 6/1/2005−3/31/2015**

Therapeutic Drug Class Description	Exenatide			OADs		
	Rank	Count	Percent	Rank	Count	Percent
NEEDLES/NEEDLELESS DEVICES	1	17,591	72.43	20	16,563	11.61
HYPOGLYCEMICS, BIGUANIDE TYPE (NON-SULFONYLUREAS)	2	17,419	71.72	1	75,643	53.04
BLOOD SUGAR DIAGNOSTICS	3	14,978	61.67	2	65,543	45.96
LIPOTROPICS	4	13,506	55.61	4	54,494	38.21
HYPOGLYCEMICS, INSULIN-RELEASE STIMULANT TYPE	5	12,579	51.79	5	49,706	34.85
HYPOTENSIVES, ACE INHIBITORS	6	10,547	43.43	3	60,170	42.19
HYPOGLYCEMICS, INSULIN-RESPONSE ENHANCER (N-S)	7	10,071	41.47	10	27,919	19.58
INSULINS	8	7,623	31.39	17	18,705	13.12
ANALGESICS, NARCOTICS	9	7,090	29.19	7	38,433	26.95
HYPOTENSIVES, ANGIOTENSIN RECEPTOR ANTAGONIST	10	6,342	26.11	13	23,153	16.23
DURABLE MEDICAL EQUIPMENT, MISCELLANEOUS (GROUP 1)	11	5,961	24.54	9	30,949	21.70
BETA-ADRENERGIC BLOCKING AGENTS	12	5,931	24.42	8	34,008	23.85
ANTI-HYPERLIPIDEMIC - HMG COA REDUCTASE INHIBITORS	13	5,548	22.84	6	41,492	29.09
NSAIDS, CYCLOOXYGENASE INHIBITOR - TYPE	14	4,935	20.32	11	25,765	18.07
PENICILLINS	15	4,646	19.13	12	24,248	17.00
SEROTONIN SPECIFIC REUPTAKE INHIBITOR (SSRIS)	16	4,548	18.73	18	18,468	12.95
MACROLIDES	17	4,471	18.41	15	21,265	14.91
GASTRIC ACID SECRETION REDUCERS	18	4,168	17.16	22	15,608	10.94
SYRINGES AND ACCESSORIES	19	4,037	16.62	21	16,533	11.59
QUINOLONES	20	4,034	16.61	16	19,781	13.87
CALCIUM CHANNEL BLOCKING AGENTS	21	3,900	16.06	14	22,085	15.49
THIAZIDE AND RELATED DIURETICS	22	3,353	13.81	19	17,022	11.94
THYROID HORMONES	23	3,322	13.68	26	12,655	8.87
LOOP DIURETICS	24	3,122	12.85	27	12,577	8.82
ANTICONVULSANTS	25	2,897	11.93	25	12,998	9.11
ANTI-ANXIETY DRUGS	26	2,743	11.29	24	13,845	9.71
GLUCOCORTICOIDS	27	2,642	10.88	23	15,196	10.66
BETA-ADRENERGIC AGENTS	28	2,563	10.55	28	12,355	8.66

Table 3.3b.The Top 200* Most Frequently Recorded Baseline Drug Dispensings Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Impact National Benchmark Database 6/1/2005−3/31/2015**

Therapeutic Drug Class Description	Exenatide			OADs		
	Rank	Count	Percent	Rank	Count	Percent
NASAL ANTI-INFLAMMATORY STEROIDS	29	2,374	9.77	32	10,415	7.30
TOPICAL ANTIFUNGALS	30	2,221	9.14	33	10,409	7.30
SKELETAL MUSCLE RELAXANTS	31	2,189	9.01	29	10,995	7.71
TOPICAL ANTI-INFLAMMATORY STEROIDAL	32	2,184	8.99	31	10,612	7.44
CEPHALOSPORINS - 1ST GENERATION	33	2,034	8.37	34	10,150	7.12
SEDATIVE-HYPNOTICS, NON-BARBITURATE	34	1,933	7.96	36	8,309	5.83
ANTIHISTAMINES - 2ND GENERATION	35	1,771	7.29	42	6,132	4.30
ANTIFUNGAL AGENTS	36	1,723	7.09	37	7,996	5.61
SEROTONIN-NOREPINEPHRINE REUPTAKE-INHIBITOR (SNRIS)	37	1,723	7.09	46	5,472	3.84
PLATELET AGGREGATION INHIBITORS	38	1,549	6.38	35	8,881	6.23
POTASSIUM REPLACEMENT	39	1,423	5.86	38	7,268	5.10
PROTON-PUMP INHIBITORS	40	1,279	5.27	30	10,875	7.63
NOREPINEPHRINE AND DOPAMINE REUPTAKE INHIBITORS (NDRIS)	41	1,279	5.27	58	4,435	3.11
ABSORBABLE SULFONAMIDES	42	1,250	5.15	39	7,263	5.09
LAXATIVES AND CATHARTICS	43	1,236	5.09	41	6,234	4.37
DRUGS TO TREAT IMPOTENCY	44	1,225	5.04	40	7,010	4.92
ALPHA/BETA-ADRENERGIC BLOCKING AGENTS	45	1,222	5.03	44	5,867	4.11
BETA-ADRENERGICS AND GLUCOCORTICOIDS COMBINATION	46	1,174	4.83	49	4,922	3.45
TETRACYCLINES	47	1,165	4.80	43	6,024	4.22
VASODILATORS, CORONARY	48	1,086	4.47	45	5,830	4.09
NARCOTIC ANTITUSSIVE-EXPECTORANT COMBINATION	49	994	4.09	51	4,760	3.34
TRICYCLIC ANTIDEPRESSANTS & RELATED NON-SELECTIVE REUPTAKE INHIBITORS	50	937	3.86	56	4,451	3.12
LEUKOTRIENE RECEPTOR ANTAGONISTS	51	902	3.71	68	3,294	2.31
HYPOGLY, INSULIN-REL STIM. & BIGUANIDE (N-S) COMBINATION	52	877	3.61	76	2,649	1.86
ESTROGENIC AGENTS	53	859	3.54	70	2,918	2.05
ANGIOTENSIN RECEPTOR ANTAGONIST/THIAZIDE AND RELATED COMBINATION	54	858	3.53	53	4,659	3.27
OPHTHALMIC ANTIBIOTICS	55	855	3.52	57	4,441	3.11

Table 3.3b.The Top 200* Most Frequently Recorded Baseline Drug Dispensings Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Impact National Benchmark Database 6/1/2005−3/31/2015**

Therapeutic Drug Class Description	Exenatide			OADs		
	Rank	Count	Percent	Rank	Count	Percent
NARCOTIC ANTITUSSIVE - 1ST GENERATION ANTIHISTAMINE	56	845	3.48	66	3,598	2.52
POTASSIUM SPARING DIURETICS IN COMBINATION	57	834	3.43	62	3,983	2.79
ANTIHISTAMINES - 1ST GENERATION	58	810	3.34	59	4,190	2.94
ORAL ANTICOAGULANTS,COUMARIN TYPE	59	804	3.31	48	5,027	3.52
ANTIVIRALS, GENERAL	60	804	3.31	60	4,078	2.86
PURINE INHIBITORS	61	786	3.24	54	4,588	3.22
ANTIEMETIC/ANTIVERTIGO AGENTS	62	764	3.15	50	4,797	3.36
TOPICAL ANTIBIOTICS	63	762	3.14	67	3,542	2.48
ACE INHIBITOR/CALCIUM CHANNEL BLOCKER COMBINATION	64	751	3.09	65	3,752	2.63
VITAMIN D PREPARATIONS	65	739	3.04	64	3,893	2.73
DIABETIC SUPPLIES	66	736	3.03	47	5,467	3.83
MIOTICS/OTHER INTRAOCULAR PRESSURE REDUCERS	67	729	3.00	63	3,894	2.73
LINCOSAMIDES	68	715	2.94	61	3,985	2.79
BENIGN PROSTATIC HYPERTROPHY/MICTURITION AGENTS	69	714	2.94	55	4,524	3.17
POTASSIUM SPARING DIURETICS	70	649	2.67	75	2,728	1.91
ANTITUSSIVES, NON-NARCOTIC	71	638	2.63	73	2,813	1.97
BONE RESORPTION SUPPRESSION AGENTS	72	593	2.44	69	3,067	2.15
ACE INHIBITOR/THIAZIDE & THIAZIDE-LIKE DIURETIC	73	575	2.37	52	4,701	3.30
SEROTONIN-2 ANTAGONIST/REUPTAKE INHIBITORS (SARIS)	74	561	2.31	71	2,915	2.04
FOLIC ACID PREPARATIONS	75	516	2.12	77	2,621	1.84
ANDROGENIC AGENTS	76	494	2.03	92	1,687	1.18
CONTRACEPTIVES, ORAL	77	489	2.01	90	1,735	1.22
ALPHA-ADRENERGIC BLOCKING AGENTS	78	483	1.99	78	2,487	1.74
HYPOTENSIVES, SYMPATHOLYTIC	79	457	1.88	74	2,790	1.96
EYE ANTIINFLAMMATORY AGENTS	80	448	1.84	79	2,478	1.74
URINARY TRACT	81	439	1.81	86	1,978	1.39
DIGITALIS GLYCOSIDES	82	436	1.80	80	2,448	1.72
ANAEROBIC ANTIPROTOZOAL-ANTIBACTERIAL AGENTS	83	432	1.78	72	2,832	1.99

Table 3.3b.The Top 200* Most Frequently Recorded Baseline Drug Dispensings Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Impact National Benchmark Database 6/1/2005−3/31/2015**

Therapeutic Drug Class Description	Exenatide			OADs		
	Rank	Count	Percent	Rank	Count	Percent
NITROFURAN DERIVATIVES	84	423	1.74	85	2,007	1.41
HYPOGLY, INSUL-RESP. ENHANCER & BIGUANIDE COMBINATION	85	419	1.73	116	1,036	0.73
ANTIMALARIAL DRUGS	86	414	1.70	97	1,475	1.03
CEPHALOSPORINS - 2ND GENERATION	87	413	1.70	82	2,080	1.46
ANTI-HYPERLIPIDEMIC - HMG COA REDUCTASE INHIBITORS & CHOLESTEROL ABSORPTION INHIBITOR	88	395	1.63	87	1,924	1.35
TOPICAL LOCAL ANESTHETICS	89	379	1.56	91	1,716	1.20
INTESTINAL MOTILITY STIMULANTS	90	372	1.53	83	2,070	1.45
CEPHALOSPORINS - 3RD GENERATION	91	367	1.51	94	1,626	1.14
DECONGESTANT - EXPECTORANT COMBINATIONS	92	364	1.50	103	1,199	0.84
EYE ANTIBIOTIC - CORTICOID COMBINATIONS	93	358	1.47	93	1,678	1.18
DENTAL AIDS AND PREPARATIONS	94	357	1.47	84	2,054	1.44
ANTIPARKINSONISM DRUGS, OTHER	95	351	1.45	98	1,438	1.01
EYE ANTIHISTAMINES	96	331	1.36	101	1,240	0.87
GENERAL BRONCHODILATOR AGENTS	97	324	1.33	88	1,922	1.35
PROGESTATIONAL AGENTS	98	320	1.32	118	1,011	0.71
2ND GENERATION ANTIHISTAMINE & DECONGESTANT COMBINATIONS	99	319	1.31	106	1,159	0.81
NARCOTIC ANALGESIC & NON-SALICYLATE ANALGESIC COMB	100	313	1.29	81	2,139	1.50
EAR PREPARATIONS, ANTIBIOTICS	101	312	1.28	96	1,497	1.05
ANTIPSYCHOTICS, ATYPICAL, DOPAMINE, & SEROTONIN ANTAGONIST	102	291	1.20	89	1,840	1.29
VAGINAL ESTROGEN PREPARATIONS	103	290	1.19	117	1,019	0.71
NASAL ANTIHISTAMINE	104	289	1.19	114	1,048	0.73
ANTI-NARCOLEPSY/ANTI-HYPERKINESIS AGENTS	105	285	1.17	121	974	0.68
VAGINAL ANTIFUNGALS	106	284	1.17	104	1,181	0.83
ANTIMIGRAINE PREPARATIONS	107	283	1.17	115	1,047	0.73
COLCHICINE	108	272	1.12	95	1,602	1.12
VITAMIN B PREPARATIONS	109	269	1.11	129	814	0.57
NARCOTIC ANTITUSSIVE-ANTICHOLINERGIC COMBINATION	110	268	1.10	110	1,147	0.80
ROSACEA AGENTS, TOPICAL	111	266	1.10	123	950	0.67

Table 3.3b.The Top 200* Most Frequently Recorded Baseline Drug Dispensings Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Impact National Benchmark Database 6/1/2005−3/31/2015**

Therapeutic Drug Class Description	Exenatide			OADs		
	Rank	Count	Percent	Rank	Count	Percent
URINARY TRACT ANESTHETIC/ANALGESIC AGENT (AZO-DYE)	112	261	1.07	105	1,174	0.82
KERATOLYTICS	113	258	1.06	134	746	0.52
HYPOGLYCEMICS, ALPHA-GLUCOSIDASE INHIBITOR TYPE (N-S)	114	257	1.06	147	617	0.43
BILE SALT SEQUESTRANTS	115	241	0.99	107	1,156	0.81
ANTIDIARRHEALS	116	234	0.96	111	1,136	0.80
TOPICAL SULFONAMIDES	117	224	0.92	120	996	0.70
RECTAL PREPARATIONS	118	224	0.92	99	1,296	0.91
NARCOTIC ANTITUSSIVE - 1ST GENERATION ANTIHISTAMINE-DECONGESTANT	119	221	0.91	122	963	0.68
EMOLLIENTS	120	211	0.87	145	634	0.44
BELLADONNA ALKALOIDS	121	206	0.85	125	924	0.65
HYPOTENSIVES, MISCELLANEOUS	122	200	0.82	113	1,131	0.79
ANAPHYLAXIS THERAPY AGENTS	123	189	0.78	138	699	0.49
ANTIHYPERLIP(HMGCOA) & CALCIUM CHANNEL BLOCKER COMBINATION	124	186	0.77	132	777	0.54
OTIC PREPARATIONS, ANTI-INFLAMMATORY-ANTIBIOTICS	125	184	0.76	139	692	0.49
UNCLASSIFIED DRUGS	126	181	0.75	100	1,267	0.89
SMOKING DETERRENT-NICOTINIC RECEPTOR PARTIAL AGONIST	127	181	0.75	109	1,149	0.81
ANTIFUNGAL ANTIBIOTICS	128	170	0.70	102	1,203	0.84
ANTIMETABOLITES	129	167	0.69	127	913	0.64
KETOLIDES	130	166	0.68	153	560	0.39
ADRENERGICS, AROMATIC, NON-CATECHOLAMINE	131	164	0.68	140	660	0.46
ANTIHYPERGLYCEMIC, AMYLIN ANALOG-TYPE	132	155	0.64	218	176	0.12
ANTICHOLINERGICS/ANTISPASMODICS	133	154	0.63	133	762	0.53
VAGINAL ANTIBIOTICS	134	147	0.61	154	559	0.39
ANTIARRHYTHMICS	135	144	0.59	112	1,133	0.79
ANALGESICS, NARCOTIC AGONIST AND NSAID COMBINATION	136	141	0.58	135	740	0.52
HYPOGLY, INSULIN-RESPONSE & INSULIN RELEASE COMBINATION	137	137	0.56	166	415	0.29
HEPARIN AND RELATED PREPARATIONS	138	135	0.56	108	1,154	0.81

Table 3.3b.The Top 200* Most Frequently Recorded Baseline Drug Dispensings Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Impact National Benchmark Database 6/1/2005−3/31/2015**

Therapeutic Drug Class Description	Exenatide			OADs		
	Rank	Count	Percent	Rank	Count	Percent
TOPICAL ANTIVIRALS	139	130	0.54	150	584	0.41
NON-NARCOTIC ANTITUSSIVE AND EXPECTORANT COMBINATION	140	129	0.53	163	445	0.31
ANALGESIC, NON-SALICYLATE, BARBITURATE, & XANTHINE COMBINATION	141	124	0.51	143	640	0.45
ANALGESIC/ANTIPYRETICS, SALICYLATES	142	122	0.50	148	613	0.43
ANTI-ULCER PREPARATIONS	143	121	0.50	130	790	0.55
HYPERGLYCEMICS	144	120	0.49	137	735	0.52
ANTIHISTAMINE AND DECONGESTANT COMBINATIONS	145	117	0.48	146	627	0.44
DRUG TX - CHRONIC INFLAMMATORY COLON DX, 5-AMINOSALICYLAT	146	117	0.48	141	655	0.46
TOPICAL IMMUNOSUPPRESSIVE AGENTS	147	116	0.48	172	391	0.27
URINARY PH MODIFIERS	148	115	0.47	157	483	0.34
IMMUNOSUPPRESSIVES	149	110	0.45	124	925	0.65
HISTAMINE H2-RECEPTOR INHIBITORS	150	110	0.45	119	1,008	0.71
OPHTHALMIC ANTI-INFLAMMATORY IMMUNOMODULATOR-TYPE	151	109	0.45	175	381	0.27
HYPOTENSIVES, VASODILATORS	152	109	0.45	126	916	0.64
ANALGESIC/ANTIPYRETICS, NON-SALICYLATE	153	109	0.45	160	450	0.32
NON-NARC ANTITUSSIVE- 1ST GENERATION ANTIHISTAMINE COMBINATION	154	107	0.44	149	593	0.42
ANTI-INFLAMMATORY TUMOR NECROSIS FACTOR INHIBITOR	155	100	0.41	155	556	0.39
INFLUENZA VIRUS VACCINES	156	99	0.41	142	654	0.46
ANTIPSYCHOTICS, ATYP, D2 PARTIAL AGONIST	157	98	0.40	151	577	0.40
URINARY TRACT ANTISPASMODIC, M(3) SELECTIVE ANTAGONIST	158	98	0.40	173	385	0.27
ANTICHOLINERGICS, QUATERNARY AMMONIUM	159	97	0.40	189	308	0.22
ANTIPSORIATICS AGENTS	160	95	0.39	164	441	0.31
VITAMIN B12 PREPARATIONS	161	95	0.39	168	410	0.29
ALPHA-2 RECEPTOR ANTAGONIST ANTIDEPRESSANTS	162	93	0.38	136	738	0.52
NOSE PREPARATIONS, MISCELLANEOUS (RX)	163	92	0.38	186	319	0.22
ANTISEPTICS, GENERAL	164	86	0.35	144	637	0.45

Table 3.3b.The Top 200* Most Frequently Recorded Baseline Drug Dispensings Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Impact National Benchmark Database 6/1/2005−3/31/2015**

Therapeutic Drug Class Description	Exenatide			OADs		
	Rank	Count	Percent	Rank	Count	Percent
ANTI-HYPERGLYCEMC-SOD/GLUCOSE COTRANSPORT2 (SGLT2) INHIBITOR	165	85	0.35	216	189	0.13
BETA-ADRENERGIC AND ANTICHOLINERGIC COMBINATIONS	166	84	0.35	131	781	0.55
EYE SULFONAMIDES	167	83	0.34	171	391	0.27
NON-NARCOTIC ANTITUSS-DECONGESTANT-EXPECTORANT COMBINATION	168	82	0.34	180	339	0.24
ESTROGEN/ANDROGEN COMBINATIONS	169	81	0.33	204	236	0.17
PRENATAL VITAMIN PREPARATIONS	170	81	0.33	128	854	0.60
EAR PREPARATIONS, MISC. ANTI-INFECTIVES	171	80	0.33	196	278	0.19
1ST GENERATION ANTIHISTAMINE-DECONGESTANT-ANTICHOLINERGIC COMBINATION	172	80	0.33	192	284	0.20
ANGIOTENSIN RECEPTOR ANTAGONIST & CALCIUM CHANNEL BLOCKR	173	77	0.32	162	445	0.31
ANTINEOPLASTICS, MISCELLANEOUS	174	77	0.32	177	361	0.25
LOCAL ANESTHETICS	175	74	0.30	159	457	0.32
ANTI-MANIA DRUGS	176	73	0.30	174	384	0.27
IRRITABLE BOWEL SYNDROME AGENT, 5HT-4	177	72	0.30	219	172	0.12
XANTHINES	178	72	0.30	170	393	0.28
BULK CHEMICALS	179	70	0.29	176	365	0.26
NON-NARCOTIC ANTITUSSIVE - 1ST GENERATION ANTIHISTAMINE-DECONGESTANT	180	70	0.29	161	446	0.31
NARCOTIC ANTITUSS-DECONGESTANT-EXPECTORANT COMBINATION	181	69	0.28	205	231	0.16
TOPICAL ANTINEOPLASTIC & PREMALIGNANT LESION AGENTS	182	69	0.28	178	345	0.24
IMMUNOMODULATORS	183	68	0.28	197	272	0.19
CHEMOTHERAPEUTICS, ANTIBACTERIAL, MISC.	184	68	0.28	191	288	0.20
IRON REPLACEMENT	185	67	0.28	179	343	0.24
TOPICAL ANTIFUNGAL/ANTIINFLAMMATORY, STERIOD AGENT	186	65	0.27	156	528	0.37
ANTI-ULCER - H.PYLORI AGENTS	187	64	0.26	165	424	0.30
SELECTIVE ESTROGEN RECEPTOR MODULATORS	188	62	0.26	194	281	0.20
PERIODONTAL COLLAGENASE INHIBITORS	189	59	0.24	193	281	0.20

Table 3.3b.The Top 200* Most Frequently Recorded Baseline Drug Dispensings Among Exenatide Initiators and Other Antidiabetic Drug Initiators, Impact National Benchmark Database 6/1/2005−3/31/2015**

Therapeutic Drug Class Description	Exenatide			OADs		
	Rank	Count	Percent	Rank	Count	Percent
HYPNOTICS, MELATONIN MT1/MT2 RECEPTOR AGONISTS	190	58	0.24	239	134	0.09
CONTRACEPTIVES, INJECTABLE	191	56	0.23	203	239	0.17
TOPICAL PREPARATIONS, ANTIBACTERIALS	192	56	0.23	202	247	0.17
ANTITHYROID PREPARATIONS	193	55	0.23	199	265	0.19
OXAZOLIDINONES	194	55	0.23	210	208	0.15
VITAMIN A DERIVATIVES	195	53	0.22	217	185	0.13
TOPICAL ANTIPARASITICS	196	53	0.22	198	270	0.19
TOPICAL AGENTS, MISCELLANEOUS	197	52	0.21	224	155	0.11
FAT ABSORPTION DECREASING AGENTS	198	52	0.21	280	75	0.05
ANOREXIC AGENTS	199	52	0.21	285	70	0.05
ACNE AGENTS, TOPICAL	200	51	0.21	213	202	0.14

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.

* Exposure drug and comparators were removed from the top 200 list. Only a proportion of drugs in the top 200 list were retained in the propensity score model via stepwise selection.

** Baseline includes 9-month period prior to drug initiation

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 4.1. Descriptive Characteristics Derived from Medical Records by Pancreatic Case Status and Exposure Status among Controls

Characteristic	Chart-Confirmed Pancreatic Cancer (N= 86)		Controls (N= 296)		*P*-Value*	Controls (N= 296)				*P*-Value*
						Exenatide (N= 70)		OADs (N= 226)		
	N	%*	N	%*		N	%*	N	%*	
Race					0.57					0.58
Non-Hispanic African American	10	15.9	15	16.1	–	0	0.0	15	18.8	–
Non-Hispanic Caucasian	50	79.4	68	73.1	–	12	92.3	56	70.0	–
Asian/Pacific Islander	1	1.6	2	2.2	–	0	0.0	2	2.5	–
Latino/Hispanic/Mexican American	1	1.6	7	7.5	–	1	7.7	6	7.5	–
Other	1	1.6	1	1.1	–	0	0.0	1	1.3	–
Missing	23	26.7	203	68.6	–	57	81.4	146	64.6	–
Body Mass Index (kg/m^2)					0.00					0.00
< 25	19	34.5	7	3.8	–	1	2.0	6	4.5	–
25-29.9	12	21.8	39	21.3	–	7	14.0	32	24.1	–
30-34.9	15	27.3	59	32.2	–	14	28.0	45	33.8	–
≥ 35	9	16.4	78	42.6	–	28	56.0	50	37.6	–
Missing	31	36.0	113	38.2	–	20	28.6	93	41.2	–
Smoking					0.27					0.07
Never	33	47.8	102	57.0	–	28	71.8	74	52.9	–
Former Smoker	22	31.9	40	22.3	–	8	20.5	32	22.9	–
Current Smoker	14	20.3	37	20.7	–	3	7.7	34	24.3	–
Missing	17	19.8	117	39.5	–	31	44.3	86	38.1	–
Alcohol Use					0.16					0.32
Never	38	56.7	83	61.0	–	18	56.3	65	62.5	–
Light	22	32.8	45	33.1	–	11	34.4	34	32.7	–
Moderate	3	4.5	7	5.1	–	3	9.4	4	3.8	–
Heavy	4	6.0	1	0.7	–	0	0.0	1	1.0	–
Missing	19	22.1	160	54.1	–	38	54.3	122	54.0	–
Diastolic Blood Pressure (mm Hg)**					0.00					0.12
Mean	0	72.0	0	77.1	–	0	75.4	0	77.6	–
Median	0	71.8	0	78.0	–	0	76.0	0	78.0	–
IQR	0	65.0 - 78.5	0	70.0 - 83.3	–	0	69.0 - 82.0	0	71.0 - 84.0	–
Missing	28	32.6	76	25.7	–	18	25.7	58	25.7	–
Systolic Blood Pressure (mm Hg)**					0.10					0.09
Mean	0	127.0	0	131.7	–	0	128.5	0	132.6	–
Median	0	126.8	0	130.0	–	0	125.2	0	130.2	–
IQR	0	112.0 - 137.3	0	122.3 - 140.0	–	0	120.8 - 136.3	0	123.4 - 140.4	–
Missing	28	32.6	76	25.7	–	18	25.7	58	25.7	–

Table 4.1. Descriptive Characteristics Derived from Medical Records by Pancreatic Case Status and Exposure Status among Controls

Characteristic	Chart-Confirmed Pancreatic Cancer (N= 86)		Controls (N= 296)		*P*-Value*	Controls (N= 296)				*P*-Value*
						Exenatide (N= 70)		OADs (N= 226)		
	N	%*	N	%*		N	%*	N	%*	
Family History of Cancers					0.01					0.03
Yes	44	78.6	62	93.9	–	16	100.0	46	92.0	–
No	12	21.4	4	6.1	–	0	0.0	4	8.0	–
Missing	30	34.9	230	77.7	–	54	77.1	176	77.9	–
Family History of Pancreatic Cancer					0.01					0.01
Yes	5	20.0	2	100.0	–	0	0.0	2	100.0	–
No	20	80.0	0	0.0	–	0	0.0	0	0.0	–
Missing	61	70.9	294	99.3	–	70	100.0	224	99.1	–
History of Chronic Pancreatitis					N/A					N/A
Yes	2	28.6	0	0.0	–	0	0.0	0	0.0	–
No	5	71.4	0	0.0	–	0	0.0	0	0.0	–
Missing	79	91.9	296	100.0	–	70	100.0	226	100.0	–
History of Gallstone Disease or Gallbladder Sludge					0.32					0.32
Yes	9	90.0	5	71.4	–	0	0.0	5	71.4	–
No	1	10.0	2	28.6	–	0	0.0	2	28.6	–
Missing	76	88.4	289	97.6	–	70	100.0	219	96.9	–
History of Cholecystectomy					N/A					N/A
Yes	19	100.0	27	100.0	–	5	100.0	22	100.0	–
No	0	0.0	0	0.0	–	0	0.0	0	0.0	–
Missing	67	77.9	269	90.9	–	65	92.9	204	90.3	–
History of Non-Alcoholic Fatty Liver Disease					N/A					N/A
Yes	3	100.0	8	100.0	–	2	100.0	6	100.0	–
No	0	0.0	0	0.0	–	0	0.0	0	0.0	–
Missing	83	96.5	288	97.3	–	68	97.1	220	97.3	–
HbA1c					1.00					0.96
< 6.5%	5	18.5	29	18.5	–	8	20.0	21	17.9	–
≥ 6.5%	22	81.5	128	81.5	–	32	80.0	96	82.1	–
Missing	59	68.6	139	47.0	–	30	42.9	109	48.2	–

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.
Note: Only 8 patients had CRP information, 2 of which were missing units therefore CRP values are not summarized.
* p-values are only calculated for non-missing values. For missing values, the percentage denominator is the number of patients. For non-missing values, the percentage denominator is the number of patients with non-missing values.
** Average of up to 3 readings collected.
Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 4.2. Descriptive Characteristics Derived from Medical Records by Thyroid Case Status and Exposure Status among Controls

Characteristic	Chart-Confirmed Thyroid Cancer (N= 83)		Controls (N= 296)		*P*-Value*	Controls (N= 296)				*P*-Value*
						Exenatide (N= 70)		OADs (N= 226)		
	N	%*	N	%*		N	%*	N	%*	
Race					0.32					0.39
Non-Hispanic African American	7	18.4	15	16.1	–	0	0.0	15	18.8	–
Non-Hispanic Caucasian	24	63.2	68	73.1	–	12	92.3	56	70.0	–
Asian/Pacific Islander	0	0.0	2	2.2	–	0	0.0	2	2.5	–
Latino/Hispanic/Mexican American	7	18.4	7	7.5	–	1	7.7	6	7.5	–
Other	0	0.0	1	1.1	–	0	0.0	1	1.3	–
Missing	45	54.2	203	68.6	–	57	81.4	146	64.6	–
Body Mass Index					0.01					0.01
< 25	0	0.0	7	3.8	–	1	2.0	6	4.5	–
25-29.9	7	12.5	39	21.3	–	7	14.0	32	24.1	–
30-34.9	31	55.4	59	32.2	–	14	28.0	45	33.8	–
≥ 35	18	32.1	78	42.6	–	28	56.0	50	37.6	–
Missing	27	32.5	113	38.2	–	20	28.6	93	41.2	–
Smoking					0.07					0.02
Never	42	73.7	102	57.0	–	28	71.8	74	52.9	–
Former Smoker	9	15.8	40	22.3	–	8	20.5	32	22.9	–
Current Smoker	6	10.5	37	20.7	–	3	7.7	34	24.3	–
Missing	26	31.3	117	39.5	–	31	44.3	86	38.1	–
Alcohol Use					0.25					0.37
Never	26	55.3	83	61.0	–	18	56.3	65	62.5	–
Light	20	42.6	45	33.1	–	11	34.4	34	32.7	–
Moderate	0	0.0	7	5.1	–	3	9.4	4	3.8	–
Heavy	1	2.1	1	0.7	–	0	0.0	1	1.0	–
Missing	36	43.4	160	54.1	–	38	54.3	122	54.0	–
Diastolic Blood Pressure**					0.30					0.12
Mean	0	78.8	0	77.1	–	0	75.4	0	77.6	–
Median	0	78.0	0	78.0	–	0	76.0	0	78.0	–
IQR	0	72.0 - 82.7	0	70.0 - 83.3	–	0	69.0 - 82.0	0	71.0 - 84.0	–
Missing	47	56.6	76	25.7	–	18	25.7	58	25.7	–
Systolic Blood Pressure**					0.34					0.09
Mean	0	134.3	0	131.7	–	0	128.5	0	132.6	–
Median	0	136.3	0	130.0	–	0	125.2	0	130.2	–
IQR	0	122.8 - 145.3	0	122.3 - 140.0	–	0	120.8 - 136.3	0	123.4 - 140.4	–
Missing	47	56.6	76	25.7	–	18	25.7	58	25.7	–

Table 4.2. Descriptive Characteristics Derived from Medical Records by Thyroid Case Status and Exposure Status among Controls

Characteristic	Chart-Confirmed Thyroid Cancer (N= 83)		Controls (N= 296)		*P*-Value*	Controls (N= 296)				*P*-Value*
						Exenatide (N= 70)		OADs (N= 226)		
	N	%*	N	%*		N	%*	N	%*	
Family History of Cancers					0.55					0.47
Yes	29	90.6	62	93.9	–	16	100.0	46	92.0	–
No	3	9.4	4	6.1	–	0	0.0	4	8.0	–
Missing	51	61.4	230	77.7	–	54	77.1	176	77.9	–
Family History of Thyroid Cancer					0.73					0.73
Yes	2	10.5	0	0.0	–	0	0.0	0	0.0	–
No	17	89.5	1	100.0	–	0	0.0	1	100.0	–
Missing	64	77.1	295	99.7	–	70	100.0	225	99.6	–
History of Benign Thyroid Neoplasm					N/A					N/A
Yes	13	100.0	1	100.0	–	0	0.0	1	100.0	–
No	0	0.0	0	0.0	–	0	0.0	0	0.0	–
Missing	70	84.3	295	99.7	–	70	100.0	225	99.6	–
History of Thyroid Diseases					0.02					0.08
Yes	39	97.5	27	81.8	–	10	83.3	17	81.0	–
No	1	2.5	6	18.2	–	2	16.7	4	19.0	–
Missing	43	51.8	263	88.9	–	58	82.9	205	90.7	–
Radiation Exposure					0.02					0.07
Yes	50	94.3	91	100.0	–	18	100.0	73	100.0	–
No	3	5.7	0	0.0	–	0	0.0	0	0.0	–
Missing	30	36.1	205	69.3	–	52	74.3	153	67.7	–
Low Iodine Diet					N/A					N/A
Yes	0	0.0	0	0.0	–	0	0.0	0	0.0	–
No	0	0.0	0	0.0	–	0	0.0	0	0.0	–
Missing	83	100.0	296	100.0	–	70	100.0	226	100.0	–
HbA1c					0.32					0.58
< 6.5%	3	10.7	29	18.5	–	8	20.0	21	17.9	–
≥ 6.5%	25	89.3	128	81.5	–	32	80.0	96	82.1	–
Missing	55	66.3	139	47.0	–	30	42.9	109	48.2	–

Note: OADs include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.

