Replication of the INSPIRE Trial in Healthcare Claims Data

DUPLICATE INSPIRE

August 30, 2021

1. RCT Details

This section provides a high-level overview of an RCT that the described real-world evidence study is trying to replicate as closely as possible given the remaining limitations inherent in the healthcare databases.

1.1 Title

The Prevention of Chronic Obstructive Pulmonary Disease Exacerbations by Salmeterol/Fluticasone Propionate or Tiotropium Bromide (INSPIRE trial)

1.2 Intended aim(s)

The objective of the study is to compare the effect of the anti-inflammatory/bronchodilator combination of salmeterol/fluticasone propionate (SFC) with the bronchodilator tiotropium bromide on the rate of moderate and/or severe exacerbations during a 2-year treatment period, and secondarily on outcomes that might relate to exacerbations.

1.3 Primary endpoint for replication and RCT finding

Health care utilization exacerbation rate.

1.4 Required power for primary endpoint and noninferiority margin (if applicable)

With a sample size of 635 patients per treatment group, the trial will have 90% power to detect at least a 15% (equal to 1.445 exacerbations per subject per year) reduction in exacerbations in the SFC group at a two-sided significance level of alpha = 0.05

1.5 Trial estimate

Rate ratio = 0.967 (95% CI 0.836–1.119) comparing SFC to tiotropium bromide (Wedzicha et al., 2008, Am J Respir Crit Care Med). HR of 0.85 was used for power assessment based on RCT statistical analysis.

2. Person responsible for implementation of replication in Aetion

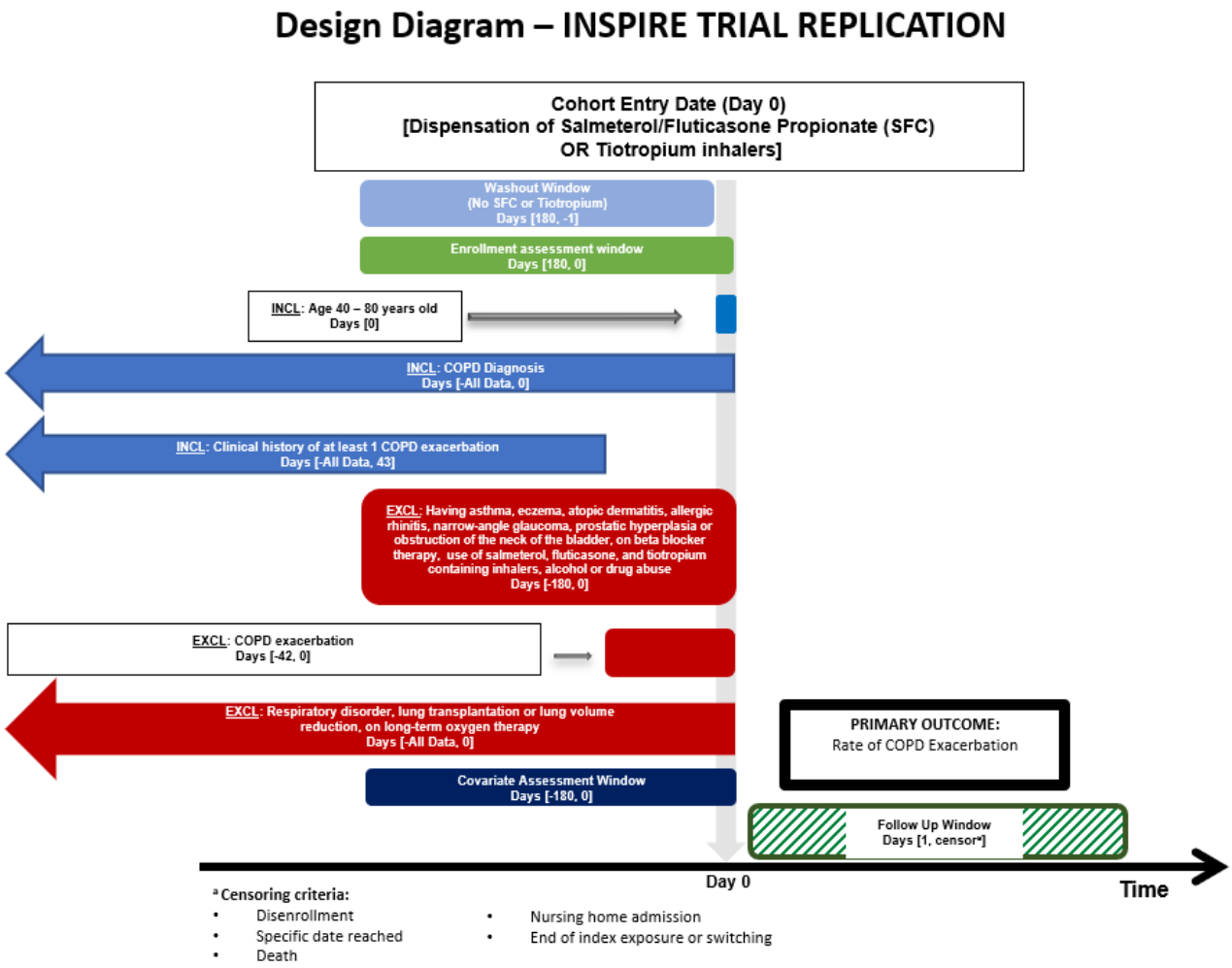
Helen Tesfaye, Pharm.D, ScM implemented the study design in the Aetion Evidence Platform. She is not responsible for the validity of design and analytic choices. All implementation steps are recorded, and implementation history is archived in the platform.

3. Data Source(s)

Optum Cliniformatics Data Mart, IBM MarketScan

4. Study Design Diagram

The study design diagram visualizes key aspects of the longitudinal study design for expediated review



5. Cohort Identification

5.1 Cohort Summary

This study will involve a new user, parallel group, propensity score matched retrospective cohort study design comparing tiotropium to salmeterol. The patients will be required to have continuous enrollment during baseline period of 180 days before initiation of SFC or tiotropium inhalers (cohort entry date).

5.2 Important steps for cohort formation

New users (defined as no use in 180 days prior to index date) of an exposure and a comparator drug will be identified.

5.2.1 Eligible cohort entry date

SFC inhaler was first approved by FDA for market availability on August 24, 2000, and tiotropium on January 30, 2004

- Optum: January 30, 2004 – March 31, 2020 (end of data availability is September 30, 2020 but excluded data generated during COVID-19 pandemic)
- Marketscan: January 30, 2004 – December 31, 2018 (end of data availability)

5.2.2 Specify inclusion/exclusion criteria for cohort entry and define the index date

Inclusion and exclusion criteria were adapted from the trial as closely as possible. Definitions for all inclusion/exclusion are provided in **Appendix A** and are summarized in the flowcharts below.