Note: Only 8 patients had CRP information, 2 of which were missing units therefore CRP values are not summarized.

* p-values are only calculated for non-missing values. For missing values, the percentage denominator is the number of patients. For non-missing values, the percentage denominator is the number of patients with non-missing values.

** Average of up to 3 readings collected.

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 5.1 Descriptive Characteristics of Pancreatic Cancer Derived from Claims from the 9 Months Prior to Case-Control Index Date

Characteristic	Chart-Confirmed Pancreatic Cancer (N= 86)		Controls (N= 296)		*P*-Value
	N	%	N	%	
Demographics					
Age					
≤ 39	0.0	0.0	17.0	5.7	0.0
40-49	6.0	7.0	45.0	15.2	0.0
50-59	32.0	37.2	113.0	38.2	0.9
60-69	35.0	40.7	96.0	32.4	0.2
≥ 70	13.0	15.1	25.0	8.4	0.1
Sex					
Male	58.0	67.4	143.0	48.3	0.0
Female	28.0	32.6	153.0	51.7	0.0
Geographic Area					
Northeast	4.0	4.7	9.0	3.0	0.5
Midwest	22.0	25.6	62.0	20.9	0.4
South	51.0	59.3	194.0	65.5	0.3
West	9.0	10.5	31.0	10.5	1.0
Unknown	0.0	0.0	0.0	0.0	N/A
Year of Case-Control Index					
2005	1.0	1.2	3.0	1.0	0.9
2006	11.0	12.8	20.0	6.8	0.1
2007	6.0	7.0	21.0	7.1	1.0
2008	6.0	7.0	38.0	12.8	0.1
2009	6.0	7.0	31.0	10.5	0.3
2010	8.0	9.3	40.0	13.5	0.3
2011	14.0	16.3	48.0	16.2	1.0
2012	9.0	10.5	32.0	10.8	0.9
2013	7.0	8.1	22.0	7.4	0.8
2014	8.0	9.3	27.0	9.1	1.0
2015	10.0	11.6	14.0	4.7	0.0
Medical History					
Peripheral neuropathy	3.0	3.5	45.0	15.2	0.0
Retinopathy	2.0	2.3	26.0	8.8	0.0
Hypertension	68.0	79.1	219.0	74.0	0.3
Hyperlipidemia	62.0	72.1	199.0	67.2	0.4
Ischemic heart disease	17.0	19.8	61.0	20.6	0.9
Myocardial infarction	2.0	2.3	8.0	2.7	0.8
Congestive heart failure	6.0	7.0	34.0	11.5	0.2

Table 5.1 Descriptive Characteristics of Pancreatic Cancer Derived from Claims from the 9 Months Prior to Case-Control Index Date

Characteristic	Chart-Confirmed Pancreatic Cancer (N= 86)		Controls (N= 296)		*P*-Value
	N	%	N	%	
Stroke/TIA	3.0	3.5	17.0	5.7	0.4
Obesity	10.0	11.6	43.0	14.5	0.5
Gastroesophageal reflux disease	24.0	27.9	46.0	15.5	0.0
Disorders of fluid, electrolyte, and acid-base balance	14.0	16.3	31.0	10.5	0.1
Other and unspecified anemias	10.0	11.6	46.0	15.5	0.4
Acute sinusitis	7.0	8.1	30.0	10.1	0.6
Nephritis and nephropathy, not specified as acute or chronic	1.0	1.2	4.0	1.4	0.9
Osteoarthrosis and allied disorders	10.0	11.6	72.0	24.3	0.0
Other and unspecified disorders of back	16.0	18.6	72.0	24.3	0.3
General symptoms	32.0	37.2	135.0	45.6	0.2
Symptoms involving skin and other integumentary tissue	27.0	31.4	52.0	17.6	0.0
Symptoms involving head and neck	10.0	11.6	29.0	9.8	0.6
Symptoms involving digestive system	36.0	41.9	42.0	14.2	0.0
Encounter for other and unspecified procedure and aftercare	48.0	55.8	121.0	40.9	0.0
General medical examination	18.0	20.9	45.0	15.2	0.2
Prescription Drug History					
Non-alcohol sedatives	20.0	23.3	81.0	27.4	0.4
Acid-suppressing drugs	25.0	29.1	64.0	21.6	0.2
Metformin	52.0	60.5	158.0	53.4	0.2
Sulfonylureas	33.0	38.4	96.0	32.4	0.3
Thiazolidinediones	16.0	18.6	63.0	21.3	0.6
Insulin glargine	26.0	30.2	73.0	24.7	0.3
Insulins	15.0	17.4	81.0	27.4	0.1
ACE inhibitors	43.0	50.0	143.0	48.3	0.8
NSAIDs	19.0	22.1	88.0	29.7	0.2
Fibrates	7.0	8.1	32.0	10.8	0.5
Statins	53.0	61.6	167.0	56.4	0.4
Hypotensives, angiotensin receptor antagonist	19.0	22.1	43.0	14.5	0.1
Calcium channel blocking agents	14.0	16.3	57.0	19.3	0.5
Anti-anxiety drugs	13.0	15.1	59.0	19.9	0.3
Serotonin specific reuptake inhibitor (SSRIs)	5.0	5.8	60.0	20.3	0.0
Analgesics, narcotics	50.0	58.1	140.0	47.3	0.1
Anticonvulsants	10.0	11.6	73.0	24.7	0.0
Skeletal muscle relaxants	9.0	10.5	46.0	15.5	0.2
Beta-adrenergic agents	8.0	9.3	32.0	10.8	0.7
Blood sugar diagnostics	59.0	68.6	142.0	48.0	0.0

Table 5.1 Descriptive Characteristics of Pancreatic Cancer Derived from Claims from the 9 Months Prior to Case-Control Index Date

Characteristic	Chart-Confirmed Pancreatic Cancer (N= 86)		Controls (N= 296)		*P*-Value
	N	%	N	%	
Lipotropics	21.0	24.4	79.0	26.7	0.7
Thyroid hormones	6.0	7.0	32.0	10.8	0.3
Thiazide and related diuretics	9.0	10.5	28.0	9.5	0.8
Loop diuretics	11.0	12.8	46.0	15.5	0.5
Penicillins	19.0	22.1	61.0	20.6	0.8
Macrolides	16.0	18.6	56.0	18.9	0.9
Quinolones	25.0	29.1	72.0	24.3	0.4
Durable medical equipment, miscellaneous (Group 1)	23.0	26.7	45.0	15.2	0.0
Diabetic supplies	9.0	10.5	12.0	4.1	0.0
Procedure					
Thyrotropin releasing hormone	20.0	23.3	69.0	23.3	1.0
T3, T4 testing	17.0	19.8	48.0	16.2	0.4
CT, soft tissue neck	1.0	1.2	1.0	0.3	0.4
Thyroid imaging	12.0	14.0	10.0	3.4	0.0
Ultrasound of head and neck	1.0	1.2	6.0	2.0	0.6
Biopsy thyroid	2.0	2.3	2.0	0.7	0.2
Thyroidectomy	0.0	0.0	0.0	0.0	N/A
Other operations on thyroid	0.0	0.0	0.0	0.0	N/A
Abdominal pain	60.0	69.8	50.0	16.9	0.0
Lipase	31.0	36.0	11.0	3.7	0.0
Amylase	36.0	41.9	13.0	4.4	0.0
Other nonspecific abnormal serum enzyme levels	9.0	10.5	7.0	2.4	0.0
Abdominal ultrasound	40.0	46.5	26.0	8.8	0.0
Biopsy of pancreas	3.0	3.5	0.0	0.0	0.0
Pancreatectomy	0.0	0.0	0.0	0.0	N/A
Endobronchial ultrasound	0.0	0.0	0.0	0.0	N/A
Magnetic resonance imaging (MRI), abdomen	16.0	18.6	5.0	1.7	0.0
Magnetic resonance cholangiopancreatography (MRCP)	0.0	0.0	0.0	0.0	N/A
Endoscopic retrograde cholangiopancreatography (ERCP)	19.0	22.1	0.0	0.0	0.0
Other operations on pancreas	1.0	1.2	0.0	0.0	0.1
X-Ray for pancreas	13.0	15.1	2.0	0.7	0.0
Micro exam of pancreas	0.0	0.0	0.0	0.0	N/A
Chest X-ray	21.0	24.4	52.0	17.6	0.2
Radiographic procedure	49.0	57.0	92.0	31.1	0.0
Basic metabolic panel	28.0	32.6	72.0	24.3	0.1
Executive profile	57.0	66.3	167.0	56.4	0.1

Table 5.1 Descriptive Characteristics of Pancreatic Cancer Derived from Claims from the 9 Months Prior to Case-Control Index Date

Characteristic	Chart-Confirmed Pancreatic Cancer (N= 86)		Controls (N= 296)		*P*-Value
	N	%	N	%	
Lipid panel	58.0	67.4	191.0	64.5	0.6
Urinalysis, automated, with microscopy	18.0	20.9	55.0	18.6	0.6
Microalbumin, quantitative	21.0	24.4	72.0	24.3	1.0
Creatinine, other source	19.0	22.1	64.0	21.6	0.9
Glucose, quantitative	15.0	17.4	38.0	12.8	0.3
Hemoglobin; glycosylated (A1C)	74.0	86.0	230.0	77.7	0.1
Thyroxine; free	11.0	12.8	34.0	11.5	0.7
Complete blood count (CBC)	47.0	54.7	134.0	45.3	0.1
Level IV - Surgical pathology, gross and microscopic examination abortion - spontaneous/missed artery, biopsy bone marrow, biopsy bone exostosis brain/meninges, other than for tumor resection breast, biopsy, not requiring microscopic evaluation (truncated)	36.0	41.9	56.0	18.9	0.0
Unlisted miscellaneous pathology test	36.0	41.9	77.0	26.0	0.0
Immunization administration, one vaccine	19.0	22.1	57.0	19.3	0.6
Ophthalmological evaluation and examination	13.0	15.1	59.0	19.9	0.3
Determination of refractive state	7.0	8.1	37.0	12.5	0.3
Handling of specimen	4.0	4.7	30.0	10.1	0.1
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A problem focused history; A problem focused examination; Straightforward medical decision making.	24.0	27.9	90.0	30.4	0.7
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: An expanded problem focused history; An expanded problem focused examination; Medical decision making of low complexity.	71.0	82.6	255.0	86.1	0.4
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A detailed history; A detailed examination; Medical decision making of moderate complexity.	75.0	87.2	255.0	86.1	0.8
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A comprehensive history; A comprehensive examination; Medical decision making of high complexity.	25.0	29.1	61.0	20.6	0.1

Table 5.1 Descriptive Characteristics of Pancreatic Cancer Derived from Claims from the 9 Months Prior to Case-Control Index Date

Characteristic	Chart-Confirmed Pancreatic Cancer (N= 86)		Controls (N= 296)		*P*-Value
	N	%	N	%	
Subsequent hospital care, per day, for the evaluation and management of a patient, which requires at least 2 of these 3 key components: An expanded problem focused interval history; An expanded problem focused examination; Medical decision making of moderate complexity.	19.0	22.1	46.0	15.5	0.2
Subsequent hospital care, per day, for the evaluation and management of a patient, which requires at least 2 of these 3 key components: An expanded problem focused interval history; An expanded problem focused examination; Medical decision making of moderate complexity.	10.0	11.6	49.0	16.6	0.3
Office consultation for a new or established patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical decision making of moderate complexity.	24.0	27.9	64.0	21.6	0.2
Emergency department visit for the evaluation and management of a patient, which requires these 3 key components: A detailed history; A detailed examination; and Medical decision making of moderate complexity.	13.0	15.1	34.0	11.5	0.4
Emergency department visit for the evaluation and management of a patient, which requires these 3 key components within the constraints imposed by the urgency of the patient's clinical condition and/or mental status: A comprehensive history; A comprehensive examination; and Medical decision making of high complexity.	29.0	33.7	59.0	19.9	0.0
Periodic comprehensive preventive medicine reevaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, established patient; 40-64 years	12.0	14.0	48.0	16.2	0.6
Procedure Category					
Diagnostic ultrasound abdomen	40.0	46.5	35.0	11.8	0.0
Magnetic resonance imaging (MRI)	19.0	22.1	64.0	21.6	0.9
Nonoperative urinary measurements	36.0	41.9	89.0	30.1	0.0
Cardiac stress tests	20.0	23.3	38.0	12.8	0.0
Electrocardiogram	48.0	55.8	146.0	49.3	0.3
Microscopic exam (smear culture)	52.0	60.5	162.0	54.7	0.3

Table 5.1 Descriptive Characteristics of Pancreatic Cancer Derived from Claims from the 9 Months Prior to Case-Control Index Date

Characteristic	Chart-Confirmed Pancreatic Cancer (N= 86)		Controls (N= 296)		*P*-Value
	N	%	N	%	
Radioisotopic scan/function	23.0	26.7	42.0	14.2	0.0
Physical therapy exercises/manipulation	12.0	14.0	64.0	21.6	0.1
Ophthalmologic/otologic diagnosis/treatment	22.0	25.6	104.0	35.1	0.1
Other diagnostic radiology	61.0	70.9	170.0	57.4	0.0
Prophylactic vaccinations	29.0	33.7	88.0	29.7	0.5
Other therapeutic procedure	67.0	77.9	226.0	76.4	0.8
Other lab	81.0	94.2	265.0	89.5	0.2
Procedure codes not elsewhere specified	80.0	93.0	250.0	84.5	0.0
Vaginal delivery	17.0	19.8	63.0	21.3	0.8
Health Care Services					
Critical care procedure	5.0	5.8	11.0	3.7	0.4
0-5 unique drugs dispensed	5.0	5.8	29.0	9.8	0.3
6-10 unique drugs dispensed	31.0	36.0	80.0	27.0	0.1
11-15 unique drugs dispensed	28.0	32.6	95.0	32.1	0.9
≥16 unique drugs dispensed	22.0	25.6	92.0	31.1	0.3
Hospitalization within 45 days of index	50.0	58.1	91.0	30.7	0.0
1 Anti-diabetic medication within 45 days of index	38.0	44.2	96.0	32.4	0.0
2 Anti-diabetic medications within 45 days of index	16.0	18.6	59.0	19.9	0.8
>2 Anti-diabetic medications within 45 days of index	8.0	9.3	35.0	11.8	0.5
Outpatient visit on index	43.0	50.0	208.0	70.3	0.0
Inpatient visit on index	43.0	50.0	88.0	29.7	0.0
	Mean	**Median (IQR)**	**Mean**	**Median (IQR)**	***P*-Value**
Days from Study Start to Index Date	2067.7	2,209.0 (1,212.0-2,878.0)	1970.7	1,977.5 (1,284.5-2,606.0)	0.5
Number of cardiovascular procedures	1.6	1.0 (0.0-3.0)	1.4	1.0 (0.0-2.0)	0.6
Pharmacy costs ($)	2896.4	2,225.2 (902.7-4,045.6)	4133.3	2,618.0 (1,114.0-4,888.1)	0.0
Medical costs ($)	5678.8	3,713.5 (1,242.3-7,607.5)	4790.9	2,142.1 (1,050.8-5,266.3)	0.3
Facility costs ($)	11034.0	4,807.2 (696.3-15,279.4)	11536.0	1,374.5 (258.4-7,312.9)	0.9
Number of inpatient days	1.9	0.0 (0.0-2.0)	1.7	0.0 (0.0-0.0)	0.8
Number of laboratory tests	27.6	21.0 (10.0-30.0)	18.5	12.0 (6.0-22.0)	0.0
Number of 3-digit diagnosis codes	23.5	23.0 (14.0-30.0)	19.5	18.0 (12.0-24.0)	0.0
Number of inpatient stays*	0.4	0.0 (0.0-1.0)	0.3	0.0 (0.0-0.0)	0.1
Number of procedures	5.0	4.0 (2.0-7.0)	4.1	3.0 (1.0-5.0)	0.1
Number of physician visits*	10.8	10.0 (5.0-13.0)	11.5	9.0 (6.0-14.0)	0.6
Emergency room visit	1.3	1.0 (0.0-2.0)	1.2	0.0 (0.0-1.0)	0.8
Number of diabetes diagnoses*	5.2	4.0 (3.0-7.0)	5.3	4.0 (2.0-6.0)	1.0
Number of diabetes drug dispensings*	5.6	5.0 (3.0-8.0)	6.6	6.0 (2.0-10.0)	0.0

* One counted per day

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 5.2 Descriptive Characteristics of Thyroid Cancer Derived from Claims from the 9 Months Prior to Case-Control Index Date

Characteristic	Chart-Confirmed Thyroid Cancer (N= 83)		Controls (N= 296)		*P*-Value
	N	%	N	%	
Demographics					
Age					
≤ 39	8.0	9.6	17.0	5.7	0.2
40-49	13.0	15.7	45.0	15.2	0.9
50-59	32.0	38.6	113.0	38.2	1.0
60-69	24.0	28.9	96.0	32.4	0.5
≥ 70	6.0	7.2	25.0	8.4	0.7
Sex					
Male	27.0	32.5	143.0	48.3	0.0
Female	56.0	67.5	153.0	51.7	0.0
Geographic Area					
Northeast	3.0	3.6	9.0	3.0	0.8
Midwest	14.0	16.9	62.0	20.9	0.4
South	52.0	62.7	194.0	65.5	0.6
West	14.0	16.9	31.0	10.5	0.1
Unknown	0.0	0.0	0.0	0.0	N/A
Year of Case-Control Index					
2005	1.0	1.2	3.0	1.0	0.9
2006	6.0	7.2	20.0	6.8	0.9
2007	6.0	7.2	21.0	7.1	1.0
2008	6.0	7.2	38.0	12.8	0.2
2009	4.0	4.8	31.0	10.5	0.1
2010	3.0	3.6	40.0	13.5	0.0
2011	16.0	19.3	48.0	16.2	0.5
2012	13.0	15.7	32.0	10.8	0.2
2013	8.0	9.6	22.0	7.4	0.5
2014	14.0	16.9	27.0	9.1	0.0
2015	6.0	7.2	14.0	4.7	0.4
Medical History					
Peripheral neuropathy	9.0	10.8	45.0	15.2	0.3
Retinopathy	6.0	7.2	26.0	8.8	0.7
Hypertension	65.0	78.3	219.0	74.0	0.4
Hyperlipidemia	57.0	68.7	199.0	67.2	0.8
Ischemic heart disease	8.0	9.6	61.0	20.6	0.0
Myocardial infarction	1.0	1.2	8.0	2.7	0.4
Congestive heart failure	4.0	4.8	34.0	11.5	0.1

Table 5.2 Descriptive Characteristics of Thyroid Cancer Derived from Claims from the 9 Months Prior to Case-Control Index Date

Characteristic	Chart-Confirmed Thyroid Cancer (N= 83)		Controls (N= 296)		*P*-Value
	N	%	N	%	
Stroke/TIA	5.0	6.0	17.0	5.7	0.9
Obesity	21.0	25.3	43.0	14.5	0.0
Gastroesophageal reflux disease	9.0	10.8	46.0	15.5	0.3
Disorders of fluid, electrolyte, and acid-base balance	10.0	12.0	31.0	10.5	0.7
Other and unspecified anemias	8.0	9.6	46.0	15.5	0.2
Acute sinusitis	13.0	15.7	30.0	10.1	0.2
Nephritis and nephropathy, not specified as acute or chronic	0.0	0.0	4.0	1.4	0.3
Osteoarthrosis and allied disorders	12.0	14.5	72.0	24.3	0.1
Other and unspecified disorders of back	12.0	14.5	72.0	24.3	0.1
General symptoms	42.0	50.6	135.0	45.6	0.4
Symptoms involving skin and other integumentary tissue	16.0	19.3	52.0	17.6	0.7
Symptoms involving head and neck	21.0	25.3	29.0	9.8	0.0
Symptoms involving digestive system	23.0	27.7	42.0	14.2	0.0
Encounter for other and unspecified procedure and aftercare	31.0	37.3	121.0	40.9	0.6
General medical examination	11.0	13.3	45.0	15.2	0.7
Prescription Drug History					
Non-alcohol sedatives	17.0	20.5	81.0	27.4	0.2
Acid-suppressing drugs	20.0	24.1	64.0	21.6	0.6
Metformin	46.0	55.4	158.0	53.4	0.7
Sulfonylureas	26.0	31.3	96.0	32.4	0.8
Thiazolidinediones	9.0	10.8	63.0	21.3	0.0
Insulin glargine	27.0	32.5	73.0	24.7	0.2
Insulins	21.0	25.3	81.0	27.4	0.7
ACE inhibitors	38.0	45.8	143.0	48.3	0.7
NSAIDs	14.0	16.9	88.0	29.7	0.0
Fibrates	12.0	14.5	32.0	10.8	0.4
Statins	48.0	57.8	167.0	56.4	0.8
Hypotensives, angiotensin receptor antagonist	14.0	16.9	43.0	14.5	0.6
Calcium channel blocking agents	19.0	22.9	57.0	19.3	0.5
Anti-anxiety drugs	16.0	19.3	59.0	19.9	0.9
Serotonin specific reuptake inhibitor (SSRIs)	15.0	18.1	60.0	20.3	0.7
Analgesics, narcotics	44.0	53.0	140.0	47.3	0.4
Anticonvulsants	13.0	15.7	73.0	24.7	0.1
Skeletal muscle relaxants	9.0	10.8	46.0	15.5	0.3
Beta-adrenergic agents	11.0	13.3	32.0	10.8	0.5
Blood sugar diagnostics	45.0	54.2	142.0	48.0	0.3

Table 5.2 Descriptive Characteristics of Thyroid Cancer Derived from Claims from the 9 Months Prior to Case-Control Index Date

Characteristic	Chart-Confirmed Thyroid Cancer (N= 83)		Controls (N= 296)		*P*-Value
	N	%	N	%	
Lipotropics	17.0	20.5	79.0	26.7	0.3
Thyroid hormones	47.0	56.6	32.0	10.8	0.0
Thiazide and related diuretics	13.0	15.7	28.0	9.5	0.1
Loop diuretics	10.0	12.0	46.0	15.5	0.4
Penicillins	23.0	27.7	61.0	20.6	0.2
Macrolides	18.0	21.7	56.0	18.9	0.6
Quinolones	13.0	15.7	72.0	24.3	0.1
Durable medical equipment, miscellaneous (Group 1)	19.0	22.9	45.0	15.2	0.1
Diabetic supplies	4.0	4.8	12.0	4.1	0.8
Procedure					
Thyrotropin releasing hormone	39.0	47.0	69.0	23.3	0.0
T3, T4 testing	36.0	43.4	48.0	16.2	0.0
CT, soft tissue neck	13.0	15.7	1.0	0.3	0.0
Thyroid imaging	14.0	16.9	10.0	3.4	0.0
Ultrasound of head and neck	53.0	63.9	6.0	2.0	0.0
Biopsy thyroid	50.0	60.2	2.0	0.7	0.0
Thyroidectomy	28.0	33.7	0.0	0.0	0.0
Other operations on thyroid	2.0	2.4	0.0	0.0	0.0
Abdominal pain	14.0	16.9	50.0	16.9	1.0
Lipase	4.0	4.8	11.0	3.7	0.6
Amylase	3.0	3.6	13.0	4.4	0.8
Other nonspecific abnormal serum enzyme levels	0.0	0.0	7.0	2.4	0.2
Abdominal ultrasound	9.0	10.8	26.0	8.8	0.6
Biopsy of pancreas	0.0	0.0	0.0	0.0	N/A
Pancreatectomy	0.0	0.0	0.0	0.0	N/A
Endobronchial ultrasound	0.0	0.0	0.0	0.0	N/A
Magnetic resonance imaging (MRI), abdomen	1.0	1.2	5.0	1.7	0.8
Magnetic resonance cholangiopancreatography (MRCP)	0.0	0.0	0.0	0.0	N/A
Endoscopic retrograde cholangiopancreatography (ERCP)	0.0	0.0	0.0	0.0	N/A
Other operations on pancreas	0.0	0.0	0.0	0.0	N/A
X-Ray for pancreas	0.0	0.0	2.0	0.7	0.5
Micro exam of pancreas	0.0	0.0	0.0	0.0	N/A
Chest X-ray	16.0	19.3	52.0	17.6	0.7
Radiographic procedure	40.0	48.2	92.0	31.1	0.0
Basic metabolic panel	27.0	32.5	72.0	24.3	0.1
Executive profile	46.0	55.4	167.0	56.4	0.9

Table 5.2 Descriptive Characteristics of Thyroid Cancer Derived from Claims from the 9 Months Prior to Case-Control Index Date

Characteristic	Chart-Confirmed Thyroid Cancer (N= 83)		Controls (N= 296)		*P*-Value
	N	%	N	%	
Lipid panel	56.0	67.5	191.0	64.5	0.6
Urinalysis, automated, with microscopy	13.0	15.7	55.0	18.6	0.5
Microalbumin, quantitative	26.0	31.3	72.0	24.3	0.2
Creatinine, other source	25.0	30.1	64.0	21.6	0.1
Glucose, quantitative	10.0	12.0	38.0	12.8	0.8
Hemoglobin; glycosylated (A1C)	66.0	79.5	230.0	77.7	0.7
Thyroxine; free	28.0	33.7	34.0	11.5	0.0
Complete blood count (CBC)	34.0	41.0	134.0	45.3	0.5
Level IV - Surgical pathology, gross and microscopic examination abortion - spontaneous/missed Artery, biopsy bone marrow, biopsy bone exostosis brain/meninges, other than for tumor resection breast, biopsy, not requiring microscopic evaluation (truncated)	40.0	48.2	56.0	18.9	0.0
Unlisted miscellaneous pathology test	44.0	53.0	77.0	26.0	0.0
Immunization administration, one vaccine	13.0	15.7	57.0	19.3	0.5
Ophthalmological evaluation and examination	13.0	15.7	59.0	19.9	0.4
Determination of refractive state	8.0	9.6	37.0	12.5	0.5
Handling of specimen	5.0	6.0	30.0	10.1	0.3
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A problem focused history; A problem focused examination; Straightforward medical decision making.	24.0	28.9	90.0	30.4	0.8
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: An expanded problem focused history; An expanded problem focused examination; Medical decision making of low complexity.	67.0	80.7	255.0	86.1	0.2
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A detailed history; A detailed examination; Medical decision making of moderate complexity.	75.0	90.4	255.0	86.1	0.3

Table 5.2 Descriptive Characteristics of Thyroid Cancer Derived from Claims from the 9 Months Prior to Case-Control Index Date

Characteristic	Chart-Confirmed Thyroid Cancer (N= 83)		Controls (N= 296)		*P*-Value
	N	%	N	%	
Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A comprehensive history; A comprehensive examination; Medical decision making of high complexity.	27.0	32.5	61.0	20.6	0.0
Subsequent hospital care, per day, for the evaluation and management of a patient, which requires at least 2 of these 3 key components: An expanded problem focused interval history; An expanded problem focused examination; Medical decision making of moderate complexity.	10.0	12.0	46.0	15.5	0.4
Subsequent hospital care, per day, for the evaluation and management of a patient, which requires at least 2 of these 3 key components: An expanded problem focused interval history; An expanded problem focused examination; Medical decision making of moderate complexity.	19.0	22.9	49.0	16.6	0.2
Office consultation for a new or established patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical decision making of moderate complexity.	31.0	37.3	64.0	21.6	0.0
Emergency department visit for the evaluation and management of a patient, which requires these 3 key components: A detailed history; A detailed examination; and Medical decision making of moderate complexity.	7.0	8.4	34.0	11.5	0.4
Emergency department visit for the evaluation and management of a patient, which requires these 3 key components within the constraints imposed by the urgency of the patient's clinical condition and/or mental status: A comprehensive history; A comprehensive examination; and Medical decision making of high complexity.	12.0	14.5	59.0	19.9	0.3
Periodic comprehensive preventive medicine reevaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/ risk factor reduction interventions, and the ordering of laboratory/ diagnostic procedures, established patient; 40-64 years.	9.0	10.8	48.0	16.2	0.2

Table 5.2 Descriptive Characteristics of Thyroid Cancer Derived from Claims from the 9 Months Prior to Case-Control Index Date

Characteristic	Chart-Confirmed Thyroid Cancer (N= 83)		Controls (N= 296)		*P*-Value
	N	%	N	%	
Procedure Category					
Diagnostic ultrasound abdomen	13.0	15.7	35.0	11.8	0.4
Magnetic resonance imaging (MRI)	17.0	20.5	64.0	21.6	0.8
Nonoperative urinary measurements	28.0	33.7	89.0	30.1	0.5
Cardiac stress tests	11.0	13.3	38.0	12.8	0.9
Electrocardiogram	55.0	66.3	146.0	49.3	0.0
Microscopic exam (smear culture)	49.0	59.0	162.0	54.7	0.5
Radioisotopic scan/function	23.0	27.7	42.0	14.2	0.0
Physical therapy exercises/manipulation	12.0	14.5	64.0	21.6	0.1
Ophthalmologic/otologic diagnosis/treatment	23.0	27.7	104.0	35.1	0.2
Other diagnostic radiology	51.0	61.4	170.0	57.4	0.5
Prophylactic vaccinations	18.0	21.7	88.0	29.7	0.1
Other therapeutic procedure	63.0	75.9	226.0	76.4	0.9
Other lab	77.0	92.8	265.0	89.5	0.4
Procedure codes not elsewhere specified	83.0	100.0	250.0	84.5	0.0
Vaginal delivery	16.0	19.3	63.0	21.3	0.7
Health Care Services					
Critical care procedure	4.0	4.8	11.0	3.7	0.6
0-5 unique drugs dispensed	7.0	8.4	29.0	9.8	0.7
6-10 unique drugs dispensed	26.0	31.3	80.0	27.0	0.4
11-15 unique drugs dispensed	26.0	31.3	95.0	32.1	0.9
≥16 unique drugs dispensed	24.0	28.9	92.0	31.1	0.7
Hospitalization within 45 days of index	11.0	13.3	91.0	30.7	0.0
1 Anti-diabetic medication within 45 days of index	30.0	36.1	96.0	32.4	0.5
2 Anti-diabetic medications within 45 days of index	10.0	12.0	59.0	19.9	0.1
>2 Anti-diabetic medications within 45 days of index	9.0	10.8	35.0	11.8	0.8
Outpatient visit on index	72.0	86.7	208.0	70.3	0.0
Inpatient visit on index	11.0	13.3	88.0	29.7	0.0

Table 5.2 Descriptive Characteristics of Thyroid Cancer Derived from Claims from the 9 Months Prior to Case-Control Index Date

Characteristic	Chart-Confirmed Thyroid Cancer (N= 83)		Controls (N= 296)		*P*-Value
	N	%	N	%	
	Mean	Median (IQR)	Mean	Median (IQR)	*P*-Value
Days from Study Start to Index Date	2,259.4	2,401.0 (1,402.0-3,095.0)	1,970.7	1,977.5 (1,284.5-2,606.0)	0.0
Number of cardiovascular procedures	1.6	1.0 (0.0-2.0)	1.4	1.0 (0.0-2.0)	0.6
Pharmacy costs ($)	3,688.2	1,796.1 (786.5-4,409.8)	4,133.3	2,618.0 (1,114.0-4,888.1)	0.5
Medical costs ($)	6,169.0	4,623.0 (1,985.1-7,825.4)	4,790.9	2,142.1 (1,050.8-5,266.3)	0.2
Facility costs ($)	14,622.7	4,078.3 (921.2-11,842.2)	11,536.0	1,374.5 (258.4-7,312.9)	0.5
Number of inpatient days	1.0	0.0 (0.0-0.0)	1.7	0.0 (0.0-0.0)	0.3
Number of laboratory tests	24.9	19.0 (10.0-30.0)	18.5	12.0 (6.0-22.0)	0.0
Number of 3-digit diagnosis codes	22.6	21.0 (15.0-30.0)	19.5	18.0 (12.0-24.0)	0.0
Number of inpatient stays*	0.2	0.0 (0.0-0.0)	0.3	0.0 (0.0-0.0)	0.1
Number of procedures	4.1	4.0 (2.0-6.0)	4.1	3.0 (1.0-5.0)	1.0
Number of physician visits*	11.3	9.0 (6.0-15.0)	11.5	9.0 (6.0-14.0)	0.9
Emergency room visit	0.5	0.0 (0.0-1.0)	1.2	0.0 (0.0-1.0)	0.0
Number of diabetes diagnoses*	4.8	4.0 (2.0-6.0)	5.3	4.0 (2.0-6.0)	0.5
Number of diabetes drug dispensings*	5.8	5.0 (2.0-8.0)	6.6	6.0 (2.0-10.0)	0.2

* One counted per day

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 6.1. The Positive Predictive Value and Sensitivity of Algorithm-Identified Cases, Optum Research Database

Algorithm-Identified Cancer	Chart-Confirmed Cases*		Positive Predictive Value	95% Confidence Interval	Sensitivity	95% Confidence Interval
	Yes	No				
Pancreatic Cancer**						
Period 1: 6/1/2005-7/31/2010						
Yes	14	2	0.88	(0.62 - 0.98)	0.54	(0.33 - 0.73)
No	12	16	–	–	–	–
Period 2: 8/1/2010-12/31/2015						
Yes	62	19	0.77	(0.66 - 0.85)	0.72	(0.61 - 0.81)
No	24	24	–	–	–	–
Period 3: 6/1/2005-6/30/2015						
Yes	76	21	0.78	(0.69 - 0.86)	0.68	(0.58 - 0.76)
No	36	40	–	–	–	–
Thyroid Cancer (all)**						
Period 1: 6/1/2005-7/31/2010						
Yes	20	1	0.95	(0.76 - 1.00)	0.69	(0.49 - 0.85)
No	9	14	–	–	–	–
Period 2: 8/1/2010-12/31/2015						
Yes	71	11	0.87	(0.77 - 0.93)	0.86	(0.76 - 0.92)
No	12	6	–	–	–	–
Period 3: 6/1/2005-6/30/2015						
Yes	91	12	0.88	(0.81 - 0.94)	0.81	(0.73 - 0.88)
No	21	20	–	–	–	–
Non-Medullary Thyroid Cancer**						
Period 1: 6/1/2005-7/31/2010						
Yes	20	1	0.95	(0.76 - 1.00)	0.77	(0.56 - 0.91)
No	6	13	–	–	–	–
Period 2: 8/1/2010-12/31/2015						
Yes	71	11	0.87	(0.77 - 0.93)	0.89	(0.80 - 0.95)
No	9	6	–	–	–	–
Period 3: 6/1/2005-6/30/2015						
Yes	91	12	0.88	(0.81 - 0.94)	0.86	(0.78 - 0.92)
No	15	19	–	–	–	–

Table 6.1. The Positive Predictive Value and Sensitivity of Algorithm-Identified Cases, Optum Research Database

Algorithm-Identified Cancer	Chart-Confirmed Cases*		Positive Predictive Value	95% Confidence Interval	Sensitivity	95% Confidence Interval
	Yes	No				
Medullary Thyroid Cancer* **						
Period 1: 6/1/2005-7/31/2010						
Yes	3	1	0.75	(0.19-0.99)	1.00	(0.29 - 1.00)
No	0	40	–	–	–	–
Period 2: 8/1/2010-12/31/2015						
Yes	3	0	1.00	(0.29 - 1.00)	1.00	(0.29 - 1.00)
No	0	97	–	–	–	–
Period 3: 6/1/2005-6/30/2015						
Yes	6	1	0.86	(0.42 - 1.00)	1.00	(0.54 - 1.00)
No	0	137	–	–	–	–
Benign Thyroid Neoplasm**						
Period 1: 6/1/2005-7/31/2010						
Yes	11	1	0.92	(0.62 - 1.00)	0.39	(0.22 - 0.59)
No	17	6	–	–	–	–
Period 2: 8/1/2010-12/31/2015						
Yes	20	0	1.00	(0.83 - 1.00)	0.35	(0.23 - 0.49)
No	37	13	–	–	–	–
Period 3: 6/1/2005-6/30/2015						
Yes	31	1	0.97	(0.84 - 1.00)	0.36	(0.26 - 0.48)
No	54	19	–	–	–	–

* Inclusion of definite cases and probable cases from adjudication

** Application of the restricted algorithm

*** Application of the relaxed algorithm

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 6.2. Prevalence of Pancreatic Disease and Diagnostic Procedures During the Follow-Up Period, Combined Database, Matched Patients 6/1/2005−6/30/2015

	6/1/2005 to 6/30/2015				6/1/2005 to 10/31/2007				11/1/2007 to 6/30/2015			
	Exenatide (N= 47,946)		OADs (N= 84,443)		Exenatide (N = 25,612)		OADs (N = 42,423)		Exenatide (N = 40,890)		OADs (N = 67,352)	
	N	%	N	%	N	%	N	%	N	%	N	%
Pancreatic Diseases												
Malignant neoplasm of pancreas	81	0.2	168	0.2	14	0.1	45	0.1	68	0.2	126	0.2
Malignant neoplasm of head of pancreas	24	0.1	55	0.1	9	0.0	20	0.0	17	0.0	43	0.1
Malignant neoplasm of body of pancreas	9	0.0	17	0.0	2	0.0	11	0.0	9	0.0	13	0.0
Malignant neoplasm of tail of pancreas	7	0.0	12	0.0	2	0.0	10	0.0	6	0.0	8	0.0
Malignant neoplasm of pancreatic duct	3	0.0	5	0.0	1	0.0	5	0.0	2	0.0	4	0.0
Malignant neoplasm of islets of langerhans	3	0.0	5	0.0	0	0.0	1	0.0	3	0.0	4	0.0
Malignant neoplasm of other specified sites of pancreas	7	0.0	21	0.0	2	0.0	17	0.0	6	0.0	14	0.0
Malignant neoplasm of pancreas, part unspecified	56	0.1	112	0.1	13	0.1	41	0.1	49	0.1	85	0.1
Benign neoplasm of the pancreas within 60 days of diagnosis of pancreatic cancer	31	0.1	49	0.1	10	0.0	15	0.0	24	0.1	38	0.1
Pancreatic Diagnostic Procedures												
Lipase	3,634	7.6	3,943	4.7	640	2.5	999	2.4	3,120	7.6	3,074	4.6
Amylase	3,372	7.0	3,535	4.2	648	2.5	1,030	2.4	2,839	6.9	2,638	3.9
Abdominal ultrasound	6,418	13.4	8,085	9.6	1,379	5.4	2,139	5.0	5,321	13.0	6,287	9.3
Biopsy of pancreas	4	0.0	12	0.0	2	0.0	8	0.0	4	0.0	6	0.0
Pancreatectomy	17	0.0	28	0.0	9	0.0	14	0.0	14	0.0	23	0.0
Endobronchial ultrasound	13	0.0	22	0.0	0	0.0	0	0.0	13	0.0	22	0.0
Magentic resonance imaging (MRI), abdomen	888	1.9	1,162	1.4	176	0.7	274	0.6	736	1.8	923	1.4
Magnetic resonance cholangiopancreatography (MRCP)	6	0.0	6	0.0	1	0.0	1	0.0	5	0.0	5	0.0
Endoscopic retrograde cholangiopancreatography (ERCP)	165	0.3	236	0.3	36	0.1	65	0.2	137	0.3	186	0.3
Other operations on pancreas	9	0.0	18	0.0	3	0.0	7	0.0	6	0.0	11	0.0
X-ray for pancreas	314	0.7	424	0.5	67	0.3	101	0.2	251	0.6	333	0.5
Micro exam of pancreas	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Abdominal pain	10,171	21.2	13,502	16.0	2,309	9.0	3,796	8.9	8,620	21.1	10,633	15.8
Other nonspecific abnormal serum enzyme levels	750	1.6	940	1.1	97	0.4	157	0.4	664	1.6	797	1.2

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.
Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.
Includes the first year of follow-up

Table 6.2a. Prevalence of Pancreatic Disease and Diagnostic Procedures During the Follow-Up Period, Optum Research Database, Matched Patients 6/1/2005−6/30/2015

	6/1/2005 to 6/30/2015				6/1/2005 to 10/31/2007				11/1/2007 to 6/30/2015			
	Exenatide (N= 32,191)		OADs (N= 57,312)		Exenatide (N= 15,906)		OADs (N= 26,333)		Exenatide (N= 27,697)		OADs (N= 46,469)	
	N	%	N	%	N	%	N	%	N	%	N	%
Pancreatic Diseases												
Malignant neoplasm of pancreas	59	0.2	117	0.2	12	0.1	29	0.1	48	0.2	89	0.2
Malignant neoplasm of head of pancreas	19	0.1	34	0.1	7	0.0	11	0.0	14	0.1	29	0.1
Malignant neoplasm of body of pancreas	6	0.0	11	0.0	2	0.0	7	0.0	6	0.0	9	0.0
Malignant neoplasm of tail of pancreas	6	0.0	8	0.0	2	0.0	7	0.0	5	0.0	6	0.0
Malignant neoplasm of pancreatic duct	1	0.0	4	0.0	1	0.0	3	0.0	0	0.0	3	0.0
Malignant neoplasm of islets of langerhans	3	0.0	4	0.0	0	0.0	1	0.0	3	0.0	3	0.0
Malignant neoplasm of other specified sites of pancreas	4	0.0	15	0.0	2	0.0	8	0.0	3	0.0	10	0.0
Malignant neoplasm of pancreas, part unspecified	37	0.1	80	0.1	11	0.1	26	0.1	31	0.1	61	0.1
Benign neoplasm of the pancreas within 60 days of diagnosis of pancreatic cancer	22	0.1	34	0.1	8	0.1	9	0.0	16	0.1	28	0.1
Pancreatic Diagnostic Procedures												
Lipase	2,481	7.7	2,713	4.7	430	2.7	668	2.5	2,135	7.7	2,130	4.6
Amylase	2,274	7.1	2,367	4.1	422	2.7	684	2.6	1,918	6.9	1,766	3.8
Abdominal ultrasound	4,312	13.4	5,423	9.5	885	5.6	1,324	5.0	3,614	13.0	4,312	9.3
Biopsy of pancreas	4	0.0	9	0.0	2	0.0	6	0.0	4	0.0	5	0.0
Pancreatectomy	14	0.0	20	0.0	6	0.0	9	0.0	13	0.0	16	0.0
Endobronchial ultrasound	12	0.0	20	0.0	0	0.0	0	0.0	12	0.0	20	0.0
Magentic resonance imaging (MRI), abdomen	584	1.8	783	1.4	111	0.7	172	0.7	489	1.8	629	1.4
Magnetic resonance cholangiopancreatography (MRCP)	4	0.0	4	0.0	1	0.0	1	0.0	3	0.0	3	0.0
Endoscopic retrograde cholangiopancreatography (ERCP)	109	0.3	160	0.3	23	0.1	34	0.1	92	0.3	132	0.3
Other operations on pancreas	7	0.0	15	0.0	2	0.0	6	0.0	5	0.0	9	0.0
X-ray for pancreas	234	0.7	314	0.5	42	0.3	60	0.2	195	0.7	258	0.6
Micro exam of pancreas	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Abdominal pain	7,251	22.5	9,571	16.7	1,624	10.2	2,584	9.8	6,186	22.3	7,611	16.4
Other nonspecific abnormal serum enzyme levels	565	1.8	730	1.3	74	0.5	111	0.4	501	1.8	629	1.4

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.
Includes the first year of follow-up.

Table 6.2b. Prevalence of Pancreatic Disease and Diagnostic Procedures During the Follow-Up Period, Impact National Benchmark Database, Matched Patients 6/1/2005−3/31/2015

	6/1/2005 to 6/30/2015				6/1/2005 to 10/31/2007				11/1/2007 to 3/31/2015			
	Exenatide (N= 15,755)		OADs (N= 27,131)		Exenatide (N= 9,706)		OADs (N= 16,090)		Exenatide (N= 13,193)		OADs (N= 20,883)	
	N	%	N	%	N	%	N	%	N	%	N	%
Pancreatic Diseases												
Malignant neoplasm of pancreas	22	0.1	51	0.2	2	0.0	16	0.1	20	0.2	37	0.2
Malignant neoplasm of head of pancreas	5	0.0	21	0.1	2	0.0	9	0.1	3	0.0	14	0.1
Malignant neoplasm of body of pancreas	3	0.0	6	0.0	0	0.0	4	0.0	3	0.0	4	0.0
Malignant neoplasm of tail of pancreas	1	0.0	4	0.0	0	0.0	3	0.0	1	0.0	2	0.0
Malignant neoplasm of pancreatic duct	2	0.0	1	0.0	0	0.0	2	0.0	2	0.0	1	0.0
Malignant neoplasm of islets of langerhans	0	0.0	1	0.0	0	0.0	0	0.0	0	0.0	1	0.0
Malignant neoplasm of other specified sites of pancreas	3	0.0	6	0.0	0	0.0	9	0.1	3	0.0	4	0.0
Malignant neoplasm of pancreas, part unspecified	19	0.1	32	0.1	2	0.0	15	0.1	18	0.1	24	0.1
Benign neoplasm of the pancreas within 60 days of diagnosis of pancreatic cancer	9	0.1	15	0.1	2	0.0	6	0.0	8	0.1	10	0.0
Pancreatic Diagnostic Procedures												
Lipase	1,153	7.3	1,230	4.5	210	2.2	331	2.1	985	7.5	944	4.5
Amylase	1,098	7.0	1,168	4.3	226	2.3	346	2.2	921	7.0	872	4.2
Abdominal ultrasound	2,106	13.4	2,662	9.8	494	5.1	815	5.1	1,707	12.9	1,975	9.5
Biopsy of pancreas	0	0.0	3	0.0	0	0.0	2	0.0	0	0.0	1	0.0
Pancreatectomy	3	0.0	8	0.0	3	0.0	5	0.0	1	0.0	7	0.0
Endobronchial ultrasound	1	0.0	2	0.0	0	0.0	0	0.0	1	0.0	2	0.0
Magentic resonance imaging (MRI), abdomen	304	1.9	379	1.4	65	0.7	102	0.6	247	1.9	294	1.4
Magnetic resonance cholangiopancreatography (MRCP)	2	0.0	2	0.0	0	0.0	0	0.0	2	0.0	2	0.0
Endoscopic retrograde cholangiopancreatography (ERCP)	56	0.4	76	0.3	13	0.1	31	0.2	45	0.3	54	0.3
Other operations on pancreas	2	0.0	3	0.0	1	0.0	1	0.0	1	0.0	2	0.0
X-ray for pancreas	80	0.5	110	0.4	25	0.3	41	0.3	56	0.4	75	0.4
Micro exam of pancreas	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Abdominal pain	2,920	18.5	3,931	14.5	685	7.1	1,212	7.5	2,434	18.4	3,022	14.5
Other nonspecific abnormal serum enzyme levels	185	1.2	210	0.8	23	0.2	46	0.3	163	1.2	168	0.8

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.
Includes the first year of follow-up.

Table 6.3. Prevalence of Thyroid Diseases and Diagnostic Procedures During the Follow-Up Period, Combined Database, Matched Patients 6/1/2005−6/30/2015

	6/1/2005 to 6/30/2015				6/1/2005 to 3/31/2010				4/1/2010 to 6/30/2015			
	Exenatide (N= 47,946)		OADs (N= 84,443)		Exenatide (N= 39,001)		OADs (N= 66,709)		Exenatide (N= 25,521)		OADs (N= 38,144)	
	N	%	N	%	N	%	N	%	N	%	N	%
Thyroid Diseases												
Malignant neoplasm of thyroid gland	109	0.2	128	0.2	62	0.2	82	0.1	48	0.2	51	0.1
Benign neoplasm of thyroid glands	61	0.1	103	0.1	29	0.1	74	0.1	37	0.1	42	0.1
Benign neoplasm of thyroid glands within 60 days of a diagnosis of thyroid cancer	183	0.4	248	0.3	98	0.3	184	0.3	96	0.4	97	0.3
Malignant neoplasm of thyroid gland within 60 days of diagnosis of benign thyroid neoplasm	135	0.3	175	0.2	80	0.2	110	0.2	58	0.2	71	0.2
Thyroid Diagnostic Procedures												
Thyrotropin releasing hormone	19,068	39.8	25,619	30.3	13,112	33.6	18,900	28.3	10,242	40.1	11,538	30.2
T3, T4 Testing	13,089	27.3	16,331	19.3	8,607	22.1	11,772	17.6	7,174	28.1	7,587	19.9
Computerized tomography (CT), soft tissue neck	728	1.5	906	1.1	387	1.0	617	0.9	378	1.5	386	1.0
Thyroid imaging	2,705	5.6	3,208	3.8	1,440	3.7	2,136	3.2	1,452	5.7	1,479	3.9
Ultrasound of head and neck	2,477	5.2	2,700	3.2	1,404	3.6	1,800	2.7	1,364	5.3	1,276	3.3
Biopsy thyroid	898	1.9	991	1.2	490	1.3	664	1.0	441	1.7	417	1.1
Thyroidectomy	163	0.3	190	0.2	100	0.3	133	0.2	84	0.3	88	0.2
Other operations on thyroid	12	0.0	16	0.0	7	0.0	12	0.0	5	0.0	5	0.0
Therapeutic radiology	926	1.9	1,517	1.8	583	1.5	1,154	1.7	374	1.5	488	1.3

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.
Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.
Includes the first year of follow-up

Table 6.3a. Prevalence of Thyroid Diseases and Diagnostic Procedures During the Follow-Up Period, Optum Research Database, Matched Patients 6/1/2005−6/30/2015

	6/1/2005 to 6/30/2015				6/1/2005 to 3/31/2010				4/1/2010 to 6/30/2015			
	Exenatide (N= 32,191)		OADs (N= 57,312)		Exenatide (N= 25,505)		OADs (N= 43,980)		Exenatide (N= 18,166)		OADs (N= 27,647)	
	N	%	N	%	N	%	N	%	N	%	N	%
Thyroid Diseases												
Malignant neoplasm of thyroid gland	72	0.2	75	0.1	38	0.1	41	0.1	34	0.2	39	0.1
Benign neoplasm of thyroid glands	41	0.1	66	0.1	18	0.1	43	0.1	27	0.1	30	0.1
Benign neoplasm of thyroid glands within 60 days of a diagnosis of thyroid cancer	110	0.3	151	0.3	55	0.2	101	0.2	63	0.3	71	0.3
Malignant neoplasm of thyroid gland within 60 days of diagnosis of benign thyroid neoplasm	88	0.3	107	0.2	49	0.2	58	0.1	41	0.2	55	0.2
Thyroid Diagnostic Procedures												
Thyrotropin releasing hormone	12,996	40.4	17,411	30.4	8,576	33.6	12,350	28.1	7,305	40.2	8,348	30.2
T3, T4 Testing	9,302	28.9	11,783	20.6	5,912	23.2	8,184	18.6	5,318	29.3	5,827	21.1
Computerized tomography (CT), soft tissue neck	493	1.5	628	1.1	259	1.0	413	0.9	259	1.4	285	1.0
Thyroid imaging	2,637	8.2	3,099	5.4	1,375	5.4	2,019	4.6	1,440	7.9	1,459	5.3
Ultrasound of head and neck	1,618	5.0	1,795	3.1	883	3.5	1,125	2.6	918	5.1	903	3.3
Biopsy thyroid	587	1.8	658	1.1	309	1.2	412	0.9	299	1.6	304	1.1
Thyroidectomy	109	0.3	133	0.2	61	0.2	82	0.2	60	0.3	69	0.2
Other operations on thyroid	10	0.0	9	0.0	6	0.0	4	0.0	4	0.0	5	0.0
Therapeutic radiology	385	1.2	644	1.1	202	0.8	428	1.0	199	1.1	282	1.0

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.
Includes the first year of follow-up.

Table 6.3b. Prevalence of Thyroid Diseases and Diagnostic Procedures During the Follow-Up Period, Impact National Benchmark Database, Matched Patients 6/1/2005−3/31/2015

	6/1/2005 to 6/30/2015				6/1/2005 to 3/31/2010				4/1/2010 to 3/31/2015			
	Exenatide (N= 15,755)		OADs (N= 27,131)		Exenatide (N= 13,496)		OADs (N= 22,729)		Exenatide (N= 7,355)		OADs (N= 10,497)	
	N	%	N	%	N	%	N	%	N	%	N	%
Thyroid Diseases												
Malignant neoplasm of thyroid gland	37	0.2	53	0.2	24	0.2	41	0.2	14	0.2	12	0.1
Benign neoplasm of thyroid glands	20	0.1	37	0.1	11	0.1	31	0.1	10	0.1	12	0.1
Benign neoplasm of thyroid glands within 60 days of a diagnosis of thyroid cancer	73	0.5	97	0.4	43	0.3	83	0.4	33	0.4	26	0.2
Malignant neoplasm of thyroid gland within 60 days of diagnosis of benign thyroid neoplasm	47	0.3	68	0.3	31	0.2	52	0.2	17	0.2	16	0.2
Thyroid Diagnostic Procedures												
Thyrotropin releasing hormone	6,072	38.5	8,208	30.3	4,536	33.6	6,550	28.8	2,937	39.9	3,190	30.4
T3, T4 Testing	3,787	24.0	4,548	16.8	2,695	20.0	3,588	15.8	1,856	25.2	1,760	16.8
Computerized tomography (CT), soft tissue neck	235	1.5	278	1.0	128	0.9	204	0.9	119	1.6	101	1.0
Thyroid imaging	68	0.4	109	0.4	65	0.5	117	0.5	12	0.2	20	0.2
Ultrasound of head and neck	859	5.5	905	3.3	521	3.9	675	3.0	446	6.1	373	3.6
Biopsy thyroid	311	2.0	333	1.2	181	1.3	252	1.1	142	1.9	113	1.1
Thyroidectomy	54	0.3	57	0.2	39	0.3	51	0.2	24	0.3	19	0.2
Other operations on thyroid	2	0.0	7	0.0	1	0.0	8	0.0	1	0.0	0	0.0
Therapeutic radiology	541	3.4	873	3.2	380	2.8	730	3.2	173	2.4	200	1.9

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.
Includes the first year of follow-up.

Table 7. Incidence of Algorithm-identified Pancreatic Cancer Among Exenatide Initiators and Other Antidiabetic Drug Initiators (Overall and by Duration of Follow-Up)---- Intent-to-Treat Analysis (Excluding Events and Person-Time in the First Year After Drug Initiation)

Duration of Follow-Up	Events	Person-Years	Cumulative Drug Duration, Cases (Years) Min	Mean	Median	Max	IR	95% CI	Unadjusted HR	95% CI	Adjusted* HR	95% CI
Combined Databases												
Overall**												
Exenatide	31	91,446	0.14	1.44	1.06	4.12	0.34	(0.23 - 0.48)	0.77	(0.48 - 1.24)	0.76	(0.47 - 1.21)
OADs	44	98,793	0.09	1.76	1.39	7.58	0.45	(0.32 - 0.60)	Ref.	–	Ref.	–
> 1 to <2 Years												
Exenatide	7	28,360	0.14	0.79	0.64	1.61	0.25	(0.10 - 0.51)	0.56	(0.23 - 1.33)	0.54	(0.23 - 1.30)
OADs	19	38,528	0.17	0.96	0.93	1.65	0.49	(0.30 - 0.77)	Ref.	–	Ref.	–
≥ 2 to <3 Years												
Exenatide	6	20,168	0.17	1.61	1.82	2.57	0.30	(0.11 - 0.65)	0.67	(0.24 - 1.86)	0.66	(0.24 - 1.85)
OADs	10	23,395	0.09	1.45	1.69	2.99	0.43	(0.20 - 0.79)	Ref.	–	Ref.	–
≥ 3 Years												
Exenatide	18	42,918	0.17	1.63	1.02	4.12	0.42	(0.25 - 0.66)	1.04	(0.52 - 2.09)	1.02	(0.51 - 2.06)
OADs	15	36,871	0.17	2.98	2.92	7.58	0.41	(0.23 - 0.67)	Ref.	–	Ref.	–
Optum Research Database												
Overall**												
Exenatide	25	61,702	0.16	1.42	1.07	4.12	0.41	(0.26 - 0.60)	0.88	(0.51 - 1.49)	0.88	(0.51 - 1.50)
OADs	32	66,039	0.17	1.81	1.51	5.39	0.48	(0.33 - 0.68)	Ref.	–	Ref.	–
> 1 to <2 Years												
Exenatide	6	19,028	0.16	0.90	0.85	1.61	0.32	(0.12 - 0.69)	0.66	(0.25 - 1.72)	0.65	(0.25 - 1.70)
OADs	14	25,839	0.17	0.96	1.03	1.65	0.54	(0.30 - 0.91)	Ref.	–	Ref.	–
≥ 2 to <3 Years												
Exenatide	4	13,682	0.17	1.56	1.82	2.44	0.29	(0.08 - 0.75)	0.77	(0.21 - 2.77)	0.78	(0.22 - 2.84)
OADs	6	15,802	0.17	1.84	2.00	2.99	0.38	(0.14 - 0.83)	Ref.	–	Ref.	–
≥ 3 Years												
Exenatide	15	28,993	0.17	1.59	1.06	4.12	0.52	(0.29 - 0.85)	1.11	(0.51 - 2.40)	1.13	(0.52 - 2.45)
OADs	12	24,398	0.55	2.78	2.76	5.39	0.49	(0.25 - 0.86)	Ref.	–	Ref.	–

Table 7. Incidence of Algorithm-identified Pancreatic Cancer Among Exenatide Initiators and Other Antidiabetic Drug Initiators (Overall and by Duration of Follow-Up)---- Intent-to-Treat Analysis (Excluding Events and Person-Time in the First Year After Drug Initiation)

Duration of Follow-Up	Events	Person-Years	Cumulative Drug Duration, Cases (Years)				IR	95% CI	Unadjusted		Adjusted*	
			Min	Mean	Median	Max			HR	95% CI	HR	95% CI
Impact National Benchmark Database												
Overall**												
Exenatide	6	29,744	0.14	1.50	0.81	3.91	0.20	(0.07 - 0.44)	0.51	(0.19 - 1.40)	0.48	(0.18 - 1.31)
OADs	12	32,755	0.09	1.64	1.01	7.58	0.37	(0.19 - 0.64)	Ref.	–	Ref.	–
> 1 to < 2 Years			.	.	.	.						
Exenatide	1	9,332	0.14	0.14	0.14	0.14	0.11	(0.00 - 0.60)	0.28	(0.03 - 2.46)	0.27	(0.03 - 2.37)
OADs	5	12,689	0.60	0.97	0.69	1.46	0.39	(0.13 - 0.92)	Ref.	–	Ref.	–
≥ 2 to <3 Years			.	.	.	.						
Exenatide	2	6,487	0.86	1.72	1.72	2.57	0.31	(0.04 - 1.11)	0.52	(0.09 - 2.92)	0.50	(0.09 - 2.81)
OADs	4	7,593	0.09	0.86	0.75	1.86	0.53	(0.14 - 1.35)	Ref.	–	Ref.	–
≥ 3 Years			.	.	.	.						
Exenatide	3	13,925	0.74	1.81	0.77	3.91	0.22	(0.04 - 0.63)	0.76	(0.15 - 3.94)	0.74	(0.14 - 3.81)
OADs	3	12,473	0.17	3.81	3.69	7.58	0.24	(0.05 - 0.70)	Ref.	–	Ref.	–

Abbreviations: IR= Incidence rate per 1,000 person-years; HR= Hazard ratio; Ref.= Reference; CI = Confidence interval.

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.

* Adjusted for unbalanced propensity score model variables including number of antidiabetic drugs, metformin, pharmacy cost, and number of unique drugs dispensed in baseline.