5.3 Flowchart of the study cohort assembly

	OPTUM		MARKETSCAN	
	Less Excluded Patients	**Remaining Patients**	**Less Excluded Patients**	**Remaining Patients**
All patients		79,335,559		200,203,908
Did not meet cohort entry criteria	-77,381,938	1,953,621	-196,683,354	3,520,554
Excluded due to insufficient enrollment	-308,951	1,644,670	-522,438	2,998,116
Excluded due to prior use of referent	-274,142	1,370,528	-362,567	2,635,549
Excluded due to prior use of exposure	-641,980	728,548	-1,225,388	1,410,161
Excluded because patient qualified in >1 exposure category	-10,386	718,162	-17,868	1,392,293

Excluded based on Missing/Unknown Age	-6	718,156	-1	1,392,292
Excluded based on Missing/Unknown Gender	-125	718,031	0	1,392,292
Excluded based on Inclusion #1 - Age 40 to 80 years old	-5	718,026	0	1,392,292
Excluded based on Inclusion #3a - Diagnosis of COPD	-471,394	246,632	-1,038,792	353,500
Excluded based on Inclusion #3b - Clinical history of at least 1 COPD Exacerbation	-110,352	136,280	-153,003	200,497
Excluded based on Exclusion #1 - COPD exacerbation in the 6 weeks prior	-33,666	102,614	-34,019	166,478
Excluded based on Exclusion #2a - Current asthma	-13,344	89,270	-13,539	152,939
Excluded based on Exclusion #2b - Current eczema, atopic dermatitis and/or allergic rhinitis	-5,978	83,292	-7,929	145,010
Excluded based on Exclusion #3 - Has a known respiratory disorder other than COPD	-15,367	67,925	-20,732	124,278
Excluded based on Exclusion #4 - Has narrow-angle glaucoma, prostatic hyperplasia or obstruction of the neck of the bladder	-3,927	63,998	-5,648	118,630
Excluded based on Exclusion #5 - Has undergone lung transplantation and/or lung volume reduction	-11	63,987	-41	118,589
Excluded based on Exclusion #7 - Requires regular (daily) long-term oxygen therapy (LTOT)	-2,422	61,565	-1,401	117,188
Excluded based on Exclusion #8 - Is receiving beta-blockers (except eye drops)	-7,770	53,795	-14,196	102,992
Excluded based on Exclusion #11 - Has evidence of alcohol, drug or solvent abuse	-945	52,850	-793	102,199
Excluded based on Exclusion #14 - Exclude use of Salmeterol, tiotropium, and fluticasone containing inhaler use	-591	52,259	-819	101,380
Final cohort		**52,259**		**101,380**

6 Variables

6.1 Exposure-related variables:

Study drug:

The study exposure of interest is initiation of SFC (LABA/ICS combination). Initiation will be defined by no use of inhaled SFC during the prior 180 days before treatment initiation (washout period).

Comparator agents:

Initiators of tiotropium inhaler defined as no use of inhaled tiotropium during the 180 days prior to index date

Patients are required to be incident users with respect to both exposure groups.

6.2 Preliminary Covariates:

- Age
- Sex
- Combined Comorbidity Index (CCI), measured over the default baseline covariate assessment period of 180 days prior to and including the index prescription date

Covariates listed above are a small subset of covariates that will ultimately be controlled in the design and analysis phase of the study. They are included in the preliminary assessment to determine the presence of adequate overlap between the two population of patients to proceed to the next phase of the study. Remaining covariates are defined only after the study has passed the initial feasibility analysis and initial power assessment and are listed in Table 1 (**Appendix B**).

6.3 Outcome variables and study follow-up:

6.3.1 Outcome variables

Effectiveness outcome variables of interest (definitions provided in **Appendix A**):

- Primary outcome: Healthcare utilization exacerbation rate per year (although the trial definition include 1) COPD hospitalizations or 2) exacerbations that required corticosteroids and/or antibiotics, in our emulation, we focused on 1) hospitalizations with COPD in the primary diagnosis position or 2) exacerbations that required corticosteroids. We did not include antibiotic use as part of the outcome definition because of our inability to determine whether the antibiotics were being used for COPD or some other indication)

- Secondary outcome:
  - All-cause death

Control outcomes of interest (control outcomes only serve to assess aspects of study validity but are not further interpreted): Pneumonia

6.3.2 Study follow-up

Both as-treated (AT) and intention-to-treat (ITT) analysis will be conducted with treatment defined as the index drug on the day of cohort entry. Because adherence in the real-world databases is expected to be much worse than in the trial, the AT analysis is the **primary** analysis, as it targets the relative rate of outcomes on treatment.

For the AT analysis, the follow-up will start the day after the initiation of SFC or tiotropium and will continue until the earliest date of the following events:

- The date of end of continued registration in the database,
- End of the study period or 730 days after cohort entry date,
- Death,
- Nursing home admission
    - Nursing home admissions are considered a censoring event because the data sources utilized typically provide little to no data on a patient, particularly on drug utilization, after admission. We will utilize this as an exclusion reason for cohorts for the same reason.
- The date of drug discontinuation, defined as the date of the last continuous treatment episode of the index drug (SFC or tiotropium) + a 60-day grace period,
- The date of switching from an exposure to comparator and vice versa,
- The date of switching to or initiation of other LAMA (excluding tiotropium) and switch or initiation to other LABA/ICS (excluding SFC), LAMA/LABA, LABA only, LAMA/LABA/ICS combination, and ICS only inhalers.

For the ITT analyses, the censoring based on the switching and treatment discontinuation will be replaced with a maximum allowed follow-up time of 365 days.

7 Initial Feasibility Analysis

Aetion report name:

Optum- https://bwh-dope.aetion.com/projects/details/1742/rwrs/71660

Marketscan- https://bwh-dope.aetion.com/projects/details/1741/rwrs/71658

Date conducted: 6/17/2021
Complete Aetion feasibility analysis using age, sex, and CCI as the only covariates and the primary endpoint (Section 6.3.1) as the outcome. No measures of association will be computed nor will incidence rates stratified by treatment group.

8 Initial Power Assessment

Aetion report name:
Optum- https://bwh-dope.aetion.com/projects/details/1742/rwrs/71659
Marketscan- https://bwh-dope.aetion.com/projects/details/1741/rwrs/71657

Date conducted: 6/17/2021

In order to complete the initial power analysis, the dummy outcome of a 90-day gap in database enrollment will be used. Complete a 1:1 PS-matched comparative analysis using this outcome. PS should include only 3 covariates: age, sex, and combined comorbidity index.

- Stop analyses until feasibility and power are reviewed by primary investigators and FDA. Reviewers evaluate the results of the analyses described above in Sections 7 and 8, including numbers of patients, patient characteristics, follow-up time, and reasons for censoring by treatment group, as well as overall rates of outcomes and study power. These parameters are re-evaluated and reported in the subsequent sections, after incorporating feedback and refining the protocol.

- Stop analyses until feasibility and power are reviewed by primary investigators, FDA, and assigned members of advisory board.

Reviewed by PI:	Shirley Wang	Date reviewed:	
Reviewed by FDA:	Ken Quinto	Date reviewed:	
Reasons for stopping analysis (if required):			

9. Balance Assessment

Optum- https://bwh-dope.aetion.com/projects/details/1742/rwrs/72363
Marketscan- https://bwh-dope.aetion.com/projects/details/1741/rwrs/72364

Date conducted: 7/14/2021

After review of initial feasibility and power analyses, complete creation of the remaining covariates from Section 6.2. Again, using the dummy outcome of a 90-day gap in database enrollment, complete a 1:1 PS-matched analysis. The PS should include the complete list of covariates.

- Provide plot of PS distributions stratified by treatment group.

  Note- Please refer to **Appendix B**.

- Report covariate balance after matching.

  Note- For Table 1, please refer to **Appendix B**.

- Report reasons for censoring by treatment group.

	Overall	Referent	Exposure
Dummy outcome	0 (0%)	0 (0%)	0 (0%)
Death	706 (0.72%)	368 (0.75%)	338 (0.69%)
Start of an additional exposure	8,037 (8.18%)	4,562 (9.28%)	3,475 (7.07%)
End of Index Exposure	63,915 (65.03%)	29,311 (59.65%)	34,604 (70.42%)
Specified date reached	2,286 (2.33%)	1,069 (2.18%)	1,217 (2.48%)
End of patient enrollment	11,722 (11.93%)	5,877 (11.96%)	5,845 (11.89%)
Switch to other LABA, LAMA + LABA/LAMA combo + LAMA/LABA/ICS combo + ICS only + NH admissions Occurred	11,612 (11.82%)	7,952 (16.18%)	3,660 (7.45%)

- Report follow-up time by treatment group.

Patient Group	Optum Median Follow-Up Time (Days) [IQR]	Marketscan Median Follow-Up Time (Days) [IQR]
Overall Patient Population	88 [88, 162]	113 [88, 180]
Referent – Tiotropium	88 [88, 160]	99 [88, 175]
Exposure – Salmeterol/Fluticasone	88 [88, 165]	120 [88, 188]

- Report overall risk of the primary outcome.

	Optum	MarketScan	Pooled
Risk per 1,000 patients	152.99	138.80	143.63

10. Final Power Assessment

Date conducted: 7/15/2021

- Re-calculate power in the appropriate excel table, using the revised number of matched patients from the PS-match in Section 9. All other parameters in the table should be the same as in Section 8.

Superiority Analysis (Pooled)	
Number of patients matched	
Reference	49,138
Exposed	49,139
Risk per 1,000 patients	143.63
Desired HR from RCT	0.85
Alpha (2-sided)	0.05
Number of events expected	14115.52551
Power	1

Superiority Analysis (Optum)	
Number of patients matched	
Reference	18,017
Exposed	18,017
Risk per 1,000 patients	152.99
Desired HR from RCT	0.85
Alpha (2-sided)	0.05
Number of events expected	5512.84166
Power	0.999976837

Superiority Analysis (Marketscan)	
Number of patients matched	
Reference	31,122
Exposed	31,122
Risk per 1,000 patients	138.80
Desired HR from RCT	0.85
Alpha (2-sided)	0.05
Number of events expected	8639.4672
Power	0.999999989

- Stop analyses until balance and final power assessment are reviewed by primary investigators, FDA, and assigned members of advisory board.

Reviewed by PI:	Shirley Wang	Date reviewed:	
Reviewed by FDA:		Date reviewed:	
Reasons for stopping analysis (if required):			

Appendix A: COPD Exacerbation (primary outcome), All-cause mortality (secondary outcome)

COPD Exacerbation

Measured 1 day after drug initiation in primary diagnosis position specified below and inpatient care setting -

COPD (Inpatient, Primary)
ICD-9 Diagnosis: 491.x, 492.x, 496
ICD-10 Diagnosis: J41.x, J42, J43.x, J44.x

OR

Measured 1 day after drug initiation in any diagnosis position specified below and inpatient and outpatient care setting AND steroid use within 14 days -

COPD (Any care setting, Any position)
ICD-9 Diagnosis: 491.x, 492.x, 496
ICD-10 Diagnosis: J41.x, J42, J43.x, J44.x

AND

Corticosteroid systemic administration and/or oral prescription of --
- Prednisone
- Prednisolone
- Methylprednisolone
- Dexamethasone
- Hydrocortisone

All-Cause Mortality

Identified using the discharge status codes-
Optum- Inpatient/Outpatient
• 20 = EXPIRED
• 21 = EXPIRED TO BE DEFINED AT STATE LEVEL
• 22 = EXPIRED TO BE DEFINED AT STATE LEVEL
• 23 = EXPIRED TO BE DEFINED AT STATE LEVEL
• 24 = EXPIRED TO BE DEFINED AT STATE LEVEL

- 25 = EXPIRED TO BE DEFINED AT STATE LEVEL
- 26 = EXPIRED TO BE DEFINED AT STATE LEVEL
- 27 = EXPIRED TO BE DEFINED AT STATE LEVEL
- 28 = EXPIRED TO BE DEFINED AT STATE LEVEL
- 29 = EXPIRED TO BE DEFINED AT STATE LEVEL
- 40 = EXPIRED AT HOME (HOSPICE)
- 41 = EXPIRED IN A MEDICAL FACILITY (HOSPICE)
- 42 = EXPIRED - PLACE UNKNOWN (HOSPICE)

Marketscan- Inpatient

- 20 - Died
- 22 - Died
- 23 - Died
- 24 - Died
- 25 - Died
- 26 - Died
- 27 - Died
- 28 - Died
- 29 - Died
- 40 - Other died status or Expired at home (Hospice claims only) (depends on year)
- 41 - Other died status or Expired in medical facility (Hospice claims only) (depends on year)
- 42 - Other died status or Expired - place unknown (Hospice claims only) (depends on year)
- 21 - Died or Disch./Transf. to court/law enforcement (depends on year)