** The duration is the time since one-year post drug initiation.

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 7.1. Incidence of Algorithm-identified Pancreatic Cancer Among Exenatide Initiators and Other Antidiabetic Drug Initiators (Overall and by Duration of Follow-Up)---Sensitivity Intent-to-Treat Analysis in Combined Database

Duration of Follow-Up	Events	Person-years	IR	95% CI	Unadjusted*		Adjusted**	
					HR	95% CI	HR	95% CI
Overall ≥ 6 months* **								
Exenatide	40	109,766	0.36	(0.26 - 0.50)	0.70	(0.47 - 1.05)	0.69	(0.46 - 1.03)
OADs	70	126,936	0.55	(0.43 - 0.70)	Ref.	–	Ref.	–
> 0 to ≤ 6 months								
Exenatide	12	22,003	0.55	(0.28 - 0.95)	0.50	(0.26 - 0.96)	0.50	(0.26 - 0.96)
OADs	39	37,004	1.05	(0.75 - 1.44)	Ref.	–	Ref.	–
> 6 months to ≤ 1 Year* **								
Exenatide	9	18,320	0.49	(0.22 - 0.93)	0.56	(0.26 - 1.19)	0.55	(0.26 - 1.18)
OADs	26	28,143	0.92	(0.60 - 1.35)	Ref.	–	Ref.	–
> 1 to < 2 Years								
Exenatide	7	28,360	0.25	(0.10 - 0.51)	0.56	(0.23 - 1.33)	0.54	(0.23 - 1.30)
OADs	19	38,528	0.49	(0.30 - 0.77)	Ref.	–	Ref.	–
≥ 2 to < 3 Years								
Exenatide	6	20,168	0.30	(0.11 - 0.65)	0.67	(0.24 - 1.86)	0.66	(0.24 - 1.85)
OADs	10	23,395	0.43	(0.20 - 0.79)	Ref.	–	Ref.	–
≥ 3 Years								
Exenatide	18	42,918	0.42	(0.25 - 0.66)	1.04	(0.52 - 2.09)	1.02	(0.51 - 2.06)
OADs	15	36,871	0.41	(0.23 - 0.67)	Ref.	–	Ref.	–

Abbreviations: IR= Incidence rate per 1,000 person-years; HR= Hazard ratio; Ref.= Reference; NC= Not calculable; CI = Confidence interval.

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.

* The unadjusted models are based on the propensity score matched cohorts, but do not adjust for any other variables.

** Adjusted for unbalanced propensity score model variables including number of antidiabetic drugs, metformin, pharmacy cost, and number of unique drugs dispensed in baseline.

*** The follow-up excludes events and person-time within six-months post-drug initiation.

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 7.2. Median Follow-Up Time Among Exenatide Initiators (Overall and by Duration of Follow-Up) in the Pancreatic Cancer Analysis----Intent-to-Treat Analysis, 6/1/2005−6/30/2015

Duration of Follow-Up	Number of Exenatide Initiators	Median Person-Years	Minimum Person-Years	Maximum Person-Years
Combined Databases				
Overall	47,946	1.97	0.01	10.02
> 0 to ≤1 Years	47,946	1.00	0.01	1.00
> 1 to <2 Years	33,657	1.00	0.00	1.00
≥ 2 to <3 Years	23,735	1.00	0.00	1.00
≥ 3 Years	16,987	2.21	0.00	7.03
Optum Research Database				
Overall	32,191	1.98	0.01	10.02
> 0 to ≤1 Years	32,191	1.00	0.01	1.00
> 1 to <2 Years	22,592	1.00	0.00	1.00
≥ 2 to <3 Years	15,988	1.00	0.00	1.00
≥ 3 Years	11,633	2.18	0.00	7.03
Impact National Benchmark Database				
Overall	15,755	1.95	0.01	9.81
> 0 to ≤1 Years	15,755	1.00	0.01	1.00
> 1 to < 2 Years	11,065	1.00	0.00	1.00
≥ 2 to <3 Years	7,747	1.00	0.00	1.00
≥ 3 Years	5,354	2.28	0.00	6.81

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 8. Incidence of Algorithm-Identified Pancreatic Cancer Among Exenatide Initiators and Other Antidiabetic Drug Initiators by Cumulative Duration of Exenatide Use (Excluding Events and Person-Time in the First Year After Drug Initiation)

Cumulatve Duration of Exenatide	Events	Person-years	IR	95% CI	Unadjusted		Adjusted*	
					RR	95% CI	RR	95% CI
Combined Database								
Non-Use	44	98,793	0.45	(0.32 - 0.60)	Ref.	–	Ref.	–
> 0 to < 1 year	15	46,398	0.32	(0.18 - 0.53)	0.72	(0.38 - 1.37)	0.84	(0.44 - 1.62)
≥ 1 to < 2 years	7	25,733	0.27	(0.11 - 0.56)	0.62	(0.27 - 1.43)	0.67	(0.29 - 1.55)
≥ 2 to < 3 years	5	10,402	0.48	(0.16 - 1.12)	1.10	(0.42 - 2.86)	1.09	(0.41 - 2.86)
≥ 3 years	4	8,913	0.45	(0.12 - 1.15)	1.03	(0.36 - 2.95)	0.89	(0.31 - 2.59)
P-value for trend	–	–	–	–		0.81		0.72
Optum Research Database								
Non-Use	32	66,039	0.48	(0.33 - 0.68)	Ref.	–	Ref.	–
> 0 to < 1 year	11	32,199	0.34	(0.17 - 0.61)	0.73	(0.35 - 1.56)	0.88	(0.41 - 1.91)
≥ 1 to < 2 years	7	16,979	0.41	(0.17 - 0.85)	0.89	(0.37 - 2.13)	0.96	(0.40 - 2.34)
≥ 2 to < 3 years	4	6,787	0.59	(0.16 - 1.51)	1.27	(0.43 - 3.75)	1.29	(0.43 - 3.86)
≥ 3 years	3	5,738	0.52	(0.11 - 1.53)	1.12	(0.33 - 3.82)	1.01	(0.29 - 3.50)
P-value for trend	–	–	–	–		0.78		0.82
Impact National Benchmark Database								
Non-Use	12	32,755	0.37	(0.19 - 0.64)	Ref.	–	Ref.	–
> 0 to < 1 year	4	14,199	0.28	(0.08 - 0.72)	0.72	(0.21 - 2.42)	0.77	(0.23 - 2.64)
≥ 1 to < 2 years	0	8,754	0.00	(0.00 - 0.34)	0.00	–	0.00	–
≥ 2 to < 3 years	1	3,616	0.28	(0.01 - 1.54)	0.71	(0.09 - 5.68)	0.64	(0.08 - 5.27)
≥ 3 years	1	3,175	0.31	(0.01 - 1.76)	0.80	(0.10 - 6.47)	0.63	(0.08 - 5.18)
P-value for trend	–	–	–	–		0.34		0.29

Abbreviations: IR= Incidence rate per 1,000 person-years; RR= Relative risk; Ref.= Reference; CI = Confidence interval.

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.

* Adjusted for number of antidiabetic drugs, metformin, pharmacy cost, number of unique drugs dispensed in baseline as well as time-varying OAD status.

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 8.1. Incidence of Algorithm-Identified Pancreatic Cancer Among Exenatide Initiators and Other Antidiabetic Drug Initiators---Sensitivity Analysis of Cumulative Duration of Drug Use in Combined Database (Excluding Events and Person-Time in the First Year After Drug Initiation)

Cumulative Duration of Drug Use	Events	Person-years	IR	95% CI	Unadjusted		Adjusted*	
					RR	95% CI	RR	95% CI
Combined Database								
Overall								
Exenatide	31	91,446	0.34	(0.23 - 0.48)	0.77	(0.45 - 1.30)	0.83	(0.48 - 1.42)
OADs	44	98,793	0.45	(0.32 - 0.60)	–	–	–	–
>0 to <1 year								
Exenatide	15	46,398	0.32	(0.18 - 0.53)	0.63	(0.28 - 1.40)	0.54	(0.24 - 1.22)
OADs	17	33,883	0.50	(0.29 - 0.80)	–	–	–	–
≥1 to <2 years								
Exenatide	7	25,733	0.27	(0.11 - 0.56)	0.73	(0.26 - 2.07)	0.70	(0.24 - 2.09)
OADs	14	32,812	0.43	(0.23 - 0.72)	–	–	–	–
≥2 years								
Exenatide	9	19,315	0.47	(0.21 - 0.88)	1.09	(0.42 - 2.82)	1.65	(0.62 - 4.42)
OADs	13	32,099	0.40	(0.22 - 0.69)	–	–	–	–

Abbreviations: IR= Incidence rate per 1,000 person-years; RR= Relative risk; Ref.= Reference; CI = Confidence interval.

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.

* Adjusted for number of antidiabetic drugs, metformin, pharmacy cost, number of unique drugs dispensed in baseline as well as time-varying OAD status.

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 8.2. Incidence of Algorithm-Identified Pancreatic Cancer by Cumulative Duration of Other Antidiabetic Drugs----Sensitivity Analysis in Combined Database (Excluding Events and Person-Time in the First Year After Drug Initiation)

Cumulative Duration of OAD Use	Events	Person-years	IR	95% CI	Unadjusted		Adjusted*	
					RR	95% CI	RR	95% CI
> 0 to < 1 year	17	33,883	0.50	(0.29 - 0.80)	–	–	Ref.	–
≥ 1 to < 2 years	14	32,812	0.43	(0.23 - 0.72)	0.73	(0.28 - 1.91)	0.71	(0.26 - 1.91)
≥ 2 to <3 years	6	15,603	0.38	(0.14 - 0.84)	0.87	(0.27 - 2.77)	0.73	(0.22 - 2.39)
≥ 3 years	7	16,496	0.42	(0.17 - 0.87)	0.81	(0.25 - 2.59)	0.53	(0.16 - 1.74)

Abbreviations: IR= Incidence rate per 1,000 person-years; RR= Relative risk; Ref.= Reference; CI = Confidence interval.

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.

* Adjusted for number of antidiabetic drugs, metformin, pharmacy cost, number of unique drugs dispensed in baseline as well as time-varying OAD status.

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 8.3. Median Follow-Up Time Among Exenatide Initiators (Overall and by Cumulative Duration of Exenatide Use) in the Pancreatic Cancer Analysis----As-Treated Analysis, 6/1/2005−6/30/2015

Cumulative Duration of Exenatide	Number of Exenatide Initiators	Median Person-Years	Minimum Person-Years	Maximum Person-Years
Combined Databases				
Overall	47,946	1.97	0.01	10.03
> 0 to < 1 year	47,946	1.02	0.01	9.98
≥ 1 to < 2 years	15,899	1.00	0.00	8.85
≥ 2 years	6,976	2.27	0.00	8.03
Optum Research Database				
Overall	32,191	1.98	0.01	10.03
> 0 to < 1 year	32,191	1.03	0.01	9.98
≥ 1 to < 2 years	10,366	1.00	0.00	8.85
≥ 2 years	4,520	2.34	0.00	8.03
Impact National Benchmark Database				
Overall	15,755	1.95	0.01	9.81
> 0 to < 1 year	15,755	1.00	0.01	9.69
≥ 1 to < 2 years	5,533	1.00	0.00	8.65
≥ 2 years	2,456	2.19	0.00	7.81

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 9. Incidence of Algorithm-Identified Pancreatic Cancer Among Exenatide Initiators and Other Antidiabetic Drug Initiators by Cumulative Dose of Exenatide Use (Excluding Events and Person-Time in the First Year After Drug Initiation)

Cumulative Dose of Exenatide	Events	Person-years	IR	95% CI	Unadjusted		Adjusted*	
					RR	95% CI	RR	95% CI
Combined Database								
Non-Use	44	98,793	0.45	(0.32 - 0.60)	Ref.	–	Ref.	–
≤ 1,500 mcg	8	34,274	0.23	(0.10 - 0.46)	0.52	(0.23 - 1.14)	0.63	(0.28 - 1.40)
> 1,500 to 6,325 mcg	9	25,131	0.36	(0.16 - 0.68)	0.80	(0.37 - 1.72)	0.86	(0.40 - 1.85)
> 6,325 mcg	14	32,041	0.44	(0.24 - 0.73)	1.01	(0.53 - 1.95)	0.99	(0.51 - 1.92)
P-value for trend	–	–	–	–		0.99		0.97
Optum Research Database								
Non-Use	32	66,039	0.48	(0.33 - 0.68)	Ref.	–	Ref.	–
≤ 1,500 mcg	5	24,764	0.20	(0.07 - 0.47)	0.43	(0.16 - 1.17)	0.54	(0.20 - 1.48)
> 1,500 to 6,325 mcg	8	17,426	0.46	(0.20 - 0.90)	0.99	(0.43 - 2.28)	1.07	(0.46 - 2.50)
> 6,325 mcg	12	19,512	0.61	(0.32 - 1.07)	1.32	(0.63 - 2.75)	1.31	(0.62 - 2.78)
P-value for trend	–	–	–	–		0.39		0.40
Impact National Benchmark Database								
Non-Use	12	32,755	0.37	(0.19 - 0.64)	Ref.	–	Ref.	–
≤ 1,500 mcg	3	9,511	0.32	(0.07 - 0.92)	0.80	(0.21 - 3.07)	0.94	(0.24 - 3.63)
> 1,500 to 6,325 mcg	1	7,705	0.13	(0.00 - 0.72)	0.33	(0.04 - 2.67)	0.34	(0.04 - 2.76)
> 6,325 mcg	2	12,528	0.16	(0.02 - 0.58)	0.41	(0.09 - 1.94)	0.37	(0.08 - 1.79)
P-value for trend	–	–	–	–		0.17		0.15

Abbreviations: IR= Incidence rate per 1,000 person-years; RR= Relative risk; Ref.= Reference; CI = Confidence interval.

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.

* Adjusted for number of antidiabetic drugs, metformin, pharmacy cost, number of unique drugs dispensed in baseline as well as time-varying OAD status.

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 9.1. Incidence of Algorithm-Identified Pancreatic Cancer by Cumulative Dose of Exenatide and Other Antidiabetic Drugs----Sensitivity Analysis in Combined Database (Excluding Events and Person-Time in the First Year After Drug Initiation)

Cumulative Dose	Events	Person-years	IR	95% CI	Unadjusted		Adjusted*	
					RR	95% CI	RR	95% CI
Combined Database								
Overall								
Exenatide	31	91,446	0.34	(0.23 - 0.48)	0.77	(0.45 - 1.30)	0.83	(0.48 - 1.42)
OADs	44	98,793	0.45	(0.32 - 0.60)	–	–	–	–
1st Tertile								
Exenatide	8	34,274	0.23	(0.10 - 0.46)	0.44	(0.17 - 1.12)	0.39	(0.15 - 1.00)
OADs	16	30,089	0.53	(0.30 - 0.86)	–	–	–	–
2nd Tertile								
Exenatide	9	25,131	0.36	(0.16 - 0.68)	0.79	(0.29 - 2.17)	0.76	(0.27 - 2.17)
OADs	12	25,783	0.47	(0.24 - 0.81)	–	–	–	–
3rd Tertile								
Exenatide	14	32,041	0.44	(0.24 - 0.73)	1.25	(0.54 - 2.90)	1.67	(0.70 - 3.99)
OADs	16	42,921	0.37	(0.21 - 0.61)	–	–	–	–

Abbreviations: IR= Incidence rate per 1,000 person-years; RR= Relative risk; Ref.= Reference; CI = Confidence interval.

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.

* Adjusted for number of antidiabetic drugs, metformin, pharmacy cost, number of unique drugs dispensed in baseline as well as time-varying OAD status.

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 9.2. Incidence of Algorithm-Identified Pancreatic Cancer by Cumulative Dose of Other Antidiabetic Drugs----Sensitivity Analysis in Combined Database (Excluding Events and Person-Time in the First Year After Drug Initiation)

Cumulative Dose of OADS	Events	Person-years	IR	95% CI	Unadjusted		Adjusted*	
					RR	95% CI	RR	95% CI
1st Tertile	16	30,077	0.53	(0.30 - 0.86)	Ref.	–	Ref.	–
2nd Tertile	12	25,800	0.47	(0.24 - 0.81)	0.80	(0.30 - 2.18)	0.72	(0.26 - 1.99)
3rd Tertile	16	42,916	0.37	(0.21 - 0.61)	0.66	(0.27 - 1.65)	0.52	(0.20 - 1.34)

Abbreviations: IR= Incidence rate per 1,000 person-years; RR= Relative risk; Ref.= Reference; CI = Confidence interval.

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.

* Adjusted for number of antidiabetic drugs, metformin, pharmacy cost, number of unique drugs dispensed in baseline as well as time-varying OAD status.

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 10. Incidence of Algorithm-Identified Thyroid Cancer among Exenatide Initiators and Other Antidiabetic Drug Initiators (Overall and by Duration of Follow-up)----Intent-to-Treat Analysis (Excluding Events and Person-Time in the First Year After Drug Initiation)

Duration of Follow-Up	Events	Person-years	Cumulative Drug Duration, Cases (Years)				IR	95% CI	Unadjusted		Adjusted*	
			Min	Mean	Median	Max			HR	95% CI	HR	95% CI
Combined Databases												
Overall**												
Exenatide	57	91,296	0.09	1.17	0.84	4.50	0.62	(0.47 - 0.81)	1.46	(0.97 - 2.18)	1.46	(0.98 - 2.19)
OADs	43	98,740	0.11	1.59	1.09	5.29	0.44	(0.32 - 0.59)	Ref.	–	Ref.	–
> 1 to < 2 Years												
Exenatide	18	28,343	0.09	0.75	0.68	1.61	0.64	(0.38 - 1.00)	1.38	(0.72 - 2.68)	1.38	(0.71 - 2.67)
OADs	18	38,522	0.11	0.77	0.68	2.00	0.47	(0.28 - 0.74)	Ref.	–	Ref.	–
≥ 2 to < 3 Years												
Exenatide	14	20,140	0.13	1.15	0.91	2.46	0.70	(0.38 - 1.17)	1.75	(0.75 - 4.08)	1.73	(0.74 - 4.05)
OADs	9	23,381	0.17	1.32	1.29	2.71	0.38	(0.18 - 0.73)	Ref.	–	Ref.	–
≥ 3 Years												
Exenatide	25	42,813	0.17	1.48	0.97	4.50	0.58	(0.38 - 0.86)	1.38	(0.73 - 2.60)	1.42	(0.75 - 2.69)
OADs	16	36,837	0.32	2.65	3.06	5.29	0.43	(0.25 - 0.71)	Ref.	–	Ref.	–
Optum Research Database												
Overall**												
Exenatide	39	61,598	0.09	1.20	0.96	4.24	0.63	(0.45 - 0.87)	1.78	(1.06 - 2.97)	1.78	(1.06 - 2.99)
OADs	24	66,011	0.17	1.59	1.08	4.65	0.36	(0.23 - 0.54)	Ref.	–	Ref.	–
> 1 to < 2 Years												
Exenatide	13	19,020	0.09	0.69	0.47	1.61	0.68	(0.36 - 1.17)	2.24	(0.92 - 5.44)	2.24	(0.92 - 5.44)
OADs	8	25,840	0.19	0.79	0.51	2.00	0.31	(0.13 - 0.61)	Ref.	–	Ref.	–
≥ 2 to < 3 Years												
Exenatide	9	13,664	0.15	1.23	0.99	2.46	0.66	(0.30 - 1.25)	1.64	(0.58 - 4.68)	1.61	(0.56 - 4.59)
OADs	6	15,795	0.17	1.44	1.34	2.71	0.38	(0.14 - 0.83)	Ref.	–	Ref.	–
≥ 3 Years												
Exenatide	17	28,914	0.17	1.58	1.48	4.24	0.59	(0.34 - 0.94)	1.53	(0.69 - 3.37)	1.57	(0.70 - 3.51)
OADs	10	24,376	0.33	2.32	2.57	4.65	0.41	(0.20 - 0.75)	Ref.	–	Ref.	–

Table 10. Incidence of Algorithm-Identified Thyroid Cancer among Exenatide Initiators and Other Antidiabetic Drug Initiators (Overall and by Duration of Follow-up)----Intent-to-Treat Analysis (Excluding Events and Person-Time in the First Year After Drug Initiation)

Duration of Follow-Up	Events	Person-years	Cumulative Drug Duration, Cases (Years)				IR	95% CI	Unadjusted		Adjusted*	
			Min	Mean	Median	Max			HR	95% CI	HR	95% CI
Impact National Benchmark Database												
Overall**												
Exenatide	18	29,698	0.13	1.10	0.83	4.50	0.61	(0.36 - 0.96)	1.05	(0.54 - 2.02)	1.05	(0.54 - 2.04)
OADs	19	32,729	0.11	1.58	1.09	5.29	0.58	(0.35 - 0.91)	Ref.	–	Ref.	–
> 1 to < 2 Years												
Exenatide	5	9,323	0.33	0.91	0.76	1.59	0.54	(0.17 - 1.25)	0.69	(0.23 - 2.04)	0.67	(0.23 - 1.99)
OADs	10	12,682	0.11	0.75	0.77	1.57	0.79	(0.38 - 1.45)	Ref.	–	Ref.	–
≥ 2 to < 3 Years												
Exenatide	5	6,477	0.13	1.02	0.84	2.42	0.77	(0.25 - 1.80)	1.95	(0.46 - 8.32)	2.04	(0.47 - 8.75)
OADs	3	7,586	0.17	1.10	1.09	2.03	0.40	(0.08 - 1.16)	Ref.	–	Ref.	–
≥ 3 Years												
Exenatide	8	13,899	0.17	1.27	0.85	4.50	0.58	(0.25 - 1.13)	1.12	(0.38 - 3.32)	1.17	(0.40 - 3.46)
OADs	6	12,461	0.32	3.21	3.85	5.29	0.48	(0.18 - 1.05)	Ref.	–	Ref.	–

Abbreviations: IR= Incidence rate per 1,000 person-years; HR= Hazard ratio; Ref.= Reference; CI = Confidence interval.

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.

* Adjusted for unbalanced propensity score model variables including number of antidiabetic drugs, metformin, pharmacy cost, and number of unique drugs dispensed in baseline.

** The duration is the time since one-year post drug initiation

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 10.1. Incidence of Algorithm-Identified Thyroid Cancer Among Exenatide Initiators and Other Antidiabetic Drug Initiators (Overall and by Duration of Follow-up)----Sensitivity Intent-to-Treat Analysis in Combined Database

Duration of Follow-Up	Events	Person-years	IR	95% CI	Unadjusted*		Adjusted**	
					HR	95% CI	HR	95% CI
Overall ≥ 6 months* **								
Exenatide	70	109,610	0.64	(0.50 - 0.81)	1.35	(0.96 - 1.92)	1.36	(0.96 - 1.94)
OADs	62	126,885	0.49	(0.37 - 0.63)	Ref.	–	Ref.	–
> 0 to ≤ 6 months								
Exenatide	18	21,999	0.82	(0.48 - 1.29)	0.81	(0.46 - 1.44)	0.83	(0.46 - 1.47)
OADs	35	37,007	0.95	(0.66 - 1.32)	Ref.	–	Ref.	–
> 6 months to ≤ 1 Year* **								
Exenatide	13	18,314	0.71	(0.38 - 1.21)	1.08	(0.53 - 2.20)	1.10	(0.54 - 2.25)
OADs	19	28,145	0.68	(0.41 - 1.05)	Ref.	–	Ref.	–
> 1 to < 2 Years								
Exenatide	18	28,343	0.64	(0.38 - 1.00)	1.38	(0.72 - 2.68)	1.38	(0.71 - 2.67)
OADs	18	38,522	0.47	(0.28 - 0.74)	Ref.	–	Ref.	–
≥ 2 to < 3 Years								
Exenatide	14	20,140	0.70	(0.38 - 1.17)	1.75	(0.75 - 4.08)	1.73	(0.74 - 4.05)
OADs	9	23,381	0.38	(0.18 - 0.73)	Ref.	–	Ref.	–
≥ 3 Years								
Exenatide	25	42,813	0.58	(0.38 - 0.86)	1.38	(0.73 - 2.60)	1.42	(0.75 - 2.69)
OADs	16	36,837	0.43	(0.25 - 0.71)	Ref.	–	Ref.	–

Abbreviations: IR= Incidence rate per 1,000 person-years; HR= Hazard ratio; Ref.= Reference; NC= Not calculable; CI = Confidence interval.

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.

* The unadjusted models are based on the propensity score matched cohorts, but do not adjust for any other variables.

** Adjusted for unbalanced propensity score model variables including number of antidiabetic drugs, metformin, pharmacy cost, and number of unique drugs dispensed in baseline.

*** The follow-up excludes events and person-time within six-months post-drug initiation.

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 10.2. Median Follow-Up Time Among Exenatide Initiators (Overall and by Duration of Follow-Up) in the Thyroid Cancer Analysis----Intent-to-Treat Analysis, 6/1/2005−6/30/2015

Duration of Follow-Up	Number of Exenatide Initiators	Median Person-Years	Minimum Person-Years	Maximum Person-Years
Combined Databases				
Overall	47,946	1.97	0.01	10.02
> 0 to ≤1 Years	47,946	1.00	0.01	1.00
> 1 to <2 Years	33,644	1.00	0.00	1.00
≥ 2 to <3 Years	23,710	1.00	0.00	1.00
≥ 3 Years	16,956	2.21	0.00	7.03
Optum Research Database				
Overall	32,191	1.98	0.01	10.02
> 0 to ≤1 Years	32,191	1.00	0.01	1.00
> 1 to <2 Years	22,586	1.00	0.00	1.00
≥ 2 to <3 Years	15,972	1.00	0.00	1.00
≥ 3 Years	11,614	2.18	0.00	7.03
Impact National Benchmark Database				
Overall	15,755	1.95	0.01	9.81
> 0 to ≤1 Years	15,755	1.00	0.01	1.00
> 1 to < 2 Years	11,058	1.00	0.00	1.00
≥ 2 to <3 Years	7,738	1.00	0.00	1.00
≥ 3 Years	5,342	2.28	0.00	6.81

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 11. Incidence of Algorithm-Identified Thyroid Cancer Among Exenatide Initiators and Other Antidiabetic Drug Initiators by Cumulative Duration of Exenatide Use (Excluding Events and Person-Time in the First Year After Drug Initiation)

Cumulative Duration of Exenatide	Events	Person-years	IR	95% CI	Unadjusted		Adjusted*	
					RR	95% CI	RR	95% CI
Combined Database								
Non-Use	43	98,740	0.44	(0.32 - 0.59)	Ref.	–	Ref.	–
> 0 to < 1 year	33	46,319	0.71	(0.49 - 1.00)	1.56	(0.93 - 2.61)	1.53	(0.91 - 2.58)
≥ 1 to < 2 years	13	25,692	0.51	(0.27 - 0.87)	1.10	(0.57 - 2.15)	1.09	(0.56 - 2.13)
≥ 2 to < 3 years	8	10,385	0.77	(0.33 - 1.52)	1.68	(0.76 - 3.70)	1.66	(0.74 - 3.69)
≥ 3 years	3	8,900	0.34	(0.07 - 0.99)	0.73	(0.22 - 2.42)	0.72	(0.22 - 2.39)
P-value for trend	–	–	–	–		0.80		0.84
Optum Research Database								
Non-Use	24	66,011	0.36	(0.23 - 0.54)	Ref.	–	Ref.	–
> 0 to < 1 year	21	32,144	0.65	(0.40 - 1.00)	1.69	(0.87 - 3.31)	1.56	(0.79 - 3.07)
≥ 1 to < 2 years	10	16,953	0.59	(0.28 - 1.08)	1.53	(0.68 - 3.42)	1.39	(0.61 - 3.15)
≥ 2 to < 3 years	6	6,773	0.89	(0.33 - 1.93)	2.30	(0.89 - 5.94)	2.12	(0.81 - 5.57)
≥ 3 years	2	5,727	0.35	(0.04 - 1.26)	0.90	(0.21 - 3.97)	0.84	(0.19 - 3.72)
P-value for trend	–	–	–	–		0.34		0.48
Impact National Benchmark Database								
Non-Use	19	32,729	0.58	(0.35 - 0.91)	Ref.	–	Ref.	–
> 0 to < 1 year	12	14,175	0.85	(0.44 - 1.48)	1.41	(0.63 - 3.16)	1.44	(0.63 - 3.28)
≥ 1 to < 2 years	3	8,739	0.34	(0.07 - 1.00)	0.57	(0.16 - 2.03)	0.60	(0.17 - 2.14)
≥ 2 to < 3 years	2	3,611	0.55	(0.07 - 2.00)	0.92	(0.20 - 4.13)	0.95	(0.21 - 4.32)
≥ 3 years	1	3,173	0.32	(0.01 - 1.76)	0.52	(0.07 - 4.04)	0.53	(0.07 - 4.10)
P-value for trend	–	–	–	–		0.41		0.45

Abbreviations: IR= Incidence rate per 1,000 person-years; RR= Relative risk; Ref.= Reference; CI = Confidence interval.

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.

* Adjusted for number of antidiabetic drugs, metformin, pharmacy cost, number of unique drugs dispensed in baseline as well as time-varying OAD status.

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 11.1. Incidence of Algorithm-Identified Thyroid Cancer Among Exenatide Initiators and Other Antidiabetic Drug Initiators---Sensitivity Analysis of Cumulative Duration of Drug Use in Combined Database (Excluding Events and Person-Time in the First Year After Drug Initiation)

Cumulative Duration of Drug Use	Events	Person-years	IR	95% CI	Unadjusted		Adjusted*	
					RR	95% CI	RR	95% CI
Combined Database								
Overall								
Exenatide	57	91,296	0.62	(0.47 - 0.81)	1.36	(0.86 - 2.17)	1.34	(0.84 - 2.15)
OADs	43	98,740	0.44	(0.32 - 0.59)	–	–	–	–
>0 to <1 year								
Exenatide	33	46,319	0.71	(0.49 - 1.00)	1.16	(0.60 - 2.25)	1.13	(0.58 - 2.20)
OADs	21	33,859	0.62	(0.38 - 0.95)	–	–	–	–
≥1 to <2 years								
Exenatide	13	25,692	0.51	(0.27 - 0.87)	2.10	(0.72 - 6.15)	1.96	(0.65 - 5.89)
OADs	8	32,802	0.24	(0.11 - 0.48)	–	–	–	–
≥2 years								
Exenatide	11	19,285	0.57	(0.28 - 1.02)	1.11	(0.47 - 2.65)	1.01	(0.40 - 2.52)
OADs	14	32,078	0.44	(0.24 - 0.73)	–	–	–	–

Abbreviations: IR= Incidence rate per 1,000 person-years; RR= Relative risk; Ref.= Reference; CI = Confidence interval.

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.

* Adjusted for number of antidiabetic drugs, metformin, pharmacy cost, number of unique drugs dispensed in baseline as well as time-varying OAD status.

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 11.2. Incidence of Algorithm-Identified Thyroid Cancer by Cumulative Duration of Other Antidiabetic Drugs----Sensitivity Analysis in Combined Database (Excluding Events and Person-Time in the First Year After Drug Initiation)

Cumulative Duration of OAD Use	Events	Person-years	IR	95% CI	Unadjusted		Adjusted*	
					RR	95% CI	RR	95% CI
> 0 to < 1 year	21	33,859	0.62	(0.38 - 0.95)	Ref.	–	Ref.	–
≥ 1 to < 2 years	8	32,802	0.24	(0.11 - 0.48)	0.39	(0.13 - 1.14)	0.43	(0.14 - 1.33)
≥ 2 to <3 years	6	15,600	0.38	(0.14 - 0.84)	0.63	(0.19 - 2.07)	0.71	(0.21 - 2.45)
≥ 3 years	8	16,479	0.49	(0.21 - 0.96)	1.00	(0.38 - 2.68)	1.14	(0.40 - 3.26)

Abbreviations: IR= Incidence rate per 1,000 person-years; RR= Relative risk; Ref.= Reference; CI = Confidence interval.

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.

* Adjusted for number of antidiabetic drugs, metformin, pharmacy cost, number of unique drugs dispensed in baseline as well as time-varying OAD status.