Appendix A

#	INSPIRE trial definitions	Implementation in routine care	References/Rationale	Color coding
	Trial details - Intended S with label change - 2 weeks run-in		**Please see the following Google drive for further details or any missing information https://drive.google.com/drive/folders/1WD618wrywYjEaXzfLTcuK-VCcnb6b-gV**	Criteria
	EXPOSURE vs. COMPARISON			Adequate mapping in claims
	Tiotropium 18 mcg once daily vs. Salmeterol/fluticasone propionate (SFC) 50/500 mcg twice daily Aim: To evaluate the effect of tiotropium compared to SFC on healthcare utilization of COPD exacerbations	SFC vs. Tiotropium Exposure: SFC Reference: Tiotropium		Intermediate mapping in claims
	PRIMARY OUTCOME			Poor mapping or cannot be measured in claims
	Primary endpoint: Healthcare utilization COPD exacerbation rate	**Measured 1 day after drug initiation in primary diagnosis position and inpatient care setting** COPD (Inpatient, Primary) ICD-9 Diagnosis: 491.x, 492.x, 496 ICD-10 Diagnosis: J41.x, J42, J43.x, J44.x OR **Measured 1 day after drug initiation in any diagnosis position any care setting AND steriod use within 14 days** COPD (Any care setting, Any position) ICD-9 Diagnosis: 491.x, 492.x, 496 ICD-10 Diagnosis: J41.x, J42, J43.x, J44.x AND **Corticosteriod systemic administration and/or oral prescription of:** - Prednisone - Prednisolone - Methylprednisolone - Dexamethasone - Hydrocortisone		Can't be measured in claims but not important for the analysis
	Tiotropium 18 mcg once daily vs. SFC 50/500 mcg twice daily			
1	40 to 80 years old	Age 40 to 80 years old at the time of drug initiation		
2	Smoking history of ≥ 10 pack years			
3a	Diagnosis of COPD	**Measured from the start of all available data to and including the day of drug initiation in any diagnosis position and in the inpatient and outpatient care setting** COPD ICD-9 Diagnosis: 491.x, 492.x, 496 ICD-10 Diagnosis: J41.x, J42, J43.x, J44.x		

Appendix A

3b	Clinical history of at least 1 COPD exacerbation	**Measured since all available data to 43 days prior to drug initiation in primary diagnosis position and inpatient care setting** COPD (Inpatient, Primary) ICD-9 Diagnosis: 491..x, 492.x, 496.0 ICD-10 Diagnosis: J41, J42.x, J43.x, J44.x OR **Measured since all available data to 43 days prior to drug initiation in any diagnosis position, inpatient and outpatient care setting AND steriod use within 30 days** COPD ICD-9 Diagnosis: 491.x, 492.x, 496.0 ICD-10 Diagnosis: J41.x, J42, J43.x, J44.x AND **Corticosteriod systemic administration and/or prescription** - Prednisone - Prednisolone - Methylprednisolone - Dexamethasone - Hydrocortisone
4	Post bronchodilator FEV1 of < 50% of predicted normal	
5	FEV1 / FVC ratio <70%	
6	Reversibility to 400 mcg albuterol of less or equal to 10% of predicted FEV1 at Visit 1	
7	A score of 2 or more on the Modified Medical Research Council dyspnea scale	
8	Free from exacerbation in the 6 weeks prior to screening	Included in the exclusion criteria
	EXCLUSION CRITERIA	
1	COPD exacerbation in the 6 weeks prior to screening	**Measured 42 days prior to and including the day of drug initiation in prescription claims** COPD (Inpatient, Any) ICD-9 Diagnosis: 491.x, 492.x, 496.0 ICD-10 Diagnosis: J41.x, J42, J43.x, J44.x **OR** COPD (Any care setting, Any position) ICD-9 Diagnosis: 491.x, 492.x, 496.0 ICD-10 Diagnosis: J41.x, J42, J43.x, J44.x AND **Corticosteriod systemic administration and/or prescription** - Prednisone - Prednisolone - Methylprednisolone - Dexamethasone - Hydrocortisone

Appendix A

2	Current asthma, eczema, atopic dermatitis and/or allergic rhinitis	**Measured 180 days prior to and including the day of drug initiation in any diagnosis position in the inpatient and outpatient care setting** Asthma (3 Diagnosis within 180 days) ICD-9 Diagnosis: 493.x ICD-10 Diagnosis: J45.x Eczema ICD-9 Diagnosis: 692.x ICD-10 Diagnosis: L23.x, L24.x Atopic dermatitis ICD-9 Diagnosis: 691.x ICD-10 Diagnosis: L20.x Allergic rhinitis ICD-9 Diagnosis: 477.x ICD10 Diagnosis: J30.x
3	Has a known respiratory disorder other than COPD (e.g. lung cancer, sarcoidosis, tuberculosis or lung fibrosis)	**Measured since all available data to and including the day of drug initiation in any diagnosis position in the inpatient and outpatient care setting** Pulmonary Fibrosis or Interstitial Lung Disease (ILD) ICD-9 Diagnosis: 515, 516.3x, 516.8, 516.9 ICD-10 Diagnosis: J84.10, J84.111, J84.112, J84.113, J84.114, J84.115, J84.116, J84.117, J84.09, J84.2, J84.89, J84.9 Sarcoidosis ICD-9 diagnosis: 135 ICD-10 diagnosis: D86.0, D86.2 Lymphangioleiomyomatosis ICD-9 diagnosis: 516.4 ICD-10 diagnosis: J84.81 Primary/Pulmonary Tuberculosis ICD-9 diagnosis: 010.x, 011.x ICD-10 diagnosis: A15.x Cystic Fibrosis ICD-9 Diagnosis: 277.0x ICD-10 Diagnosis: E84.xx Pulmonary Hypertension/Other Pulmonary Heart Disease ICD-9 Diagnosis: 416.xx
4	Has narrow-angle glaucoma, prostatic hyperplasia or obstruction of the neck of the bladder that in the opinion of the investigator should prevent the subject from entering the study	**Measured 180 days prior to and including the day of drug initiation in any diagnosis position in the inpatient and outpatient care setting** Narrow-angle Glaucoma ICD-9 Diagnosis: 365.02, 36s.06, 365.2x ICD-10 Diagnosis: H40.03x, H40.2xx, Prostatic hyperplasia or obstruction of the neck of the bladder ICD-9 Diagnosis: 600.x ICD-10 Diagnosis: N40.x **OR** **At least one 30-day supply presciption claims for oral:** Alfuzosin, doxazosin, tamsulosin, silodosin, finasteride 5 mg, dutasteride