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 11.3. Median Follow-Up Time Among Exenatide Initiators (Overall and by Cumulative Duration of Exenatide Use) in the Thyroid Cancer Analysis----As-Treated Analysis, 6/1/2005−6/30/2015

Cumulative Duration of Exenatide	Number of Exenatide Initiators	Median Person-Years	Minimum Person-Years	Maximum Person-Years
Combined Databases				
Overall	47,946	1.97	0.01	10.03
> 0 to < 1 year	47,946	1.02	0.01	9.98
≥ 1 to < 2 years	15,886	1.00	0.00	8.85
≥ 2 years	6,968	2.27	0.00	8.03
Optum Research Database				
Overall	32,191	1.98	0.01	10.03
> 0 to < 1 year	32,191	1.03	0.01	9.98
≥ 1 to < 2 years	10,361	1.00	0.00	8.85
≥ 2 years	4,516	2.33	0.00	8.03
Impact National Benchmark Database				
Overall	15,755	1.95	0.01	9.81
> 0 to < 1 year	15,755	1.00	0.01	9.69
≥ 1 to < 2 years	5,525	1.00	0.00	8.65
≥ 2 years	2,452	2.19	0.00	7.81

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 12. Incidence of Algorithm-Identified Thyroid Cancer Among Exenatide Initiators and Other Antidiabetic Drug Initiators by Cumulative Dose of Exenatide Use (Excluding Events and Person-Time in the First Year After Drug Initiation)

Cumulative Dose of Exenatide	Events	Person-years	IR	95% CI	Unadjusted		Adjusted*	
					RR	95% CI	RR	95% CI
Combined Database								
Non-Use	43	98,740	0.44	(0.32 - 0.59)	Ref.	–	Ref.	–
≤ 1,500 mcg	25	34,177	0.73	(0.47 - 1.08)	1.61	(0.93 - 2.79)	1.59	(0.91 - 2.77)
> 1,500 to 6,325 mcg	15	25,101	0.60	(0.33 - 0.99)	1.31	(0.69 - 2.47)	1.28	(0.67 - 2.42)
> 6,325 mcg	17	32,018	0.53	(0.31 - 0.85)	1.15	(0.62 - 2.12)	1.13	(0.61 - 2.12)
P-value for trend	–	–	–	–		0.67		0.71
Optum Research Database								
Non-Use	24	66,011	0.36	(0.23 - 0.54)	Ref.	–	Ref.	–
≤ 1,500 mcg	16	24,696	0.65	(0.37 - 1.05)	1.68	(0.82 - 3.42)	1.55	(0.75 - 3.19)
> 1,500 to 6,325 mcg	11	17,410	0.63	(0.32 - 1.13)	1.64	(0.75 - 3.58)	1.49	(0.67 - 3.28)
> 6,325 mcg	12	19,491	0.62	(0.32 - 1.08)	1.60	(0.74 - 3.43)	1.47	(0.67 - 3.22)
P-value for trend	–	–	–	–		0.22		0.33
Impact National Benchmark Database								
Non-Use	19	32,729	0.58	(0.35 - 0.91)	Ref.	–	Ref.	–
≤ 1,500 mcg	9	9,481	0.95	(0.43 - 1.80)	1.58	(0.66 - 3.77)	1.62	(0.67 - 3.94)
> 1,500 to 6,325 mcg	4	7,691	0.52	(0.14 - 1.33)	0.86	(0.28 - 2.70)	0.88	(0.28 - 2.76)
> 6,325 mcg	5	12,527	0.40	(0.13 - 0.93)	0.66	(0.23 - 1.89)	0.69	(0.24 - 1.99)
P-value for trend	–	–	–	–		0.39		0.43

Abbreviations: IR= Incidence rate per 1,000 person-years; RR= Relative risk; Ref.= Reference; CI = Confidence interval.

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.

* Adjusted for number of antidiabetic drugs, metformin, pharmacy cost, number of unique drugs dispensed in baseline as well as time-varying OAD status.

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 12.1. Incidence of Algorithm-Identified Thyroid Cancer by Cumulative Dose of Exenatide and Other Antidiabetic Drugs---- Sensitivity Analysis in Combined Database (Excluding Events and Person-Time in the First Year After Drug Initiation)

Cumulative Dose	Events	Person-years	IR	95% CI	Unadjusted		Adjusted*	
					RR	95% CI	RR	95% CI
Combined Database								
Overall								
Exenatide	57	91,296	0.62	(0.47 - 0.81)	1.36	(0.86 - 2.17)	1.34	(0.84 - 2.15)
OADs	43	98,740	0.44	(0.32 - 0.59)	Ref.	–	Ref.	–
1st Tertile								
Exenatide	25	34,177	0.73	(0.47 1.08)	1.35	(0.64 - 2.85)	1.26	(0.59 - 2.68)
OADs	15	30,051	0.50	(0.28 0.82)	Ref.	–	Ref.	–
2nd Tertile								
Exenatide	15	25,101	0.60	(0.33 - 0.99)	1.36	(0.54 - 3.41)	1.62	(0.63 - 4.16)
OADs	13	25,779	0.50	(0.27 - 0.86)	Ref.	–	Ref.	–
3rd Tertile								
Exenatide	17	32,018	0.53	(0.31 - 0.85)	1.32	(0.61 - 2.89)	1.13	(0.50 - 2.55)
OADs	15	42,910	0.35	(0.20 - 0.58)	Ref.	–	Ref.	–

Abbreviations: IR= Incidence rate per 1,000 person-years; RR= Relative risk; Ref.= Reference; CI = Confidence interval.

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.

* Adjusted for number of antidiabetic drugs, metformin, pharmacy cost, number of unique drugs dispensed in baseline as well as time-varying OAD status.

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 12.2. Incidence of Algorithm-Identified Thyroid Cancer by Cumulative Dose of Other Antidiabetic Drugs----Sensitivity Analysis in Combined Database (Excluding Events and Person-Time in the First Year After Drug Initiation)

Cumulative Dose of OADs	Events	Person-years	IR	95% CI	Unadjusted		Adjusted*	
					RR	95% CI	RR	95% CI
1st Tertile	15	30,046	0.50	(0.28 - 0.82)	Ref.	–	Ref.	–
2nd Tertile	13	25,783	0.50	(0.27 - 0.86)	0.79	(0.29 - 2.15)	0.88	(0.32 - 2.43)
3rd Tertile	15	42,911	0.35	(0.20 - 0.58)	0.72	(0.30 - 1.75)	0.84	(0.33 - 2.17)

Abbreviations: IR= Incidence rate per 1,000 person-years; RR= Relative risk; Ref.= Reference; CI = Confidence interval.

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and insulins.

* Adjusted for number of antidiabetic drugs, metformin, pharmacy cost, number of unique drugs dispensed in baseline as well as time-varying OAD status.

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 13. Incidence of Algorithm-Identified Pancreatic and Thyroid Cancer Among Patients with and without Concurrent Use of Insulins----Intent-to-Treat Analysis (Excluding Events and Person-Time in the First Year After Drug Initiation), Combined Database

	Events	Person-Years	IR	95% CI
Pancreatic Cancer				
Concurrent use of exenatide and insulins	4	14,023	0.3	(0.1 - 0.7)
Exenatide without concurrent use of insulins	27	77,424	0.4	(0.2 - 0.5)
Concurrent use of OADs and insulins	20	42,454	0.5	(0.3 - 0.7)
OADs without concurrent use of insulins	24	56,340	0.4	(0.3 - 0.6)
Thyroid Cancer				
Concurrent use of exenatide and insulins	8	14,016	0.6	(0.3 - 1.1)
Exenatide without concurrent use of insulins	49	77,280	0.6	(0.5 - 0.8)
Concurrent use of OADs and insulins	19	42,444	0.5	(0.3 - 0.7)
OADs without concurrent use of insulins	24	56,296	0.4	(0.3 - 0.6)

Abbreviations: IR= Incidence rate per 1,000 person-years; Ref.= Reference; CI = Confidence interval.

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

Table 14. Relative Risks of Chart-Confirmed Pancreatic and Thyroid Cancer Comparing Exenatide Initiators with Other Antidiabetic Drug Initiators in the Nested Case-Control Study*

	Cases (N= 169)		Controls (N= 296)		Crude RR (95% CI)	Adjusted RR (95% CI)**
	N	%	N	%		
Pancreatic Cancer						
Exenatide	4	5.4	70	94.6	0.17 (0.06 - 0.50)	0.48 (0.25 - 0.91)
OADs	82	26.6	226	73.4	Ref.	Ref.
Thyroid Cancer						
Exenatide	12	14.6	70	85.4	0.74 (0.37 - 1.50)	0.87 (0.59 - 1.29)
OADs	71	23.9	226	76.1	Ref.	Ref.

Abbreviations: RR= Relative risk; Ref.= Reference; CI = Confidence interval.

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, non-sulfonylureas, pramlintide, alpha-glucosidase inhibitors, and

* Data from ORD database only

** Adjusted for age, gender, race, BMI, alcohol, smoking, systolic blood pressure, hemoglobin A1c, visit type (in- or outpatient) on index, number of inpatient visits in calendar block, and number of outpatient visits in calendar block. .

Follow-up ended 6/30/2015.

Table 15. Incidence of Algorithm-Identified Subgroups of Thyroid Neoplasm among Exenatide Initiators and Other Antidiabetic Drug Initiators----Intent-to-Treat Analysis (Excluding Events and Person-Time in the First Year After Drug Initiation), Combined Database

	Events	Person-Years	IR	95% CI
Benign Thyroid Neoplasm				
Exenatide	11	91,469	0.12	(0.06 - 0.22)
OADs	11	98,847	0.11	(0.06 - 0.20)
Medullary Thyroid Cancer				
Exenatide	2	91,296	0.02	(0.00 - 0.08)
OADs	3	98,740	0.03	(0.01 - 0.09)
Non-Medullary Thyroid Cancer				
Exenatide	55	91,296	0.60	(0.45 - 0.78)
OADs	40	98,740	0.41	(0.29 - 0.55)

Abbreviations: IR= Incidence rate per 1,000 person-years; CI = Confidence interval.

Note: OADs (other antidiabetic drugs) include metformin, thiazolidinediones, sulfonylureas, pramlintide, alpha-glucosidase

Follow-up ended 6/30/2015 in the ORD and 3/31/2015 in Impact.

16. FIGURES

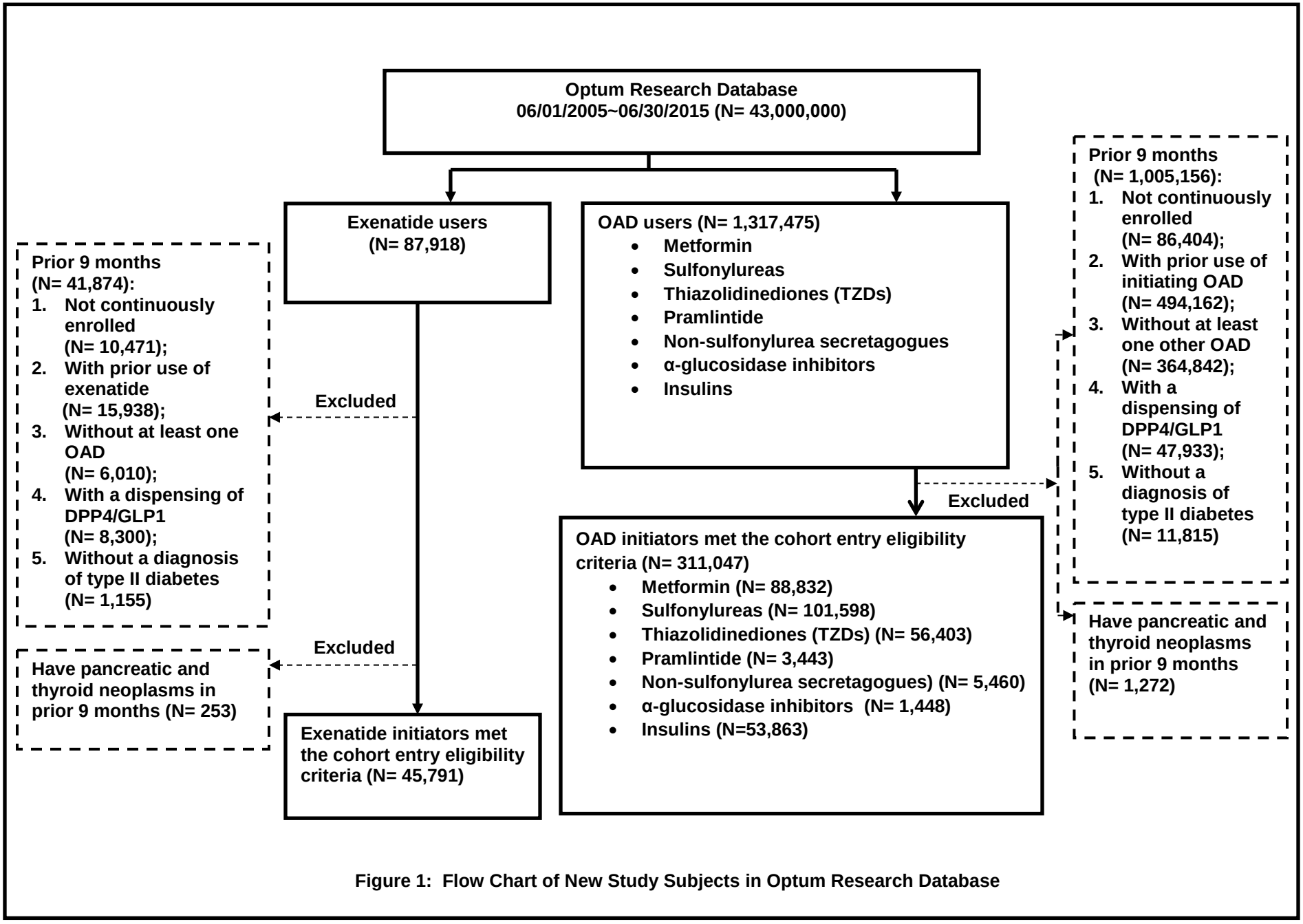


Figure 1: Flow Chart of New Study Subjects in Optum Research Database

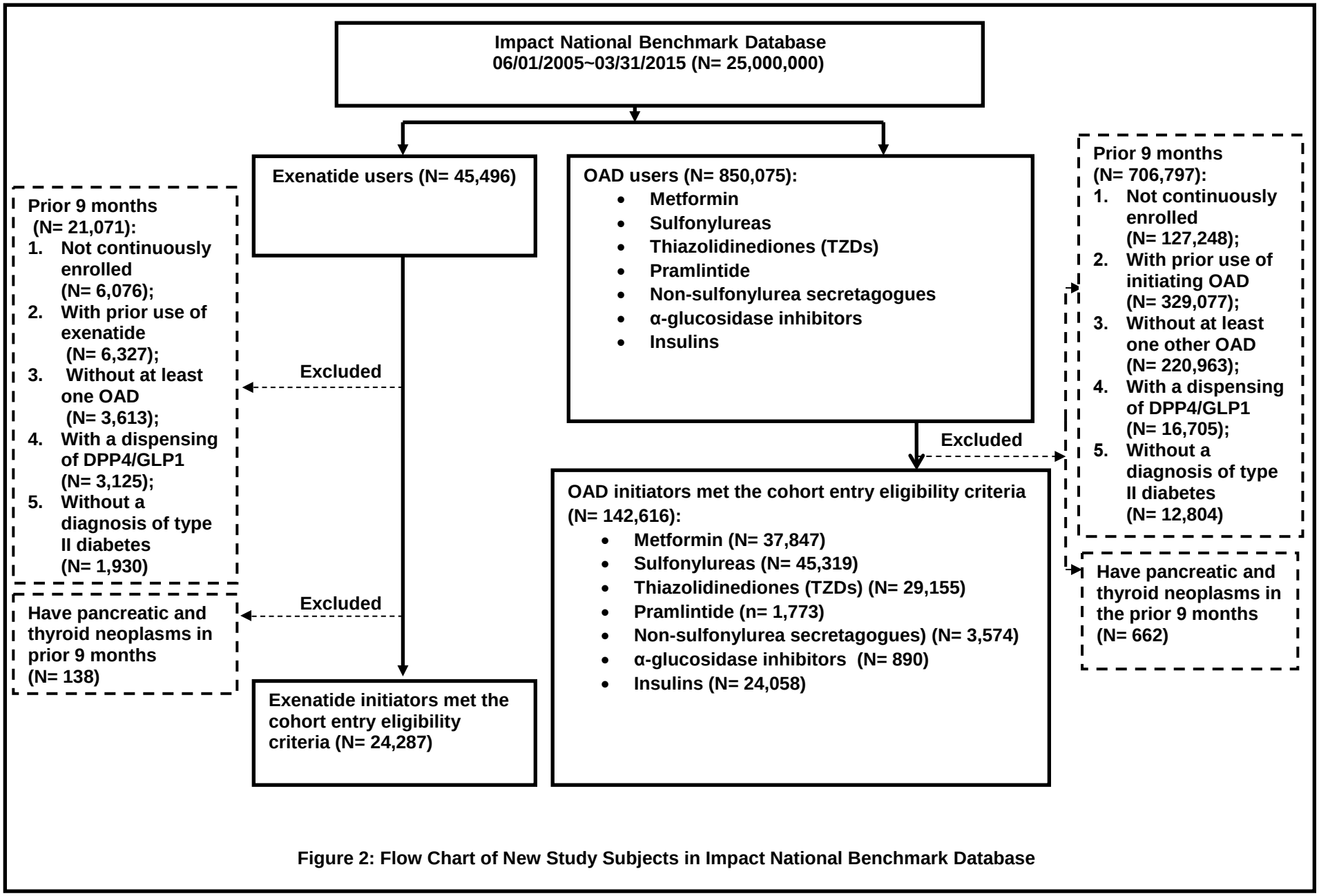


Figure 2: Flow Chart of New Study Subjects in Impact National Benchmark Database

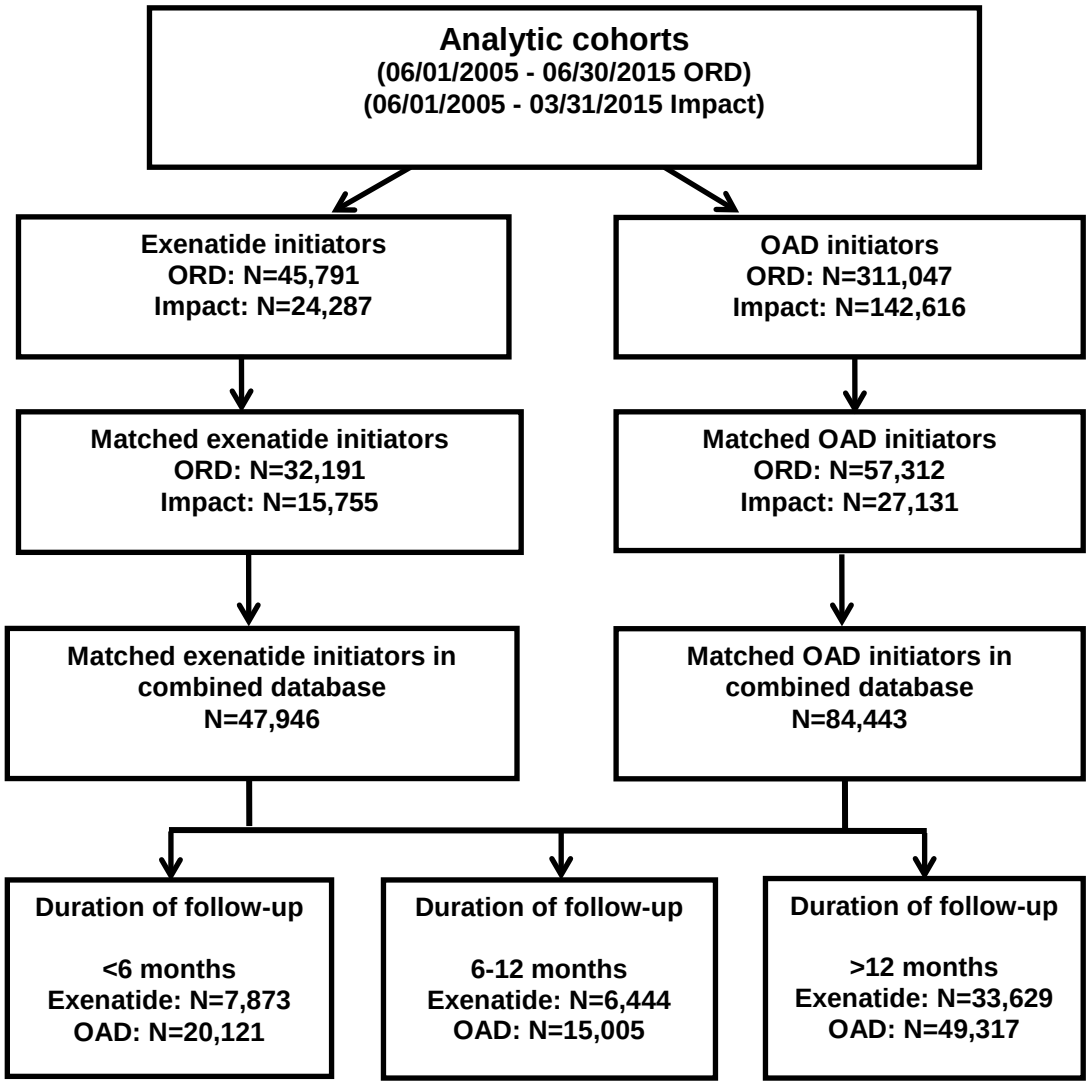


Figure 3: Flow Chart for Combined Initiators in Analytic File

Figure 4a Distribution of Propensity Score by Study Cohorts Before Matching

Optum Research Database

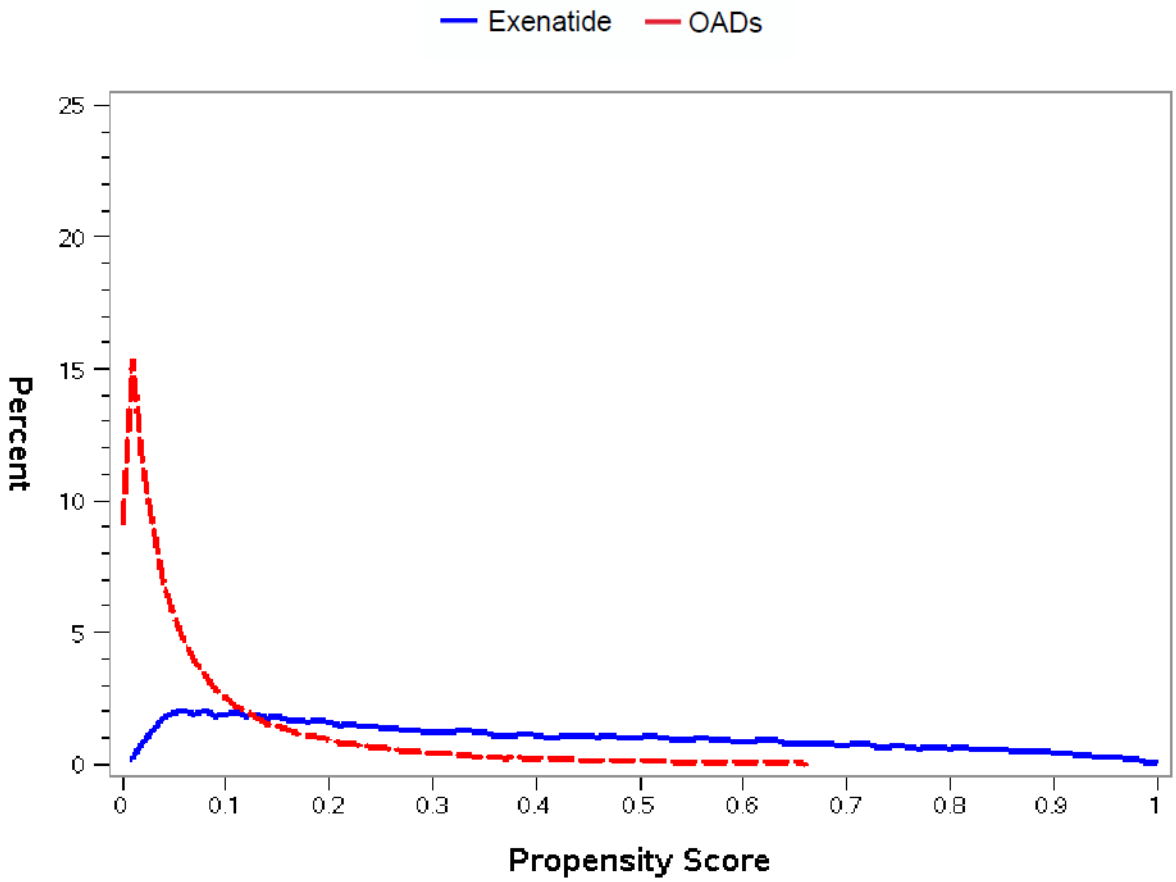


Figure 4b Distribution of Propensity Score by Study Cohorts Before Matching

Impact Database

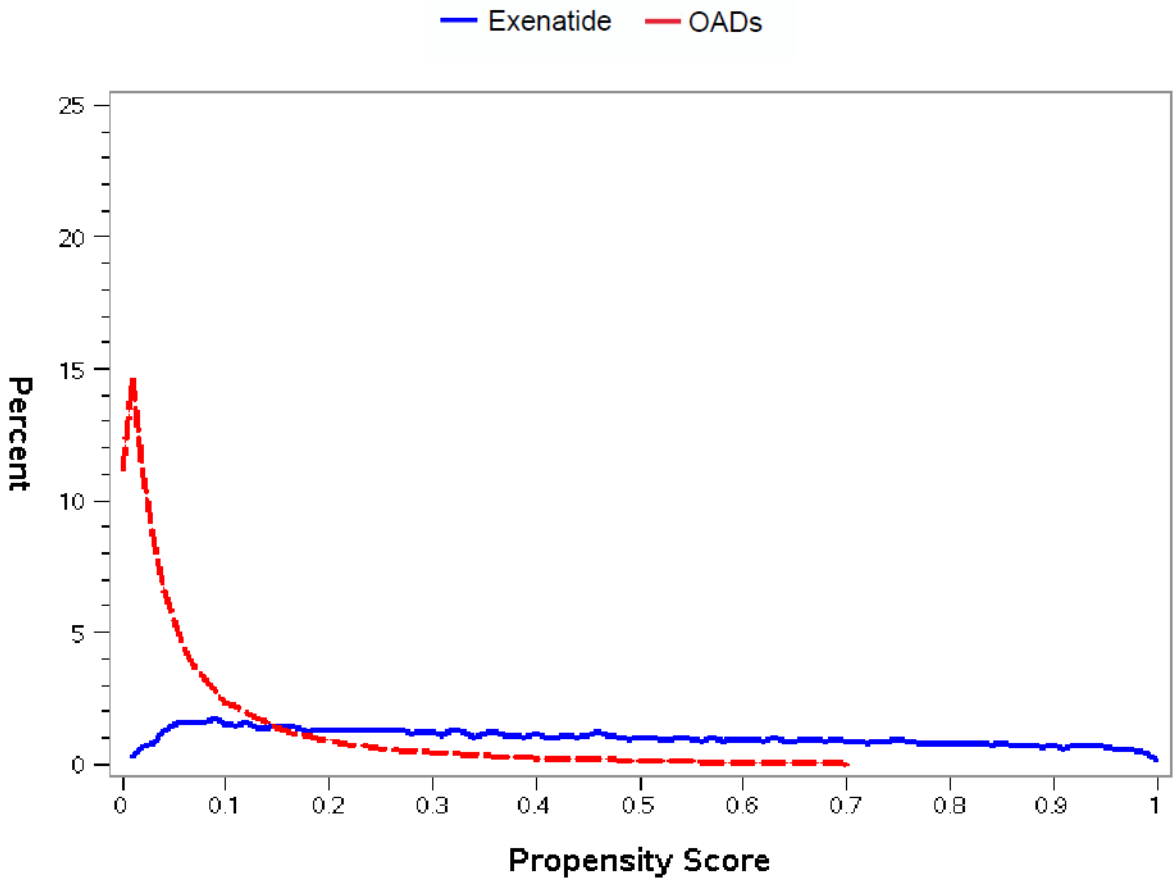


Figure 5a Distribution of Propensity Score by Study Cohorts After Matching

Optum Research Database

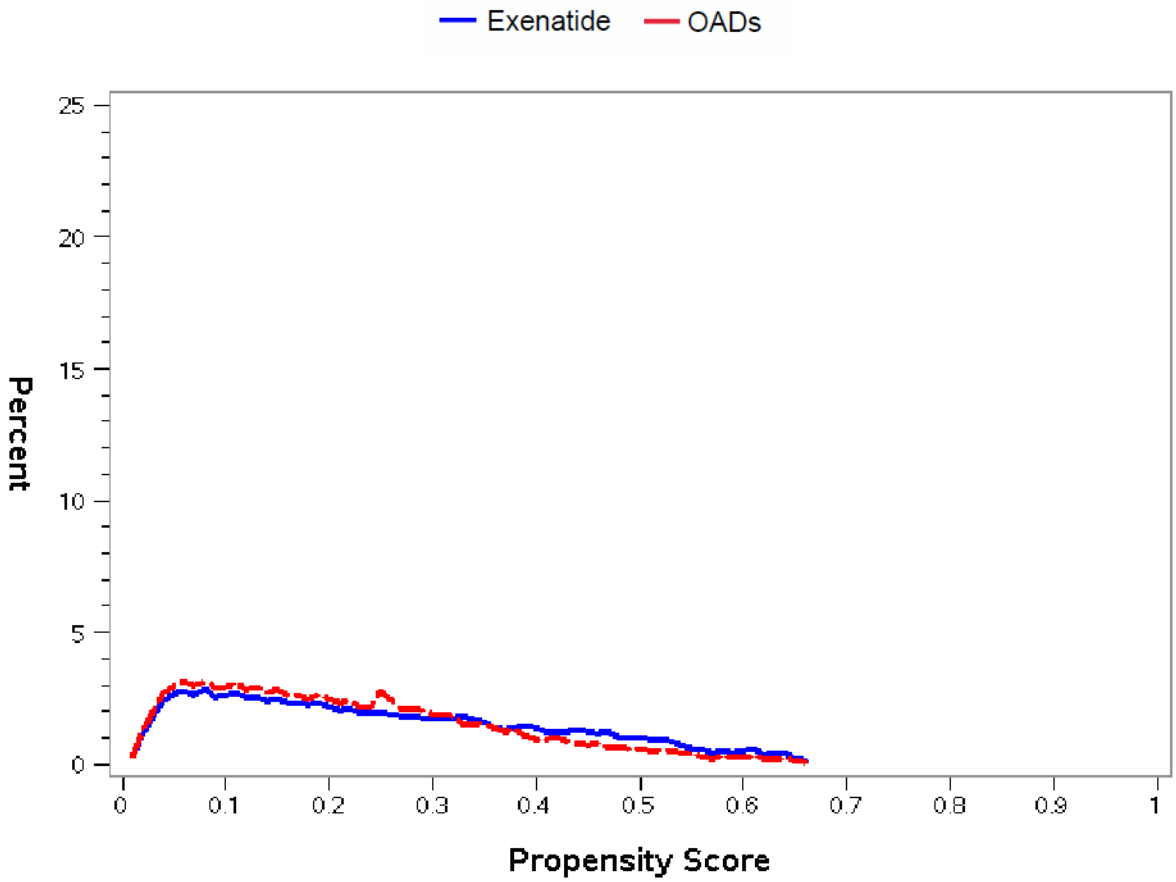


Figure 5b Distribution of Propensity Score by Study Cohorts After Matching

Impact Database

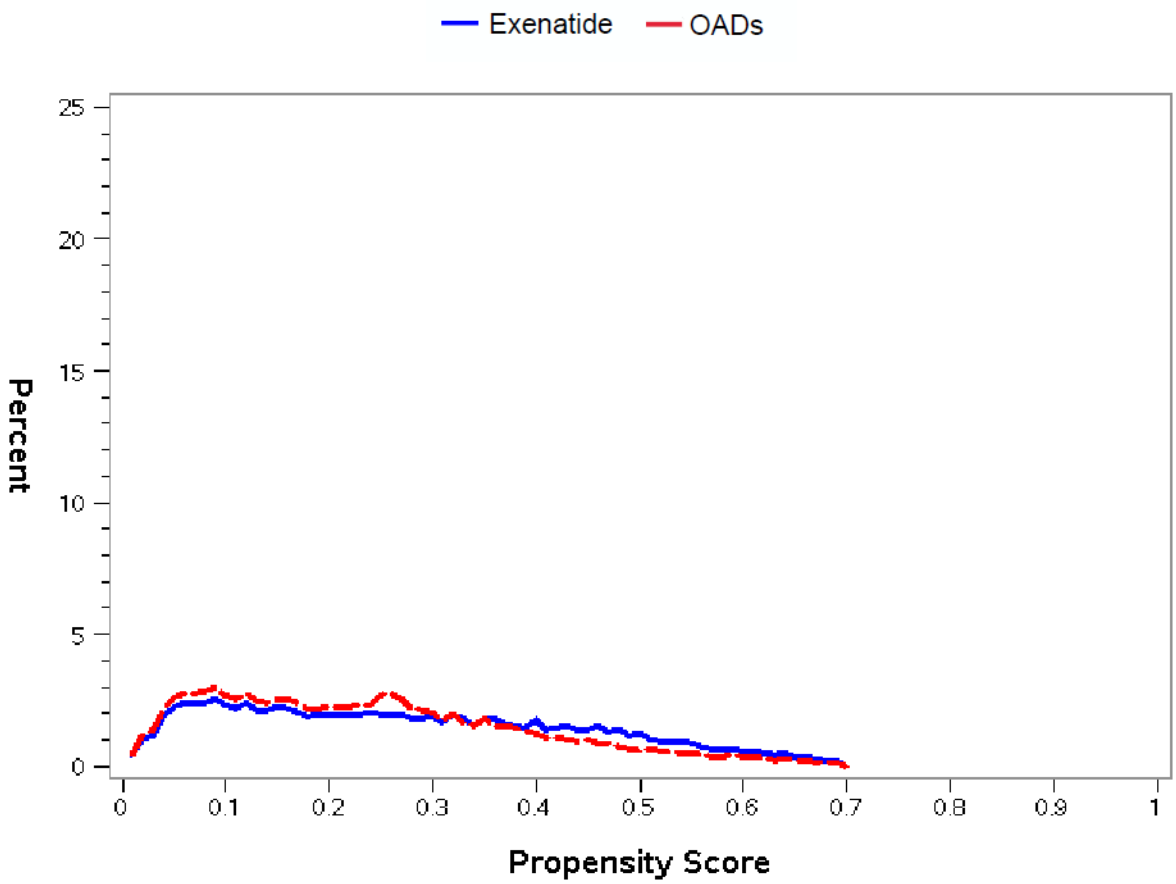


Figure 6 Survival Plot for Time to Algorithm–Identified Pancreatic Cancer Stratified by Initiating Drug Cohort – Combined Database