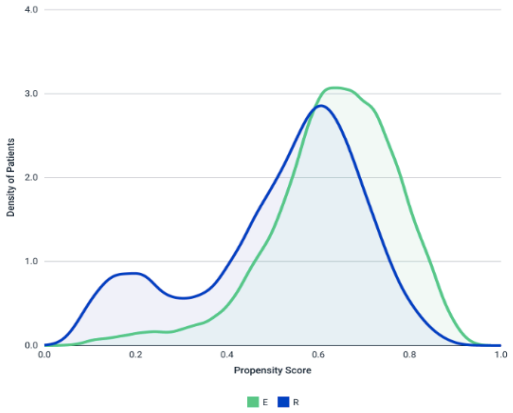
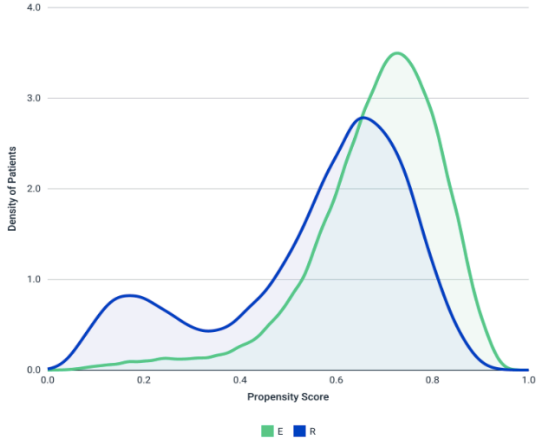
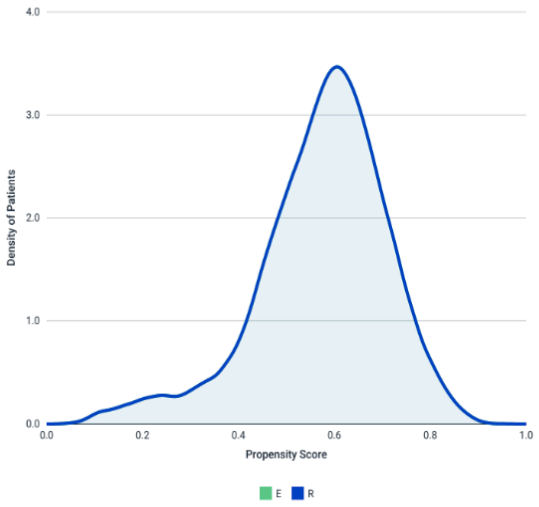
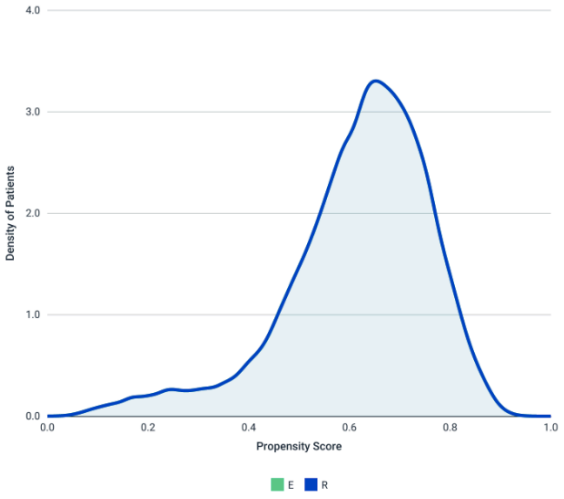
Appendix A

5	Has undergone lung transplantation and/or lung volume reduction	**Measured since all available data to and including the day of drug initiation in any diagnosis position in the inpatient and outpatient care setting** Lung transplant ICD-9 Diagnosis: V42.6, 996.84 ICD-10 Diagnosis: Z94.2, T86.810, T86.811, T86.819 ICD-9 Procedure: 33.5x ICD-10 Procedure: 0BYM0Z0, 0BYM0Z1, 0BYM0Z2, 0BYK0Z0, 0BYK0Z1, 0BYK0Z2, 0BYL0Z0, 0BYL0Z1, 0BYL0Z2 CPT-4 Code: 32850 - 32856 Lung volume reduction surgery (LVRS) ICD-9 Procedure: 32.22, 32.3x ICD-10 Procedure: 0BBC0ZZ, 0BBC4ZZ, 0BBD0ZZ, 0BBD4ZZ, 0BBF0ZZ, 0BBF4ZZ, 0BBG0ZZ, 0BBG4ZZ, 0BBH0ZZ, 0BBH4ZZ, 0BBJ0ZZ, 0BBJ4ZZ, 0BBK0ZZ, 0BBK4ZZ, 0BBL0ZZ, 0BBL4ZZ, 0BBM0ZZ, 0BBM4ZZ CPT/HCPCS codes: 32491, 32672, G0302, G0303, G0304, G0305
6	Female who is a nursing mother	
7	Requires regular (daily) long-term oxygen therapy (LTOT)	**Measured since all available data to and including the day of drug initiation in any diagnosis position in the inpatient and outpatient care setting** LTOT ICD-9 Diagnosis: V46.2 ICD-10 Diagnosis: Z99.81 CPT/HCPCS code: E0424, E0441, E0443
8	Is receiving beta-blockers (except eye drops)	**Measured 180 days prior to and including the day of drug initiation with prescription for oral:** Acebutolol, Atenolol, Betaxolol, Bisoprolol, Carteolol, Carvedilol, Labetalol, Metoprolol, Metiranolol, Nebivolol, Nadolol, Propranolol, Pindolol, Sotalol, Penbutolol, Oxprenolol
9	Has a serious, uncontrolled disease likely to interfere with the study	
10	Has received any other investigational drugs within the 4 weeks prior to Visit 1	
11	Has, in the opinion of the investigator, evidence of alcohol, drug or solvent abuse	**Measured 180 days prior to and including the day of drug initiation in any diagnosis position in the inpatient and outpatient care setting** Alcohol Abuse or Dependence ICD-9 diagnosis: 291.xx, 303.xx, 305.0x, 571.0x, 571.1x, 571.2x, 571.3x, 357.5x, 425.5x, E860.0x, V11.3x ICD-10 diagnosis: F10.x, K70.x, G62.1, I42.6, 099.31x Drug Abuse or Dependence ICD-9 diagnosis: 292.xx, 304.xx, 305.2x-305.9x, 648.3x ICD-10 diagnosis: F11.x, F12.x, F13.x, F14.x, F15.x, F16.x, F17.2x, F18.x, F19.x, F55.2, G62.0, 099.32x
12	Has a known or suspected hypersensitivity to beta2-agonists, inhaled corticosteroids, anticholinergic agents or any components of the formulations (e.g. lactose or milk protein)	

Appendix A

13	Exclude use of Salmeterol, tiotropium, and fluticasone containing inhaler use within 180 days prior to CED	**Measured 180 days prior to and including the day of drug initiation in prescription claims** **Brand names -** STIOLTO RESPIMAT SEREVENT SEREVENT DISKUS ARNUITY ELLIPTA BREO ELLIPTA TRELEGY ELLIPTA FLOVENT HFA FLOVENT DISKUS ARMONAIR RESPICLICK ARMONAIR **OR** **Generic name -** TIOTROPIUM BROMIDE/OLODATEROL HCL SALMETEROL XINAFOATE

Appendix A

Optum	MarketScan
BEFORE PS MATCHING	
	
The c-statistics for the propensity score model, pre-matching was 0.689. The post-matching c-statistic was 0.523.	The c-statistics for the propensity score model, pre-matching was 0.7. The post-matching c-statistic was 0.516.
	