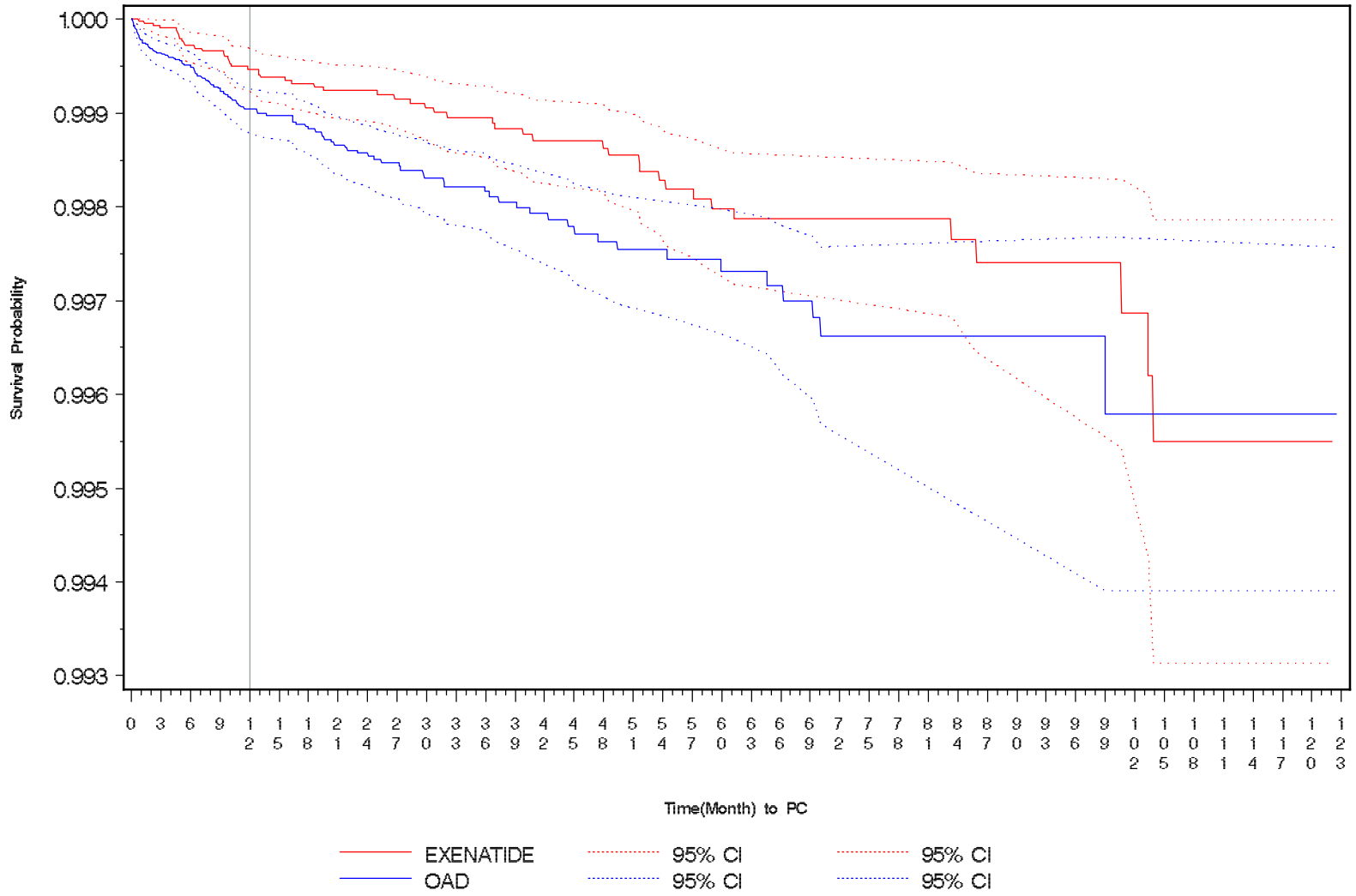


Figure 7: Histogram Plot of Cumulative Exenatide Duration,
As-Treated Analysis, Pancreatic Cancer, Combined Database,
(Excluding Events and Person-Time in the First Year After Drug Initiation)

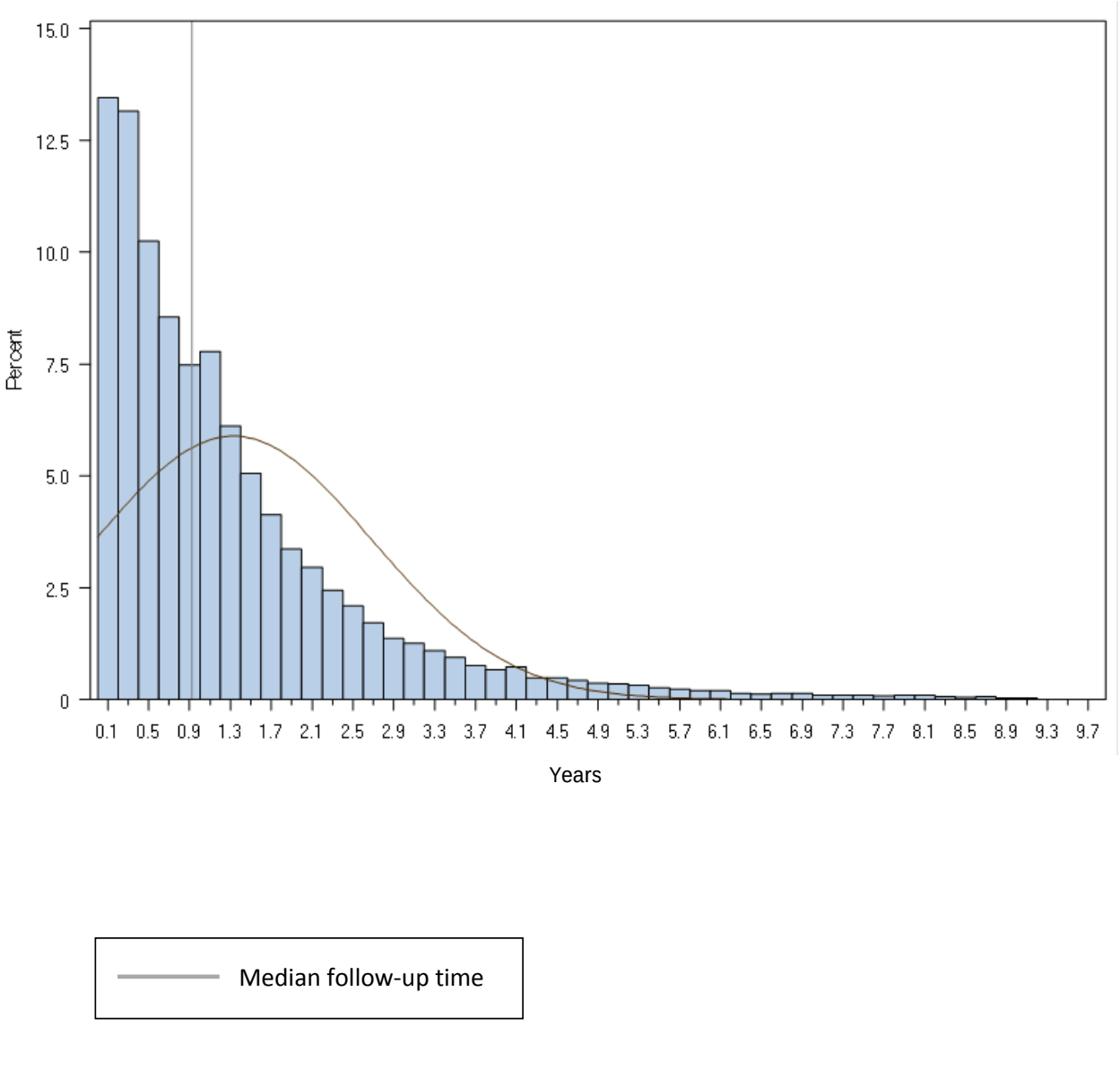


Figure 8: Histogram Plot of Cumulative Exenatide Duration,
As-Treated Analysis, Pancreatic Cancer, ORD Database
(Excluding Events and Person-Time in the First Year After Drug Initiation)

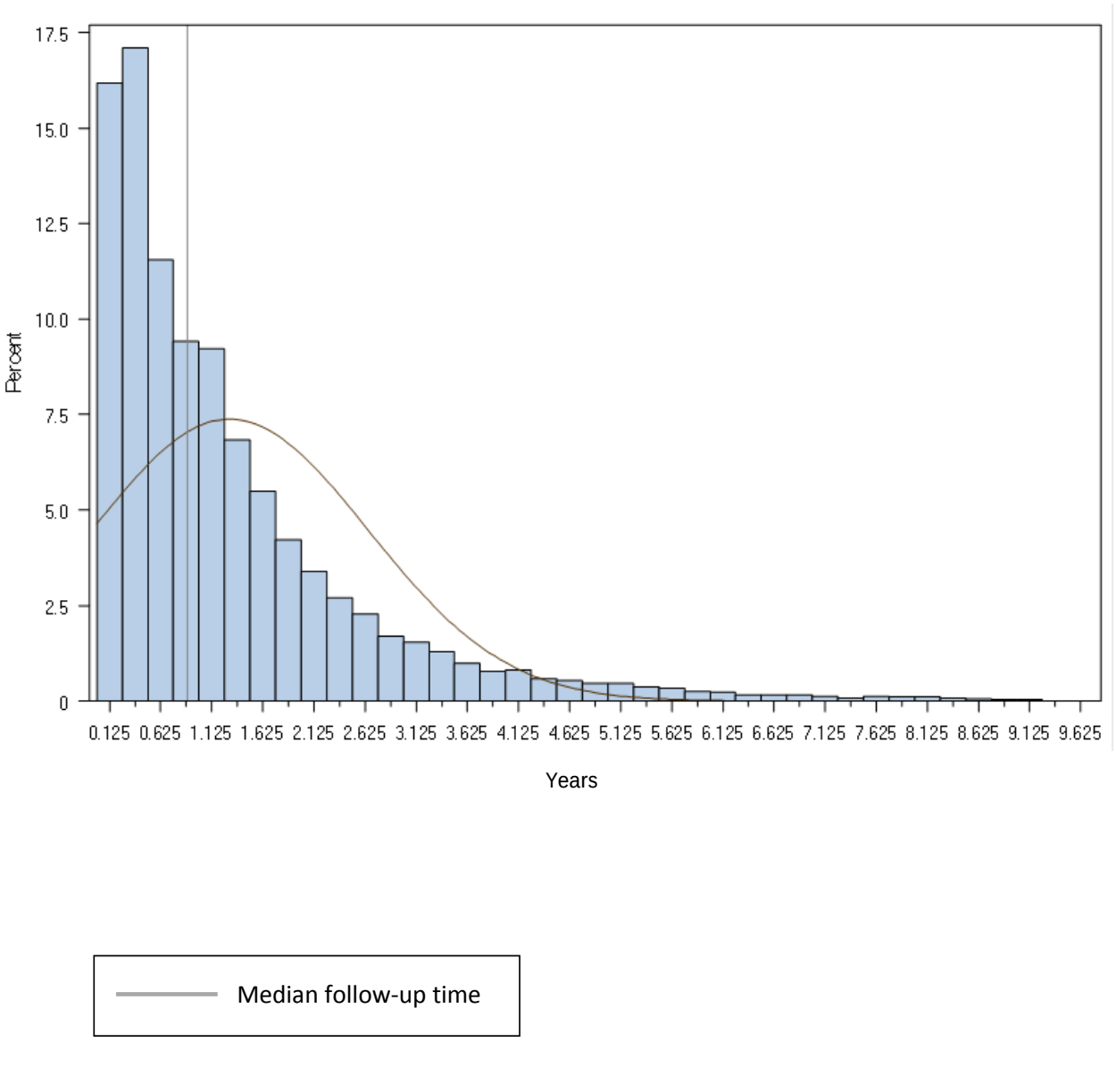


Figure 9: Histogram Plot of Cumulative Exenatide Duration,
As-Treated Analysis, Pancreatic Cancer, Impact Database
(Excluding Events and Person-Time in the First Year After Drug Initiation)

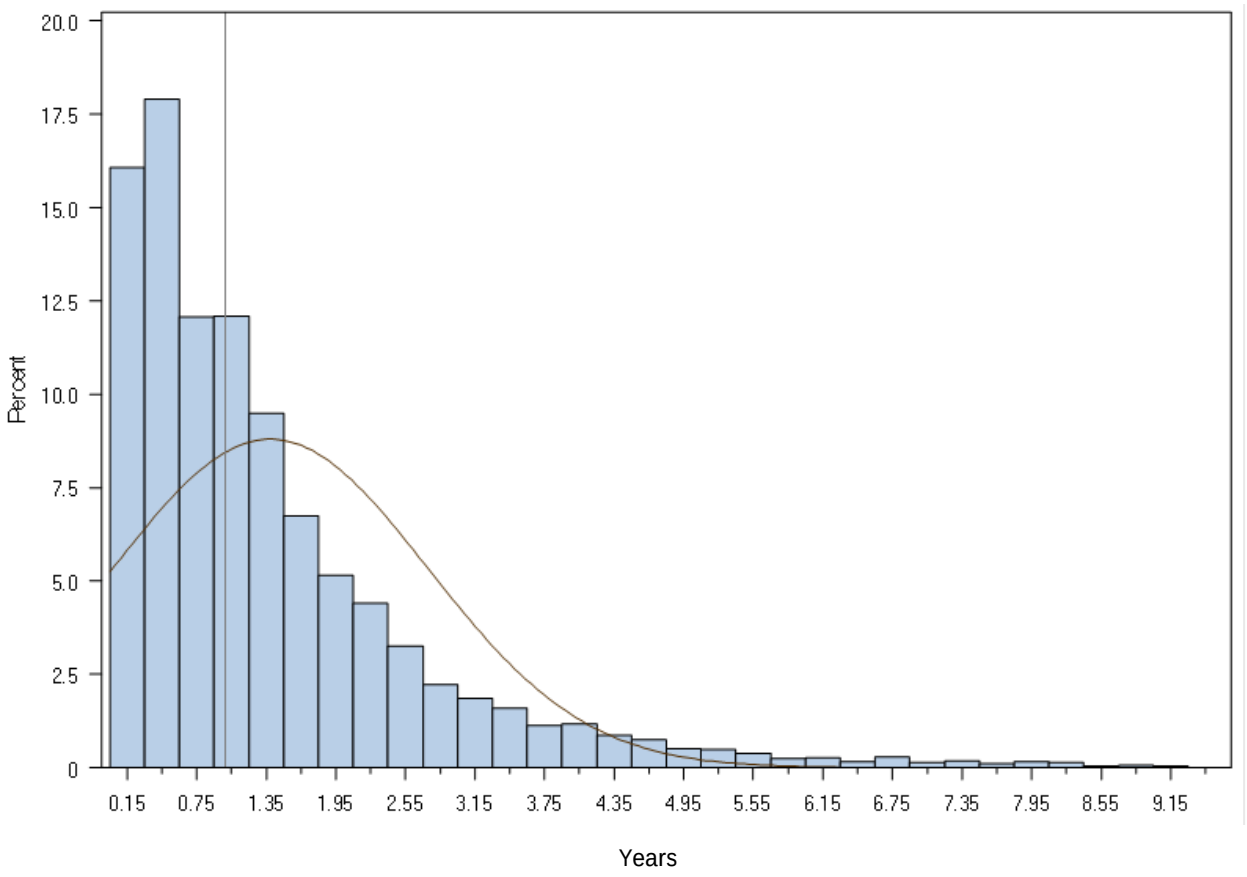


Figure 10: Histogram Plot of Cumulative OAD Duration,
As-Treated Analysis, Pancreatic Cancer, Combined Database
(Excluding Events and Person-Time in the First Year After Drug Initiation)

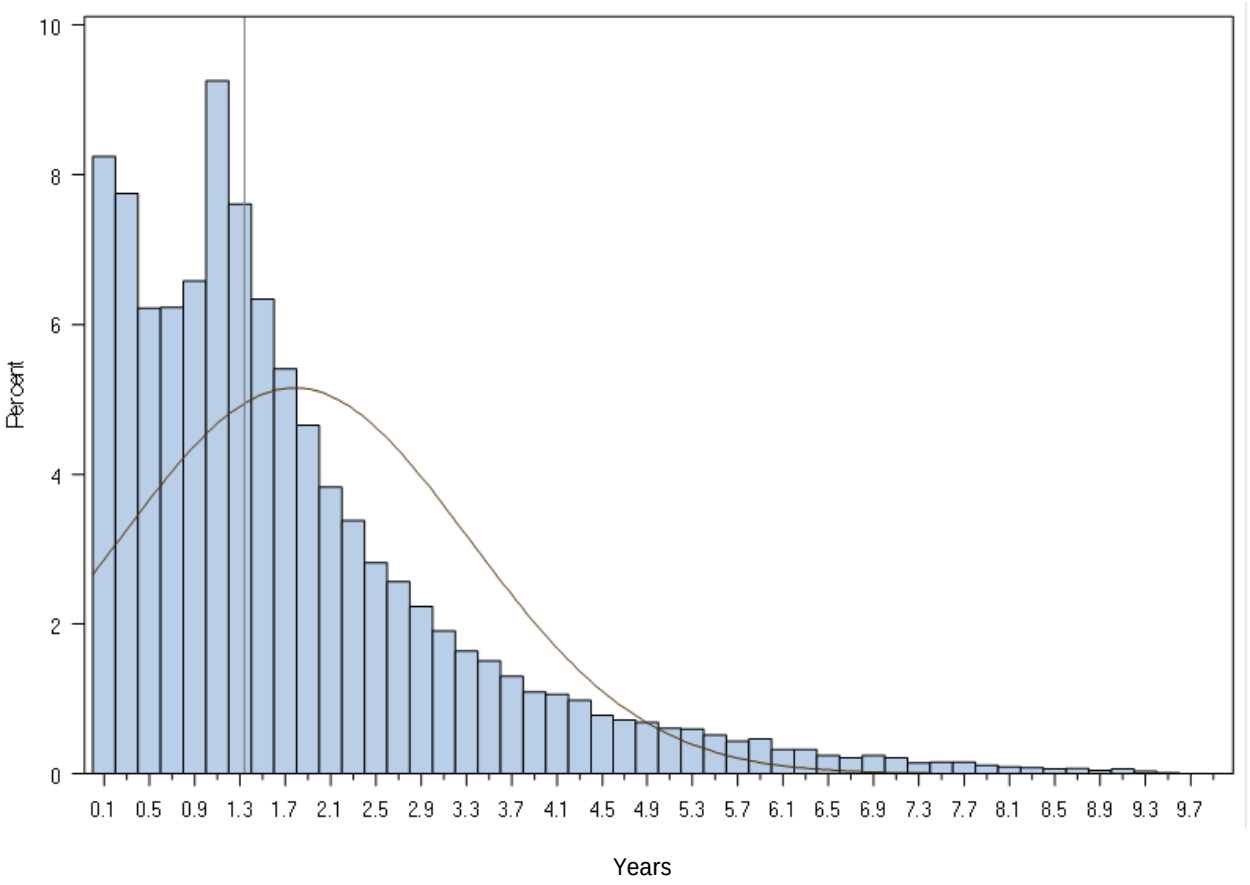


Figure 11: Histogram Plot of Cumulative OAD Duration,
As-Treated Analysis, Pancreatic Cancer, ORD Database
(Excluding Events and Person-Time in the First Year After Drug Initiation)

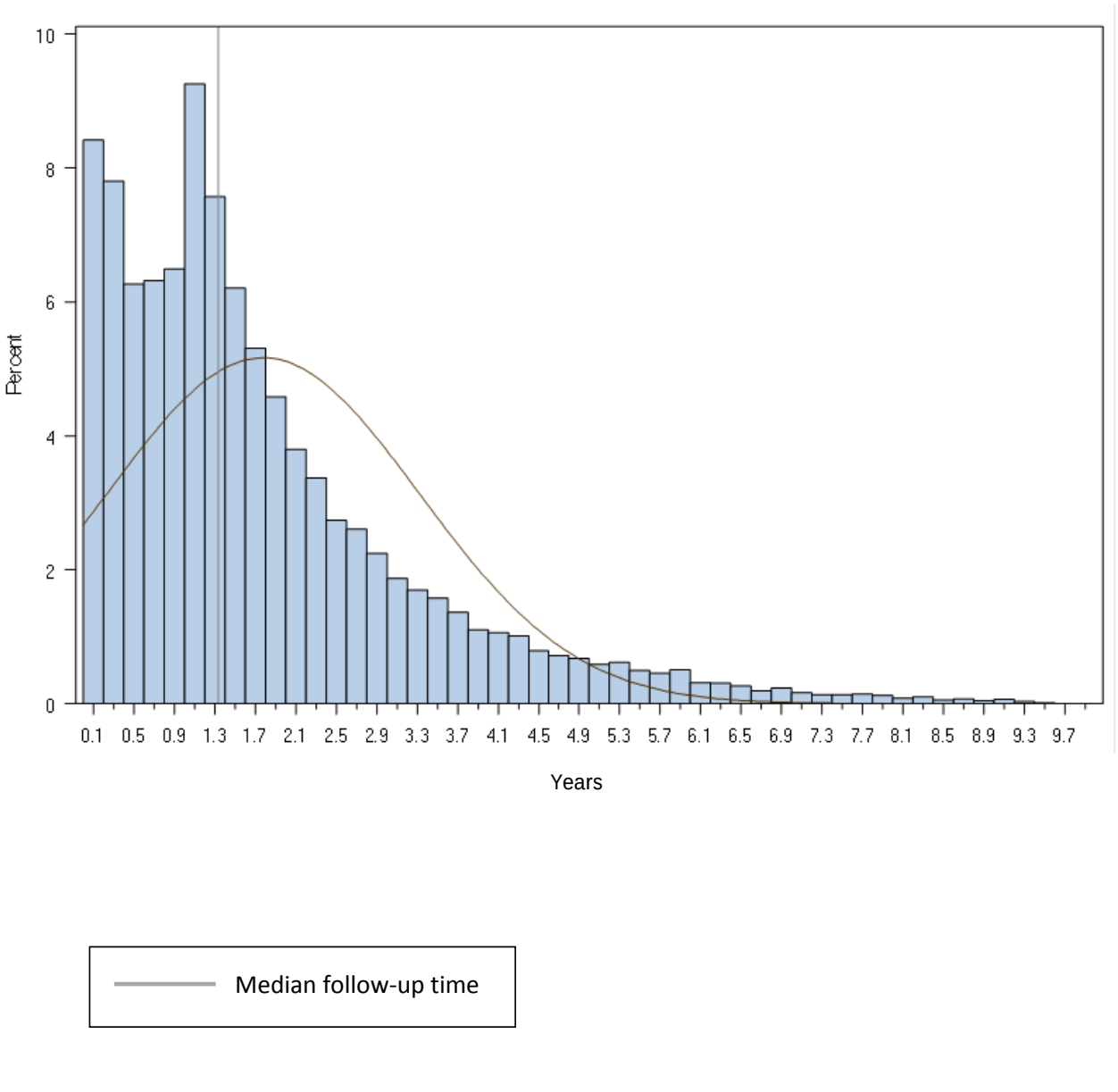


Figure 12: Histogram Plot of Cumulative OAD Duration,
As-Treated Analysis, Pancreatic Cancer, Impact Database
(Excluding Events and Person-Time in the First Year After Drug Initiation)

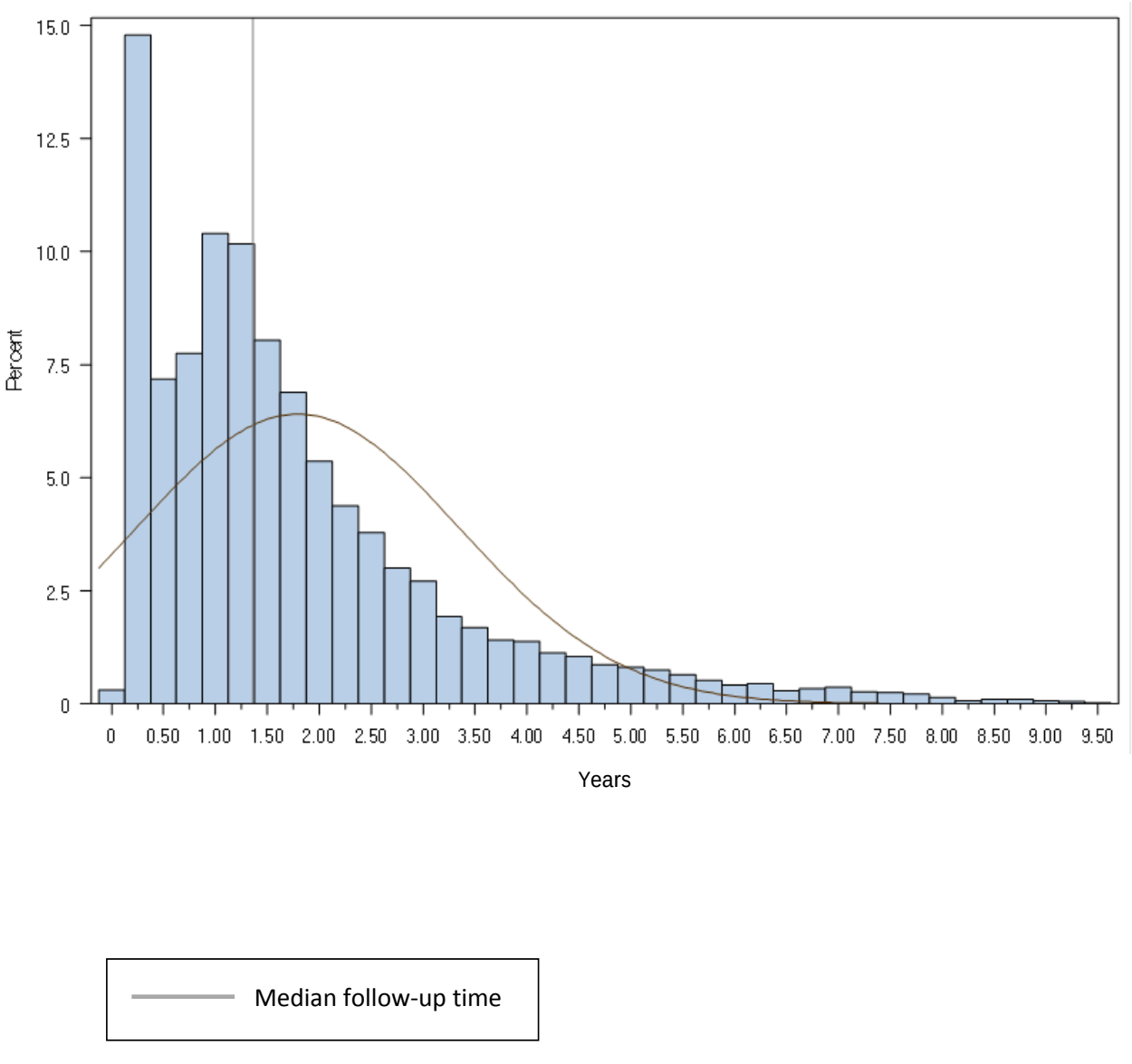


Figure 13 Survival Plot for Time to Algorithm—Identified Thyroid Cancer Stratified by Initiating Drug Cohort — Combined Database