Appendix B

UNMATCHED

	OPTUM			MARKETSCAN			POOLED		
	Referent - Tiotropium	Exposure - Salmeterol/Fluticasone	St. Diff	Referent - Tiotropium	Exposure - Salmeterol/Fluticasone	St. Diff	Referent - Tiotropium	Exposure - Salmeterol/Fluticasone	St. Diff
Number of patients	21,689	30,570		36,727	64,653		58,416	95,223	
Calendar Time - Year of Initiation (2004 - 2020)									
...2004-2006; n (%)	1,330 (6.1%)	3,505 (11.5%)	-0.1915	5,640 (15.4%)	15,357 (23.8%)	-0.2128	6,970 (11.9%)	18,862 (19.8%)	-0.218
...2007-2008; n (%)	2,190 (10.1%)	3,669 (12.0%)	-0.0606	5,594 (15.2%)	11,223 (17.4%)	-0.0596	7,784 (13.3%)	14,892 (15.6%)	-0.065
...2009-2011; n (%)	4,060 (18.7%)	6,299 (20.6%)	-0.0478	9,988 (27.2%)	17,461 (27.0%)	0.0045	14,048 (24.0%)	23,760 (25.0%)	-0.023
...2012-2015; n (%)	6,704 (30.9%)	8,124 (26.6%)	0.0951	11,489 (31.3%)	15,233 (23.6%)	0.1732	18,193 (31.1%)	23,357 (24.5%)	0.148
...2016-2018; n (%)	5,091 (23.5%)	6,116 (20.0%)	0.0849	4,016 (10.9%)	5,379 (8.3%)	0.0883	9,107 (15.6%)	11,495 (12.1%)	0.101
...2019-Mar. 2020; n (%)	2,314 (10.7%)	2,857 (9.3%)	0.0467				2,314 (10.7%)	2,857 (9.3%)	0.047
DMG - Age									
...mean (sd)	67.67 (10.33)	64.58 (13.34)	0.2590	65.73 (11.22)	62.49 (14.22)	0.2530	66.45 (10.90)	63.16 (13.94)	0.263
...median [IQR]	68.00 [60.00, 75.00]	66.00 [56.00, 74.00]	0.1676	64.00 [58.00, 74.00]	62.00 [54.00, 73.00]	0.1562	65.49 (10.90)	63.28 (13.94)	0.177
DMG - Gender									
...Male; n (%)	7,779 (35.9%)	10,307 (33.7%)	0.0462	14,471 (39.4%)	22,933 (35.5%)	0.0806	22,250 (38.1%)	33,240 (34.9%)	0.067
...Female; n (%)	13,910 (64.1%)	20,263 (66.3%)	-0.0462	22,256 (60.6%)	41,720 (64.5%)	-0.0806	36,166 (61.9%)	61,983 (65.1%)	-0.067
DMG - Geographic region									
...Northeast; n (%)	2,144 (9.9%)	2,997 (9.8%)	0.0034	5,662 (15.4%)	10,090 (15.6%)	-0.0055	7,806 (13.4%)	13,087 (13.7%)	-0.009
...South; n (%)	9,881 (45.6%)	13,979 (45.7%)	-0.0020	13,969 (38.0%)	23,938 (37.0%)	0.0207	23,850 (40.8%)	37,917 (39.8%)	0.020
...North Central; n (%)	4,602 (21.2%)	6,546 (21.4%)	-0.0049	12,524 (34.1%)	21,068 (32.6%)	0.0318	17,126 (29.3%)	27,614 (29.0%)	0.007
...West; n (%)	5,062 (23.3%)	7,048 (23.1%)	0.0047	4,572 (12.4%)	9,557 (14.8%)	-0.0701	9,634 (16.5%)	16,605 (17.4%)	-0.024
DRS - Combined comorbidity score, 180 days									
...mean (sd)	1.43 (1.73)	1.20 (1.67)	0.1353	1.13 (1.45)	0.94 (1.39)	0.1338	1.24 (1.56)	1.02 (1.49)	0.144
...median [IQR]	1.00 [0.00, 2.00]	1.00 [0.00, 2.00]	0.0000	1.00 [0.00, 2.00]	1.00 [0.00, 1.00]	0.0000	1.00 (1.56)	1.00 (1.49)	0.000
DRS - Frailty Score: Empirical Version (mean)									
...mean (sd)	0.18 (0.06)	0.17 (0.06)	0.1667	0.17 (0.05)	0.16 (0.05)	0.2000	0.17 (0.05)	0.16 (0.05)	0.200
...median [IQR]	0.17 [0.14, 0.21]	0.16 [0.13, 0.20]	0.1667	0.16 [0.13, 0.19]	0.15 [0.12, 0.18]	0.2000	0.16 (0.05)	0.15 (0.05)	0.200
PLM - Smoking ; n (%)	6,731 (31.0%)	5,954 (19.5%)	0.2671	6,588 (17.9%)	6,674 (10.3%)	0.2197	13,319 (22.8%)	12,628 (13.3%)	0.249
PLM - Pneumonia ; n (%)	1,409 (6.5%)	1,750 (5.7%)	0.0334	2,786 (7.6%)	4,561 (7.1%)	0.0192	4,195 (7.2%)	6,311 (6.6%)	0.024
PLM - Oxygen usage; n (%)	1,538 (7.1%)	1,440 (4.7%)	0.1020	3,158 (8.6%)	3,635 (5.6%)	0.1170	4,696 (8.0%)	5,075 (5.3%)	0.109
PLM - Respiratory arrest/dependence on oxygen ; n (%)	699 (3.2%)	539 (1.8%)	0.0898	1,088 (3.0%)	1,177 (1.8%)	0.0785	1,787 (3.1%)	1,716 (1.8%)	0.084
PLM - CiPAP/BiPAP use; n (%)	904 (4.2%)	1,314 (4.3%)	-0.0050	1,943 (5.3%)	3,038 (4.7%)	0.0275	2,847 (4.9%)	4,352 (4.6%)	0.014
PLM - Pulmonary rehabilitation ; n (%)*	75 (0.3%)	46 (0.2%)	0.0200	150 (0.4%)	103 (0.2%)	0.0366	225 (0.4%)	149 (0.2%)	0.037
PLM - Moderate COPD exacerbation - [Count with 365 to 181 days before CED]*									
...mean (sd)	1.37 (2.84)	1.13 (2.47)	0.0902	1.05 (2.25)	0.83 (1.81)	0.1077	1.17 (2.49)	0.93 (2.05)	0.105
...median [IQR]	0.28 [0.00, 1.53]	0.21 [0.00, 1.00]	0.0263	0.05 [0.00, 1.00]	0.08 [0.00, 1.00]	-0.0147	0.14 (2.49)	0.12 (2.05)	0.009
PLM - Moderate COPD exacerbation - [Count 180 to 31 days before CED]*									
...mean (sd)	0.95 (2.07)	0.72 (1.68)	0.1220	0.68 (1.51)	0.52 (1.22)	0.1166	0.78 (1.74)	0.58 (1.38)	0.127
...median [IQR]	0.00 [0.00, 1.00]	0.00 [0.00, 0.84]	0.0000	0.00 [0.00, 0.81]	0.00 [0.00, 0.66]	0.0000	0.00 (1.74)	0.00 (1.38)	0.000
PLM - Moderate COPD exacerbation - [Count with 30 days to CED]*									
...mean (sd)	0.02 (0.10)	0.01 (0.08)	0.1104	0.01 (0.08)	0.01 (0.07)	0.0000	0.01 (0.09)	0.01 (0.07)	0.000
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (0.09)	0.00 (0.07)	0.000
PLM - Moderate exacerbations >=1 in 365 days before CED; n (%)	15,357 (70.8%)	21,008 (68.7%)	0.0457	23,550 (64.1%)	41,555 (64.3%)	-0.0042	38,907 (66.6%)	62,563 (65.7%)	0.019
PLM - Moderate exacerbations >=2 in 365 days before CED ; n (%)	9,947 (45.9%)	11,428 (37.4%)	0.1731	13,956 (38.0%)	19,175 (29.7%)	0.1761	23,903 (40.9%)	30,603 (32.1%)	0.184
PLM - Severe COPD exacerbation - [Count with 365 to 181 days before CED] *									
...mean (sd)	0.03 (0.18)	0.03 (0.17)	0.0000	0.05 (0.21)	0.04 (0.19)	0.0499	0.04 (0.20)	0.04 (0.18)	0.000
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (0.20)	0.00 (0.18)	0.000
PLM - Severe COPD exacerbation - [Count with 180 to 31 days before CED] *									
...mean (sd)	0.02 (0.14)	0.02 (0.12)	0.0000	0.03 (0.16)	0.02 (0.14)	0.0665	0.03 (0.15)	0.02 (0.13)	0.071
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (0.15)	0.00 (0.13)	0.000
PLM - Severe COPD exacerbation - [Count with 30 days lookback] *									
...mean (sd)	0.00 (0.01)	0.00 (0.01)	0.0000	0.00 (0.01)	0.00 (0.01)	0.0000	0.00 (0.01)	0.00 (0.01)	0.000
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (0.01)	0.00 (0.01)	0.000
PLM - Severe exacerbations >=1 in 365 days before CED; n (%)	1,333 (6.1%)	1,499 (4.9%)	0.0527	3,221 (8.8%)	4,394 (6.8%)	0.0746	4,554 (7.8%)	5,893 (6.2%)	0.063
PLM - Severe exacerbations >=2 in 365 days before CED ; n (%)	118 (0.5%)	128 (0.4%)	0.0149	265 (0.7%)	326 (0.5%)	0.0259	383 (0.7%)	454 (0.5%)	0.026
PLM - GOLD C/D Status ; n (%)	7,067 (32.6%)	7,801 (25.5%)	0.1569	12,368 (33.7%)	16,852 (26.1%)	0.1666	19,435 (33.3%)	24,653 (25.9%)	0.163
PRX - LABA only; n (%)	299 (1.4%)	100 (0.3%)	0.1200	1,170 (3.2%)	338 (0.5%)	0.2014	1,469 (2.5%)	438 (0.5%)	0.165
PRX - LAMA (except tiotropium) inhalers ; n (%)	123 (0.6%)	159 (0.5%)	0.0135	184 (0.5%)	175 (0.3%)	0.0317	307 (0.5%)	334 (0.4%)	0.015
PRX - ICS only inhalers ; n (%)	2,727 (12.6%)	4,010 (13.1%)	-0.0149	6,319 (17.2%)	11,104 (17.2%)	0.0000	9,046 (15.5%)	15,114 (15.9%)	-0.011
PRX - LABA/LAMA inhaler use ; n (%)	146 (0.7%)	96 (0.3%)	0.0567	83 (0.2%)	45 (0.1%)	0.0258	229 (0.4%)	141 (0.1%)	0.060
PRX - Other LABA/ICS combination ; n (%)	3,473 (16.0%)	901 (2.9%)	0.4595	5,501 (15.0%)	1,484 (2.3%)	0.4638	8,974 (15.4%)	2,385 (2.5%)	0.464
PRX - COPD Maintenance therapy inhalers ; n (%)	3,942 (18.2%)	1,224 (4.0%)	0.4640	6,296 (17.1%)	1,719 (2.7%)	0.4968	10,238 (17.5%)	2,943 (3.1%)	0.488
PRX - SAMA inhaler use ; n (%)	765 (3.5%)	1,171 (3.8%)	-0.0160	1,653 (4.5%)	2,912 (4.5%)	0.0000	2,418 (4.1%)	4,083 (4.3%)	-0.010
PRX - SABA use ; n (%)	10,165 (46.9%)	14,075 (46.0%)	0.0180	16,966 (46.2%)	29,037 (44.9%)	0.0261	27,131 (46.4%)	43,112 (45.3%)	0.022
PRX - SABA/SAMA use; n (%)	2,485 (11.5%)	3,905 (12.8%)	-0.0398	4,865 (13.2%)	9,933 (15.4%)	-0.0629	7,350 (12.6%)	13,838 (14.5%)	-0.056
PRX - Antibiotics treatment (180 days to 31 days before CED); n (%)	8,080 (37.3%)	11,493 (37.6%)	-0.0062	14,869 (40.5%)	27,269 (42.2%)	-0.0345	22,949 (39.3%)	38,762 (40.7%)	-0.029