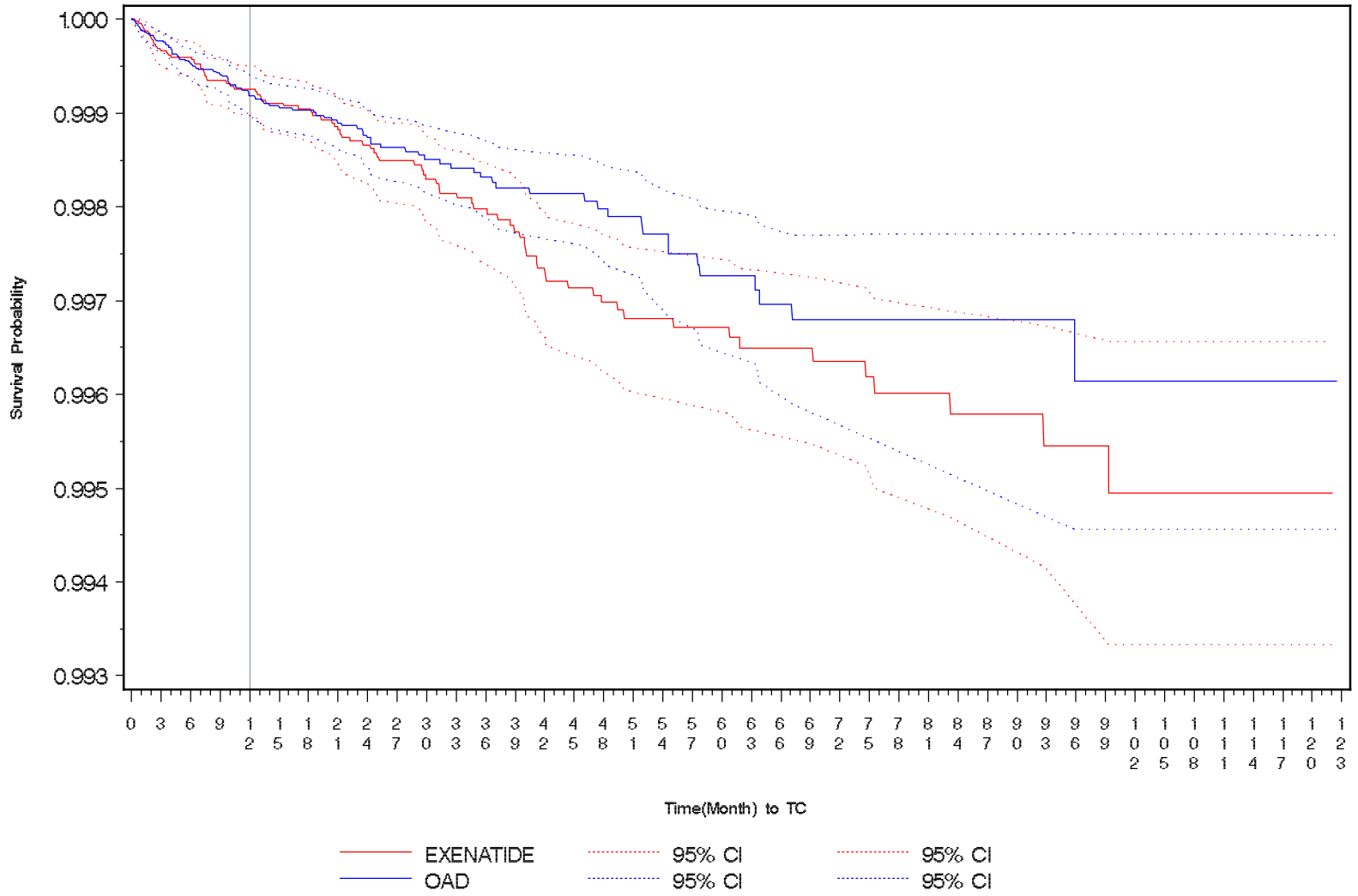


Figure 14: Histogram Plot of Cumulative Exenatide Duration,
As-Treated Analysis, Thyroid Cancer, Combined Database
(Excluding Events and Person-Time in the First Year After Drug Initiation)

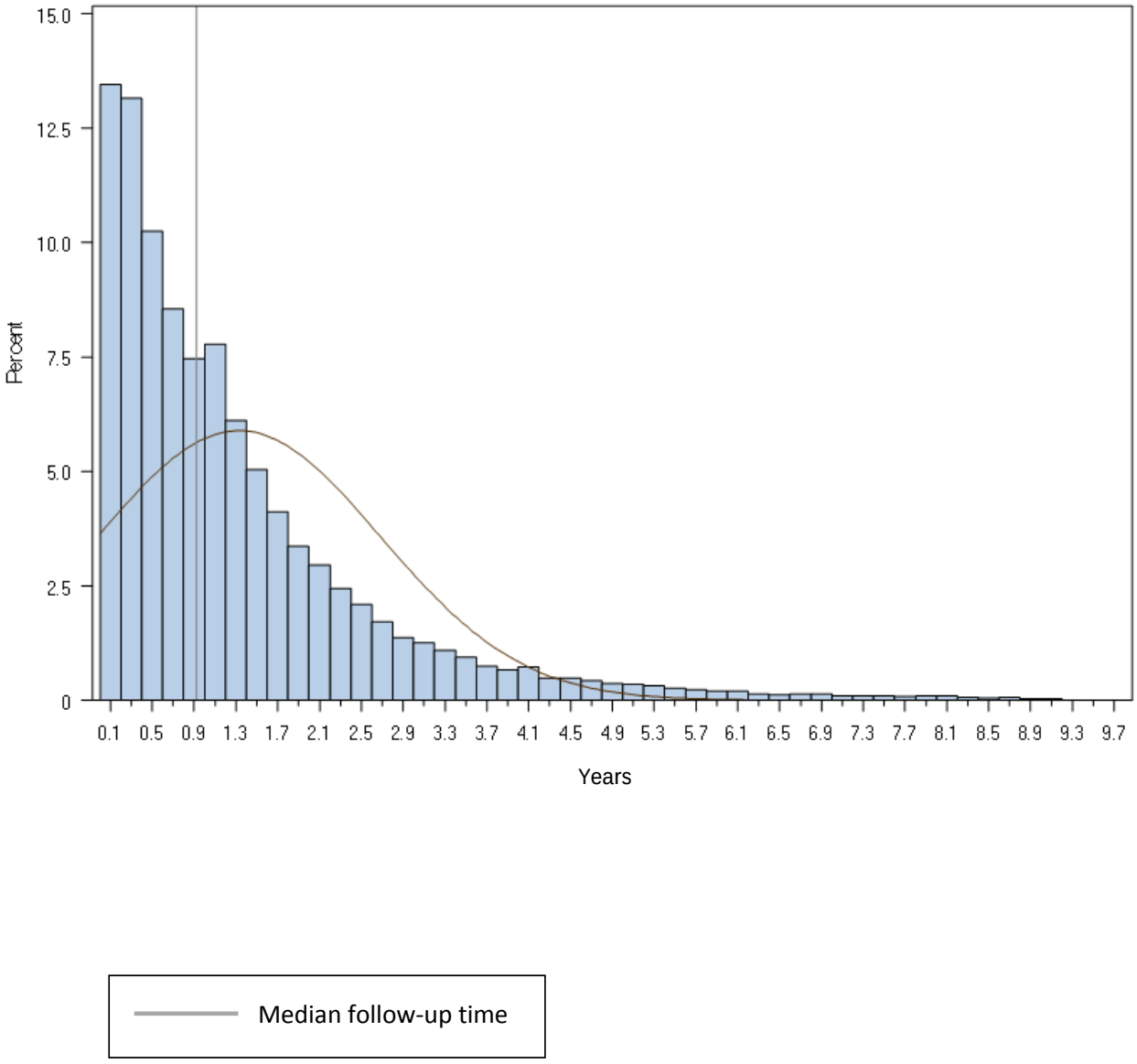


Figure 15: Histogram Plot of Cumulative Exenatide Duration,
As-Treated Analysis, Thyroid Cancer, ORD Database
(Excluding Events and Person-Time in the First Year After Drug Initiation)

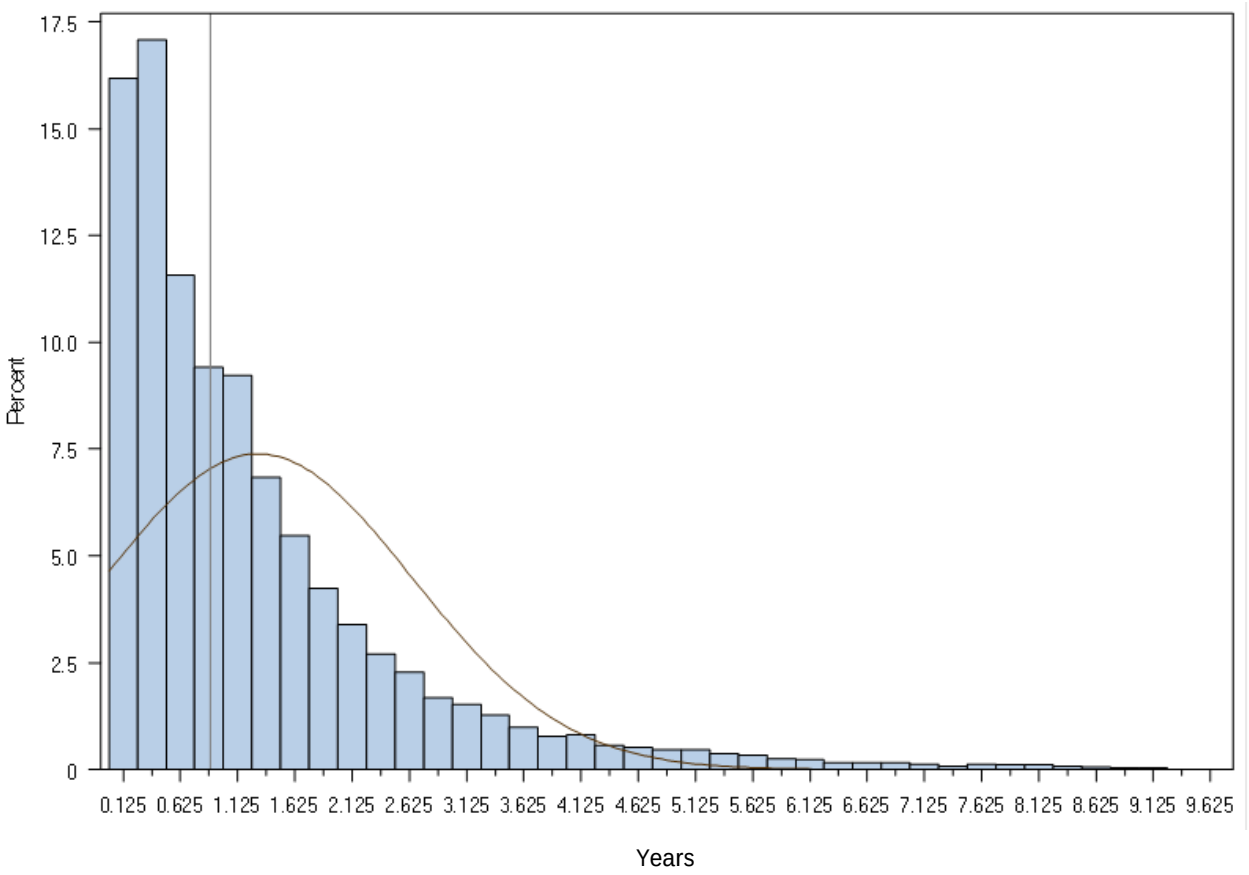


Figure 16: Histogram Plot of Cumulative Exenatide Duration,
As-Treated Analysis, Thyroid Cancer, Impact Database
(Excluding Events and Person-Time in the First Year After Drug Initiation)

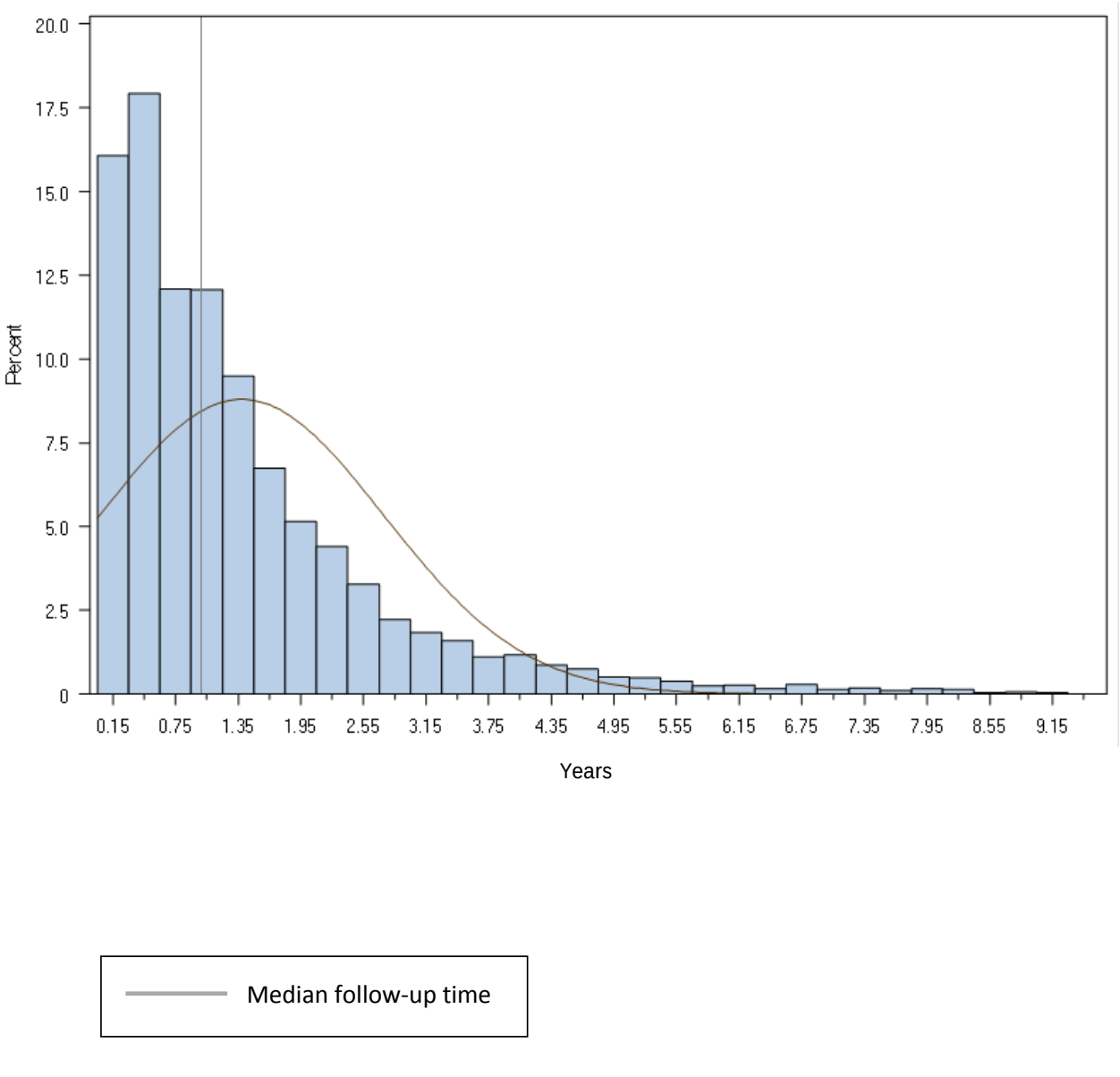


Figure 17: Histogram Plot of Cumulative OAD Duration,
As-Treated Analysis, Thyroid Cancer, Combined Database
(Excluding Events and Person-Time in the First Year After Drug Initiation)

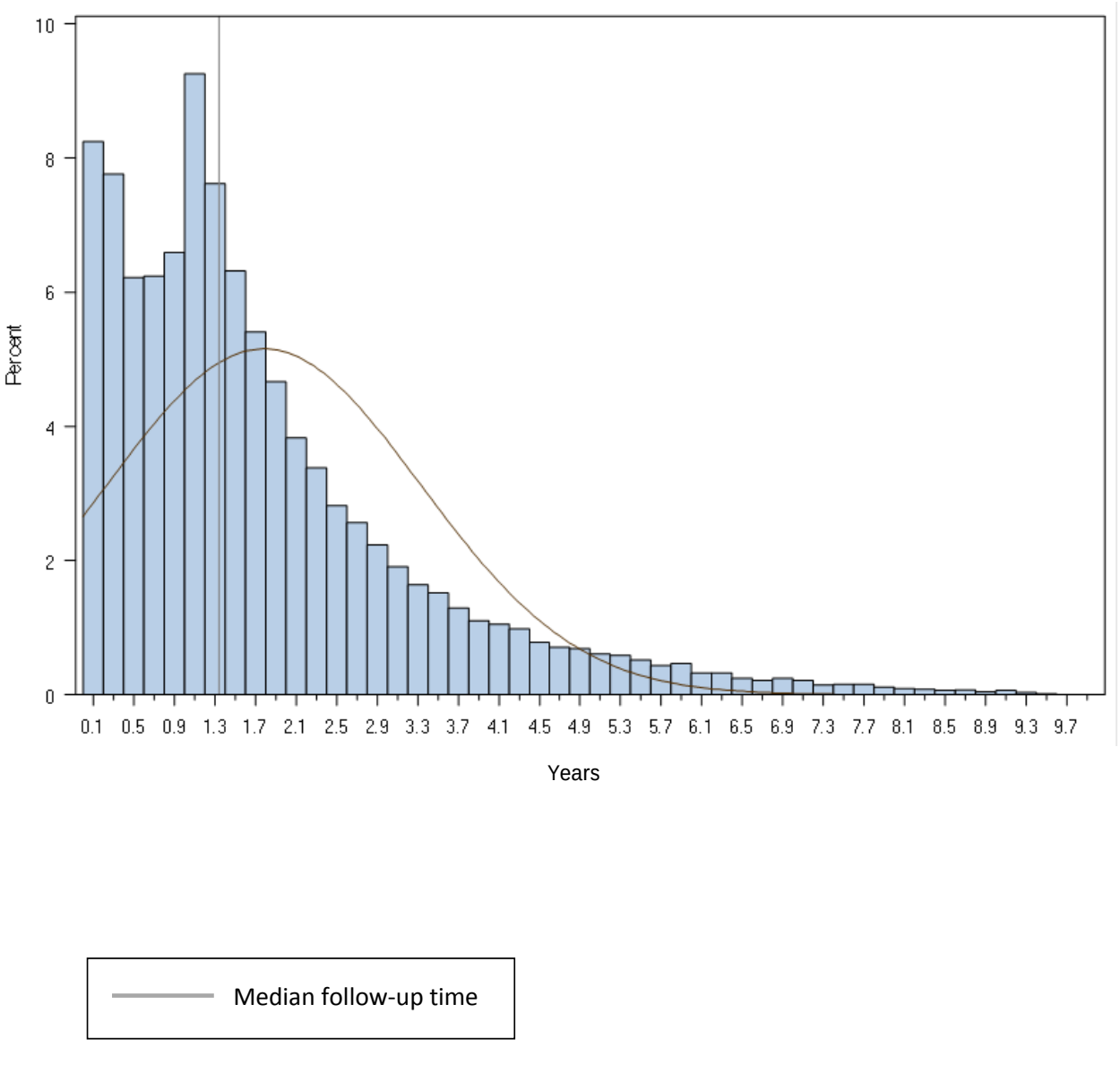


Figure 18: Histogram Plot of Cumulative OAD Duration,
As-Treated Analysis, Thyroid Cancer, ORD Database
(Excluding Events and Person-Time in the First Year After Drug Initiation)

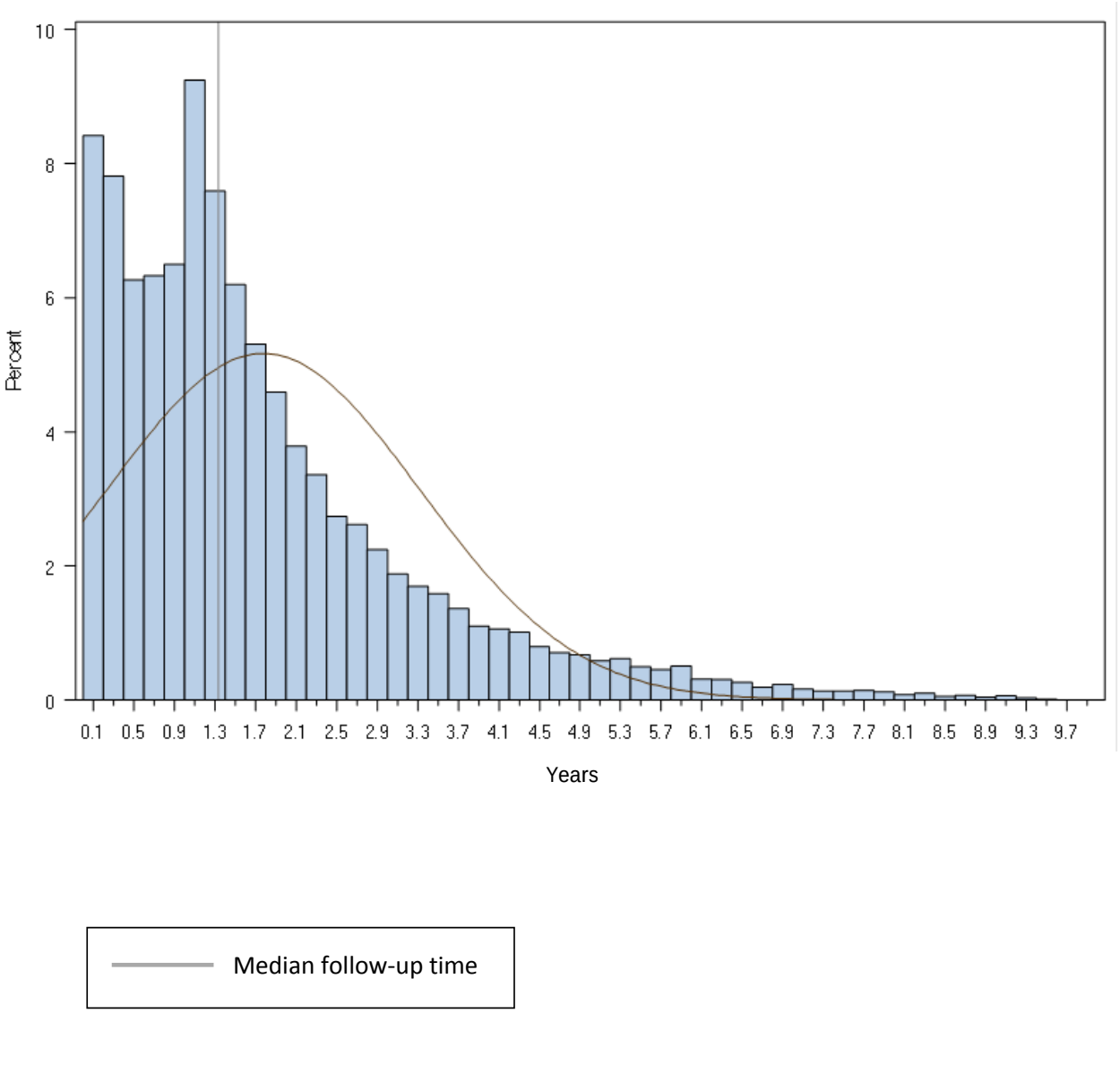


Figure 19: Histogram Plot of Cumulative OAD Duration,
As-Treated Analysis, Thyroid Cancer, Impact Database
(Excluding Events and Person-Time in the First Year After Drug Initiation)

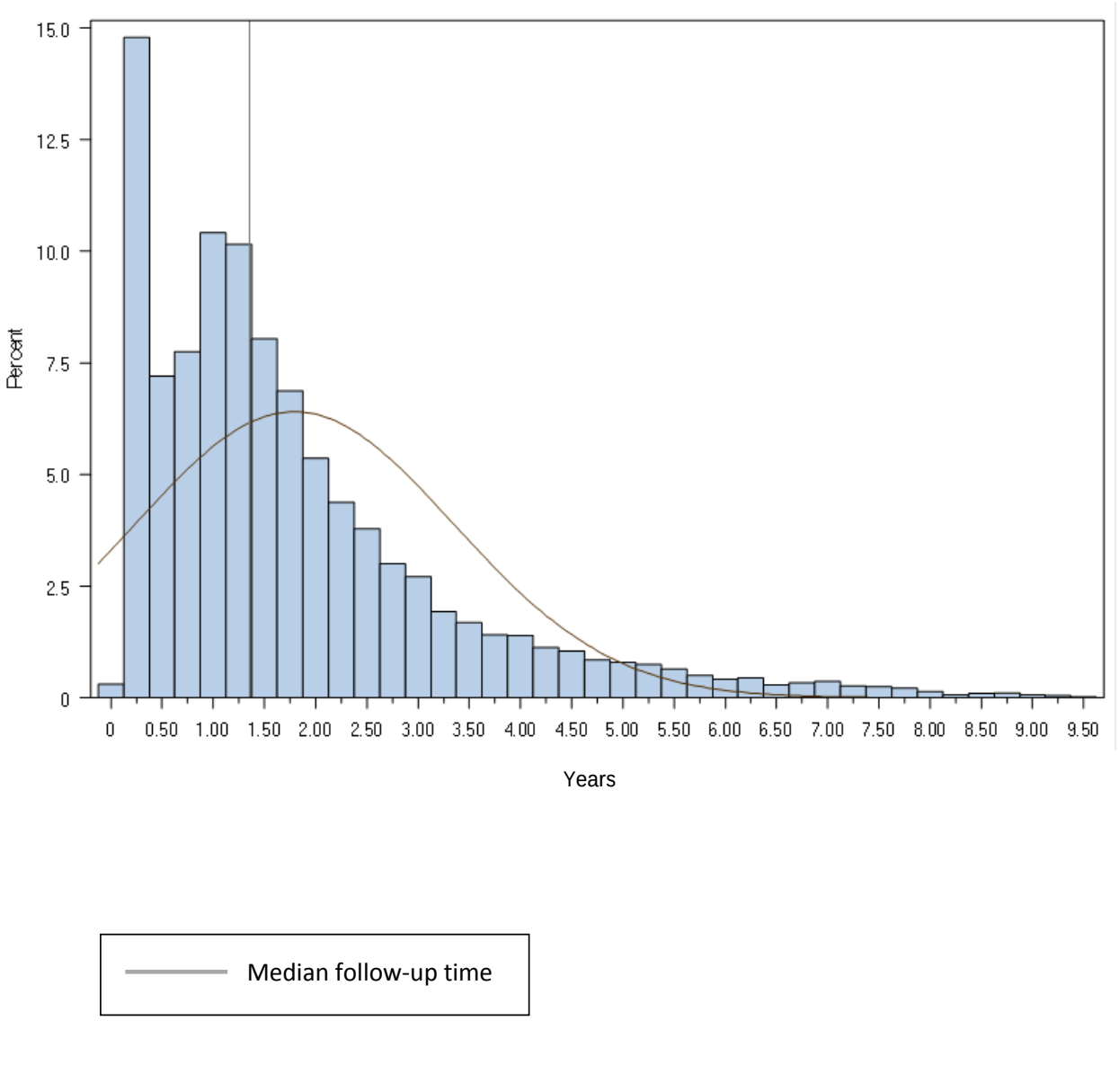


Figure 20: Histogram Plot of Total Follow-Up Time for Exenatide Initiators

Intention-to-Treat Analysis, Pancreatic Outcome, Combined Database

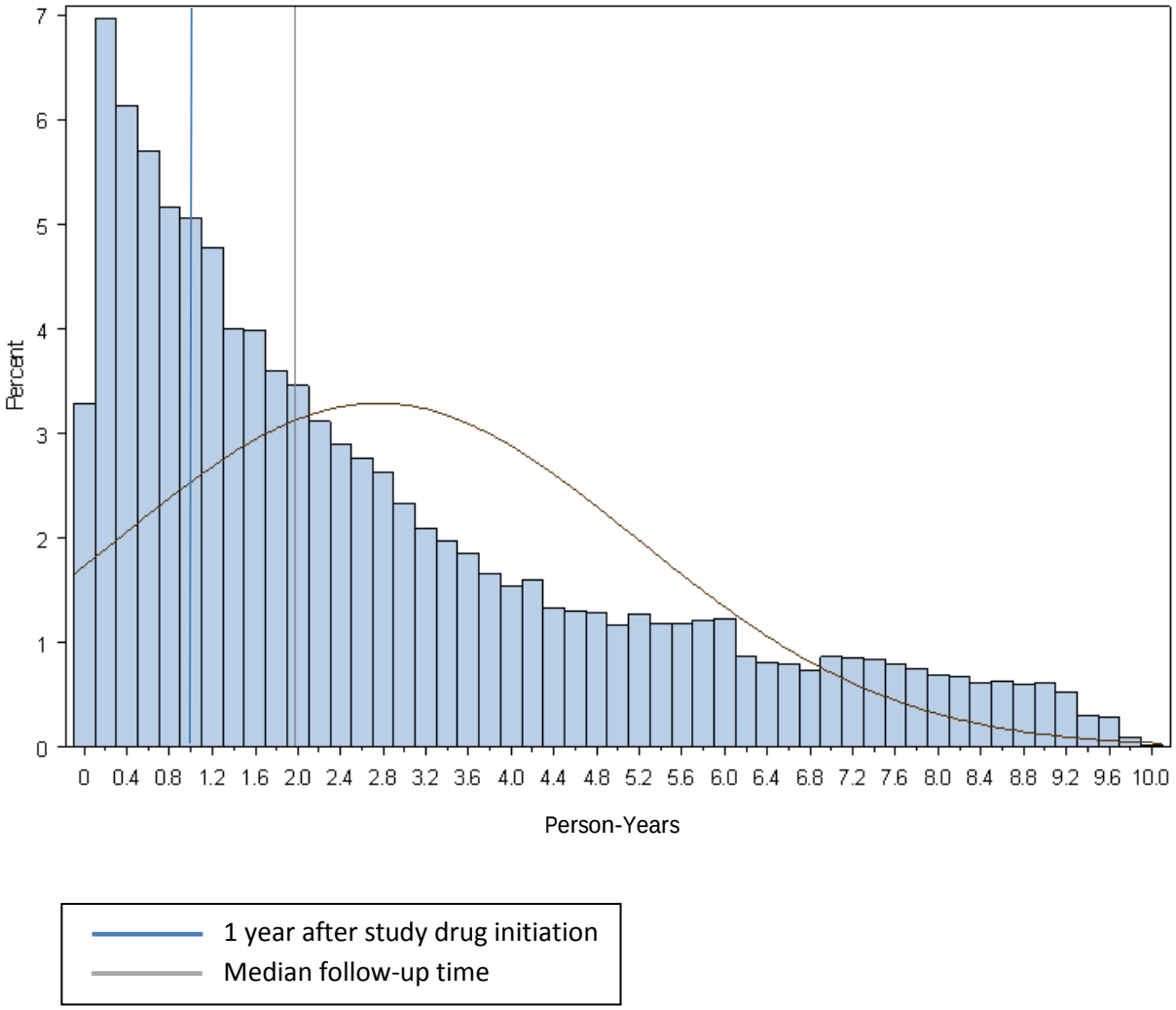


Figure 21: Histogram Plot of Total Follow-Up Time for Exenatide Initiators

Intention-to-Treat Analysis, Pancreatic Outcome, ORD Database

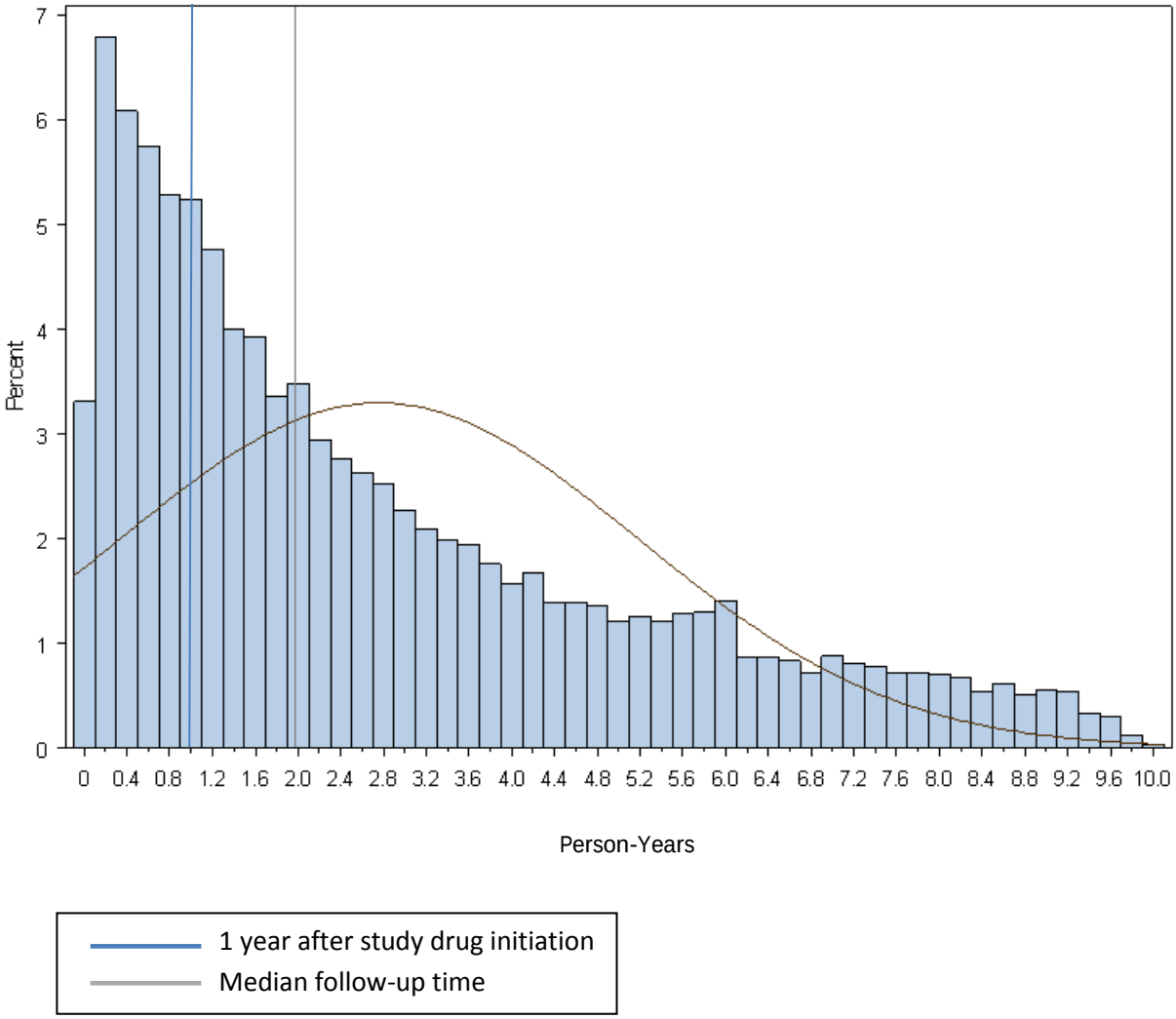


Figure 22: Histogram Plot of Total Follow-Up Time for Exenatide Initiators

Intention-to-Treat Analysis, Pancreatic Outcome, Impact Database

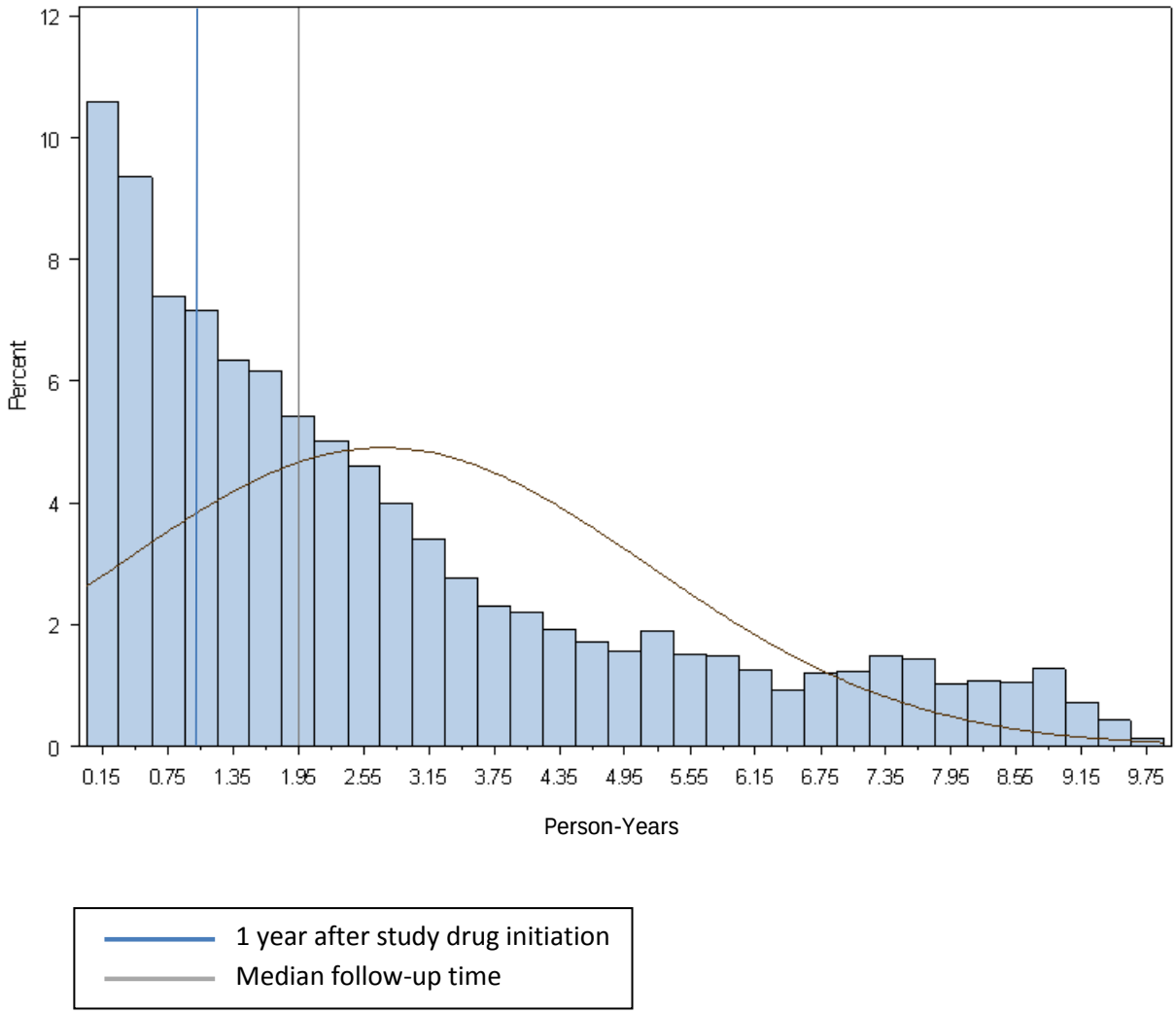


Figure 23: Evaluation of the Confounding Caused by Smoking Needed to Explain the Apparent Relative Risk of Pancreatic Cancer, Combined Databases

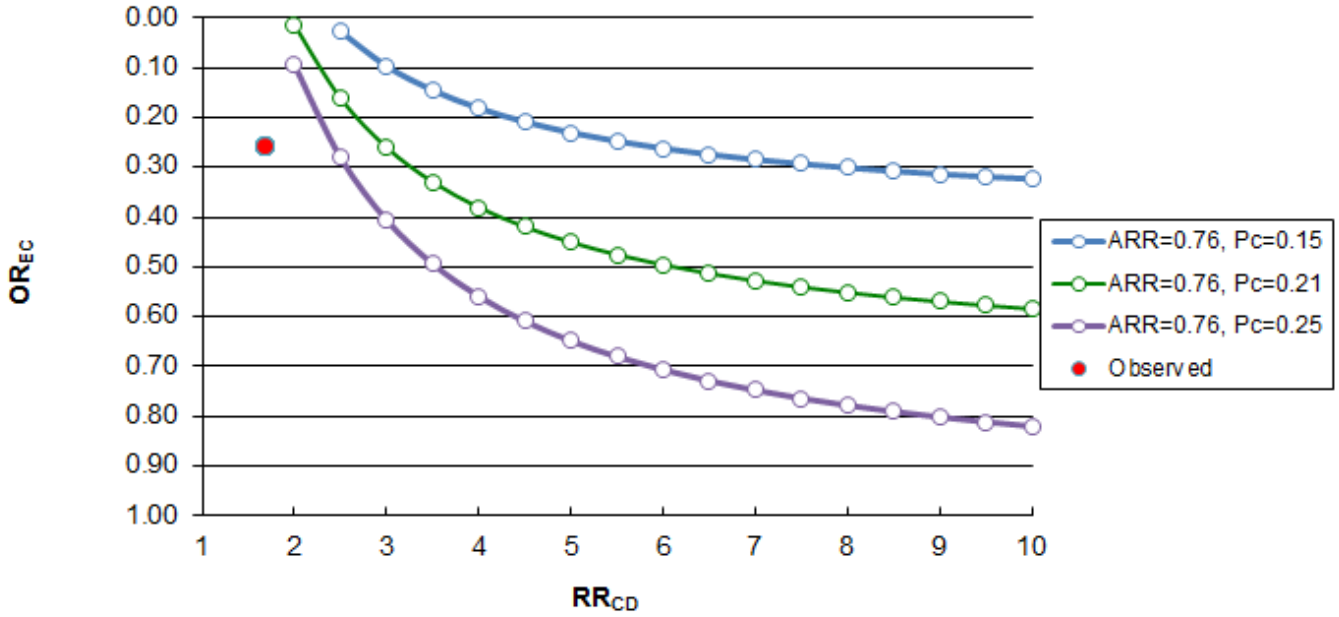


Figure 24: Evaluation of the Confounding Caused by Obesity Needed to Explain the Apparent Relative Risk of Pancreatic Cancer, Combined Databases

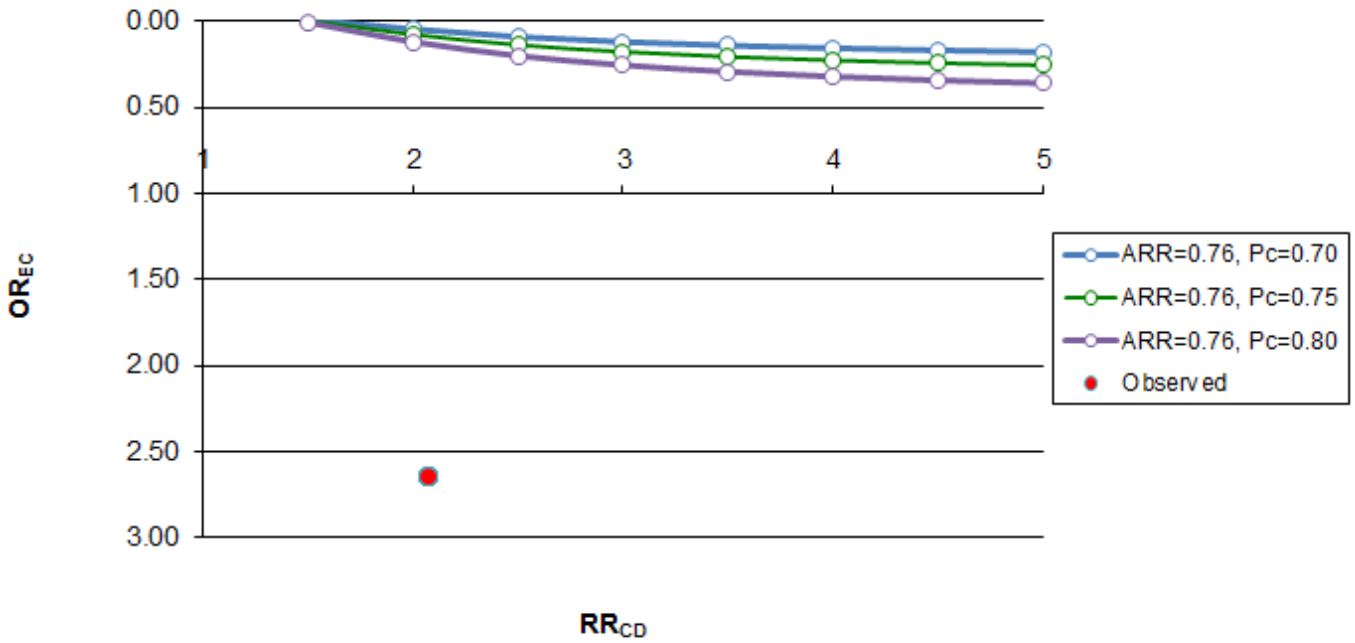


Figure 25: Histogram Plot of Total Follow-Up Time for Exenatide Initiators

Intention-to-Treat Analysis, Thyroid Outcome, Combined Database

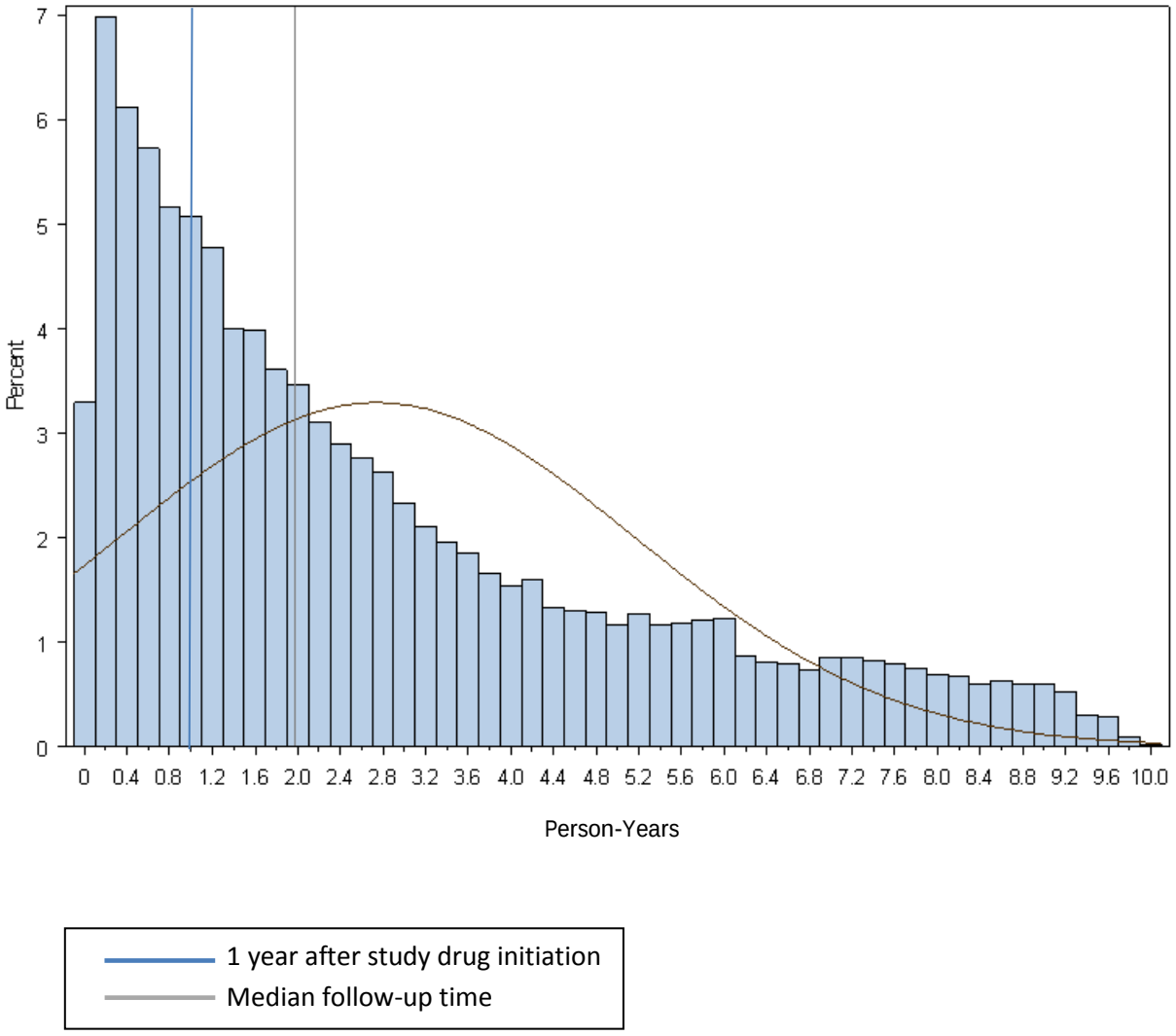


Figure 26: Histogram Plot of Total Follow-Up Time for Exenatide Initiators

Intention-to-Treat Analysis, Thyroid Outcome, ORD Database

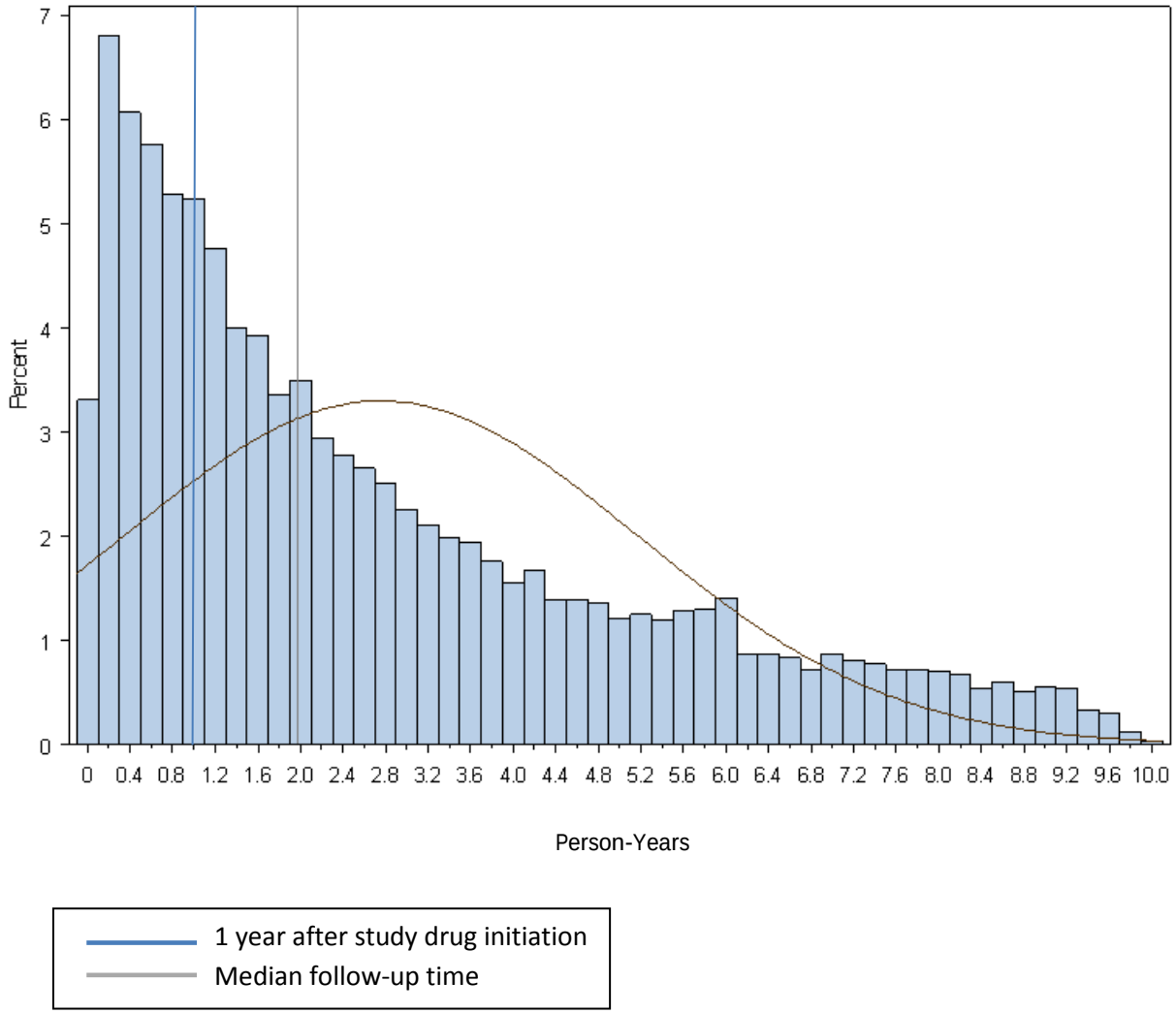


Figure 27: Histogram Plot of Total Follow-Up Time for Exenatide Initiators

Intention-to-Treat Analysis, Thyroid Outcome, Impact Database

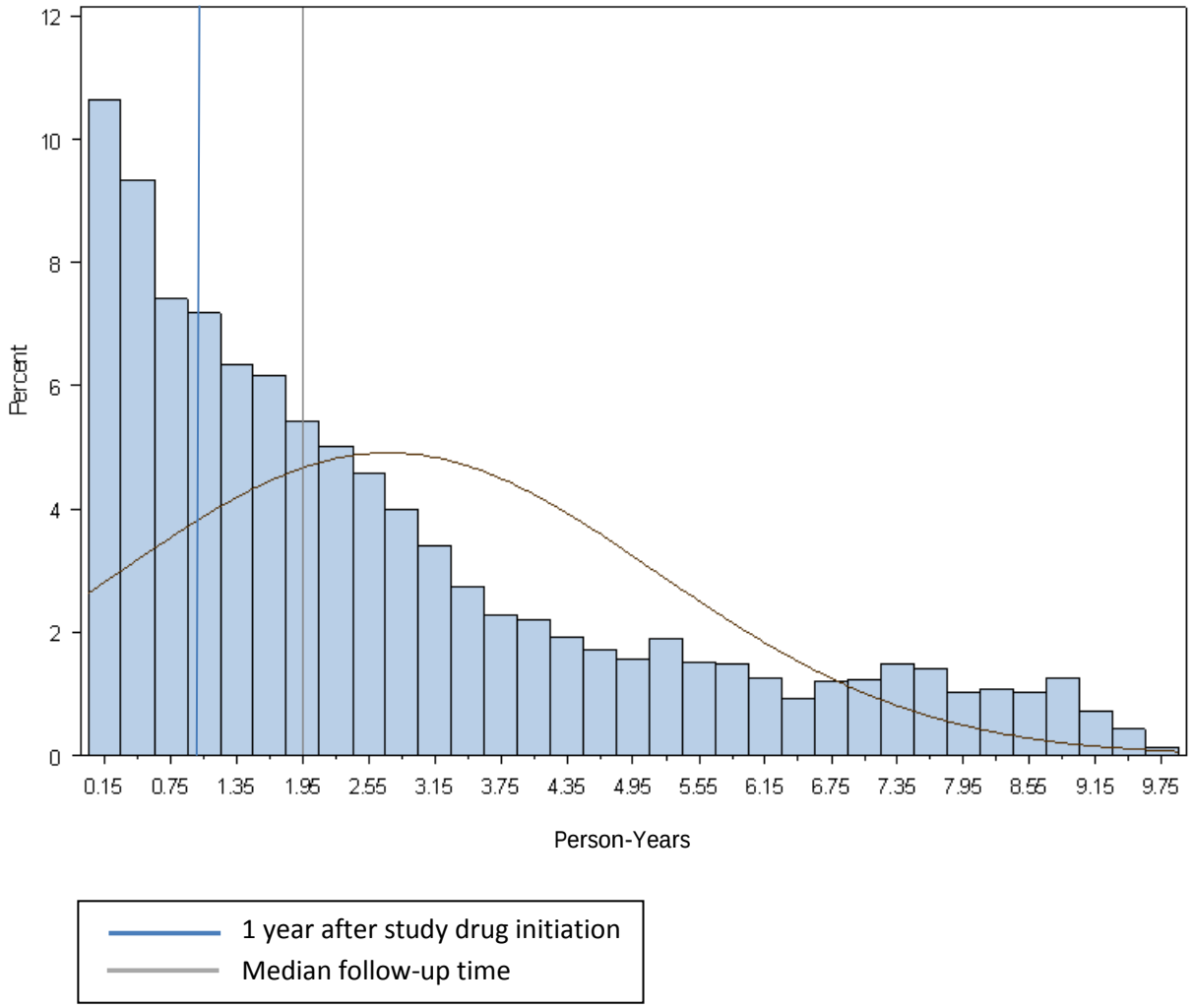


Figure 28: Evaluation of the Confounding Caused by Smoking Needed to Explain the Apparent Relative Risk of Thyroid Cancer, Combined Databases

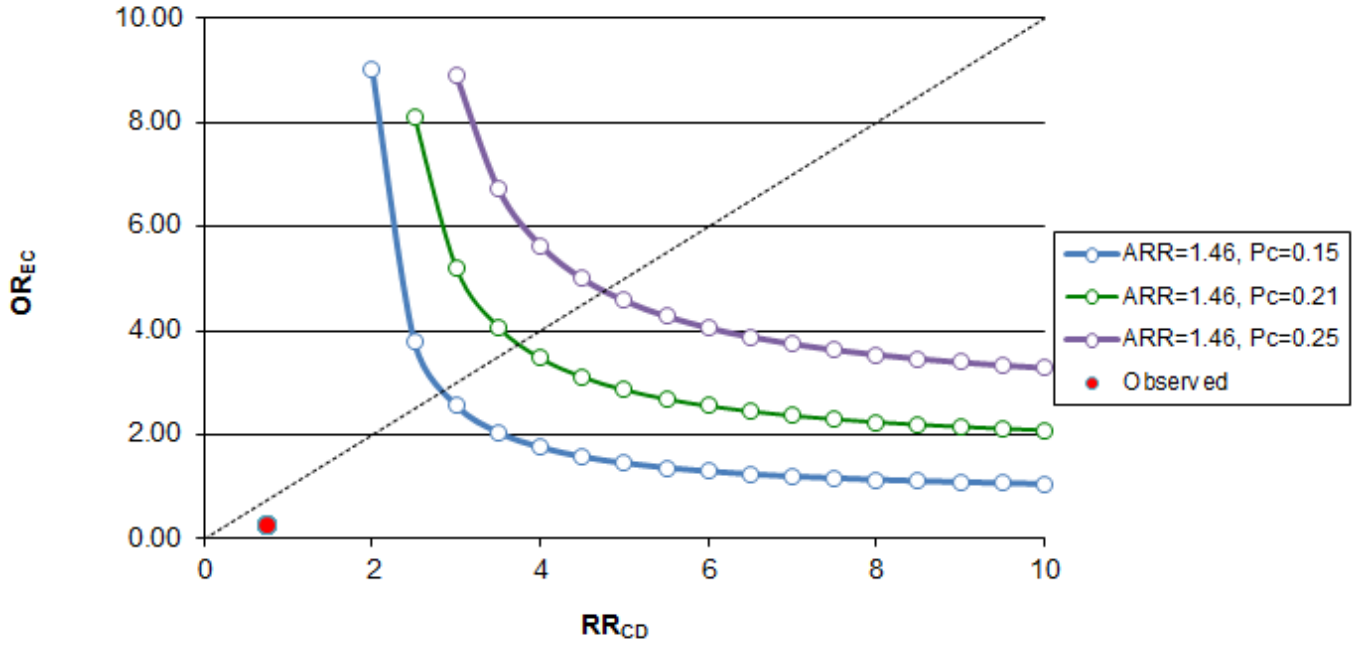
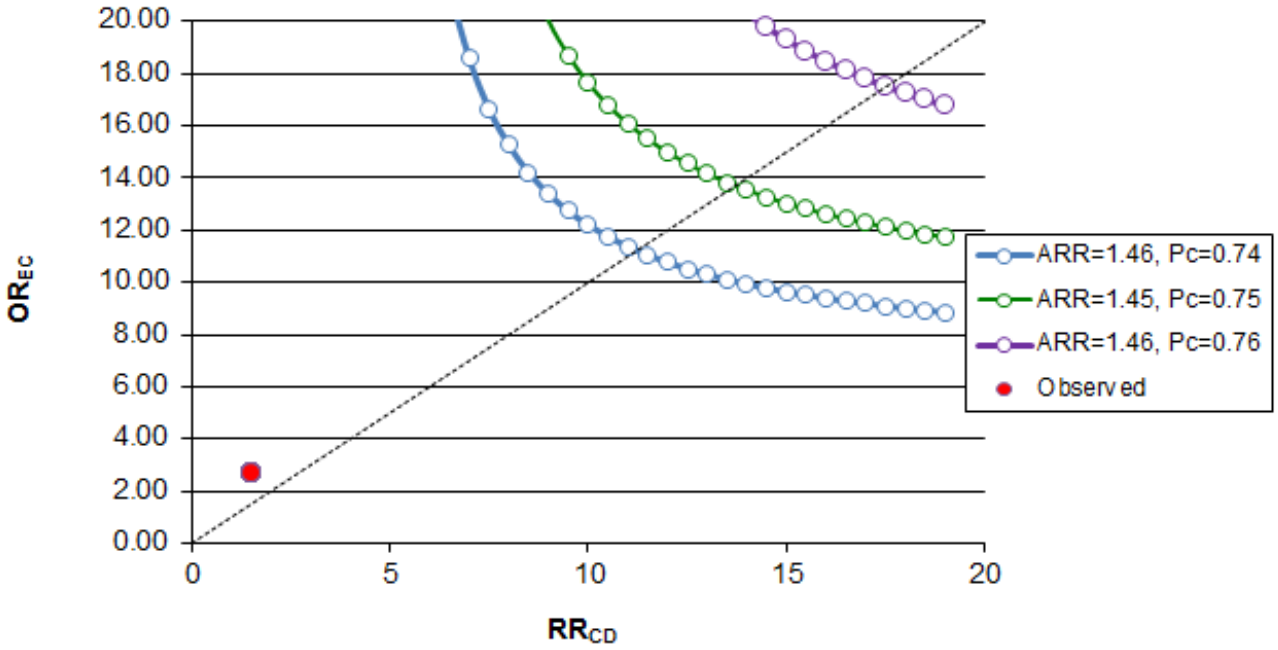


Figure 29: Evaluation of the Confounding Caused by Obesity Needed to Explain the Apparent Relative Risk of Thyroid Cancer, Combined Databases



17. APPENDICES

Annex 1. List of stand-alone documents

Table J List of stand-alone documents.

Document reference number	Title
Appendix 1	Incidence of Pancreatic Malignancy and Thyroid Neoplasm in Type 2 Diabetes Mellitus Patients who Initiate Exenatide Compared to Other Antihyperglycemic Drugs—Phase 2 (Extended Accrual and Follow-up). Revised Final Protocol Prepared by Optum for AstraZeneca Pharmaceuticals LP 18 December 2015.
Appendix 2	Incidence of Pancreatic Malignancy and Thyroid Neoplasm in Type 2 Diabetes Mellitus Patients who Initiate Exenatide Compared to Other Antihyperglycemic Drugs. Revised Final Report Prepared for Eli Lilly and Company 25 July 2013.
Appendix 3	Other Antidiabetic Drugs [OADs] Considered for Cohort Entry, Excluding Dipeptidyl Peptidase-4 [DPP-4] Inhibitors and Glucagon-like Peptide-1 [GLP-1] Receptor Agonists.
Appendix 4	Predefined Algorithms for Pancreatic Cancer and Thyroid Neoplasm.
Appendix 5	Codes for Pancreatic Cancer and Thyroid Neoplasm.
Appendix 6	Adjudication Forms.
Appendix 7	Summary of Statistical Analyses.

Annex 2. Additional information

No additional information.