Appendix B

PRX - Antibiotics treatment (30 days to CED); n (%)	3,096 (14.3%)	5,872 (19.2%)	-0.1315	6,246 (17.0%)	14,851 (23.0%)	-0.1504	9,342 (16.0%)	20,723 (21.8%)	-0.149
PRX - Systemic Corticosteroids (with CPT) (180 days to 31 days before CED); n (%)	6,911 (31.9%)	9,913 (32.4%)	-0.0107	11,593 (31.6%)	20,935 (32.4%)	-0.0172	18,504 (31.7%)	30,848 (32.4%)	-0.015
PRX - Systemic Corticosteroids (with CPT) (30 days to CED); n (%)	1,106 (5.1%)	3,126 (10.2%)	-0.1928	2,576 (7.0%)	8,168 (12.6%)	-0.1892	3,682 (6.3%)	11,294 (11.9%)	-0.196
PRX - Roflumilast; n (%)	67 (0.3%)	42 (0.1%)	0.0448	162 (0.4%)	76 (0.1%)	0.0601	229 (0.4%)	118 (0.1%)	0.060
CVD - Unstable angina/MI; n (%)	593 (2.7%)	643 (2.1%)	0.0392	701 (1.9%)	1,029 (1.6%)	0.0229	1,294 (2.2%)	1,672 (1.8%)	0.029
CVD - Stable Angina ; n (%)	403 (1.9%)	486 (1.6%)	0.0229	573 (1.6%)	834 (1.3%)	0.0251	976 (1.7%)	1,320 (1.4%)	0.024
CVD - Any Heart failure (HF) ; n (%)	1,334 (6.2%)	1,649 (5.4%)	0.0342	2,076 (5.7%)	3,132 (4.8%)	0.0404	3,410 (5.8%)	4,781 (5.0%)	0.035
CVD - Atrial fibrillation; n (%)	1,091 (5.0%)	1,261 (4.1%)	0.0432	1,764 (4.8%)	2,458 (3.8%)	0.0493	2,855 (4.9%)	3,719 (3.9%)	0.049
CVD - Other dysrythmias ; n (%)*	1,576 (7.3%)	1,894 (6.2%)	0.0439	2,195 (6.0%)	3,210 (5.0%)	0.0439	3,771 (6.5%)	5,104 (5.4%)	0.047
CVD - Valve disorder ; n (%)	277 (1.3%)	332 (1.1%)	0.0184	336 (0.9%)	612 (0.9%)	0.0000	613 (1.0%)	944 (1.0%)	0.000
CVD - Implantable cardioverter defibrillator ; n (%)*	69 (0.3%)	82 (0.3%)	0.0000	111 (0.3%)	109 (0.2%)	0.0200	180 (0.3%)	191 (0.2%)	0.020
CVD - CABG/PCI; n (%)	521 (2.4%)	534 (1.7%)	0.0494	464 (1.3%)	595 (0.9%)	0.0384	985 (1.7%)	1,129 (1.2%)	0.042
CVD - Coronary atherosclerosis and other forms of chronic ischemic heart disease; n (%)	2,581 (11.9%)	2,968 (9.7%)	0.0709	4,121 (11.2%)	5,577 (8.6%)	0.0871	6,702 (11.5%)	8,545 (9.0%)	0.082
CVD - Stroke/TIA ; n (%)	641 (3.0%)	713 (2.3%)	0.0436	943 (2.6%)	1,546 (2.4%)	0.0128	1,584 (2.7%)	2,259 (2.4%)	0.019
CVD - Peripheral Vascular Disease (PVD) or PVD Surgery; n (%)	1,693 (7.8%)	1,661 (5.4%)	0.0968	1,776 (4.8%)	2,384 (3.7%)	0.0545	3,469 (5.9%)	4,045 (4.2%)	0.078
CVD - Hyperlipidemia ; n (%)	9,573 (44.1%)	12,176 (39.8%)	0.0872	10,218 (27.8%)	15,419 (23.8%)	0.0915	19,791 (33.9%)	27,595 (29.0%)	0.106
CVD - Hypertension; n (%)	11,323 (52.2%)	14,593 (47.7%)	0.0901	13,871 (37.8%)	21,783 (33.7%)	0.0856	25,194 (43.1%)	36,376 (38.2%)	0.100
CRX - ACEi or ARB; n (%)	8,168 (37.7%)	11,243 (36.8%)	0.0186	13,292 (36.2%)	22,744 (35.2%)	0.0209	21,460 (36.7%)	33,987 (35.7%)	0.021
CRX - Mineralocorticoid receptor antagonist ; n (%)	325 (1.5%)	516 (1.7%)	-0.0159	778 (2.1%)	1,227 (1.9%)	0.0143	1,103 (1.9%)	1,743 (1.8%)	0.007
CRX - Loop or Thiazide diuretics; n (%)	4,670 (21.5%)	6,398 (20.9%)	0.0147	8,382 (22.8%)	14,759 (22.8%)	0.0000	13,052 (22.3%)	21,157 (22.2%)	0.002
CRX - Statins and other lipid lowering agents; n (%)	8,977 (41.4%)	11,512 (37.7%)	0.0757	14,474 (39.4%)	23,089 (35.7%)	0.0765	23,451 (40.1%)	34,601 (36.3%)	0.078
CRX - CCB and other antihypertensives; n (%)	4,813 (22.2%)	6,332 (20.7%)	0.0365	8,069 (22.0%)	13,275 (20.5%)	0.0367	12,882 (22.1%)	19,607 (20.6%)	0.037
CRX - Digoxin ; n (%)*	314 (1.4%)	440 (1.4%)	0.0000	923 (2.5%)	1,584 (2.5%)	0.0000	1,237 (2.1%)	2,024 (2.1%)	0.000
CRX - Nitrates; n (%)*	702 (3.2%)	908 (3.0%)	0.0115	1,615 (4.4%)	2,613 (4.0%)	0.0199	2,317 (4.0%)	3,521 (3.7%)	0.016
OCM - Type 1 or 2 DM; n (%)	4,453 (20.5%)	6,394 (20.9%)	-0.0099	6,166 (16.8%)	10,874 (16.8%)	0.0000	10,619 (18.2%)	17,268 (18.1%)	0.003
OCM - Occurrence of Diabetic retinopathy/nephropathy/neuropathy; n (%)*	1,266 (5.8%)	1,801 (5.9%)	-0.0043	1,080 (2.9%)	1,727 (2.7%)	0.0121	2,346 (4.0%)	3,528 (3.7%)	0.016
OCM - Hypertensive nephropathy; n (%)*	689 (3.2%)	848 (2.8%)	0.0235	453 (1.2%)	611 (0.9%)	0.0294	1,142 (2.0%)	1,459 (1.5%)	0.038
OCM - Hypotension ; n (%)*	383 (1.8%)	423 (1.4%)	0.0319	466 (1.3%)	621 (1.0%)	0.0281	849 (1.5%)	1,044 (1.1%)	0.035
OCM - Hyperkalemia ; n (%)*	210 (1.0%)	269 (0.9%)	0.0103	219 (0.6%)	297 (0.5%)	0.0135	429 (0.7%)	566 (0.6%)	0.012
OCM - CKD II, III, or IV; n (%)	1,196 (5.5%)	1,533 (5.0%)	0.0224	665 (1.8%)	968 (1.5%)	0.0236	1,861 (3.2%)	2,501 (2.6%)	0.036
OCM - HD/PD/ESRD; n (%)*	73 (0.3%)	96 (0.3%)	0.0000	155 (0.4%)	268 (0.4%)	0.0000	228 (0.4%)	364 (0.4%)	0.000
OCM - Osteoporosis; n (%)	2,569 (11.8%)	3,180 (10.4%)	0.0446	3,643 (9.9%)	5,889 (9.1%)	0.0273	6,212 (10.6%)	9,069 (9.5%)	0.037
OCM - Sleep apnea ; n (%)	2,011 (9.3%)	2,533 (8.3%)	0.0353	3,369 (9.2%)	4,832 (7.5%)	0.0615	5,380 (9.2%)	7,365 (7.7%)	0.054
OCM - Fractures ; n (%)	939 (4.3%)	1,250 (4.1%)	0.0100	1,631 (4.4%)	2,887 (4.5%)	-0.0048	2,570 (4.4%)	4,137 (4.3%)	0.005
OCM - Other Arthritis, Arthropathies and Musculoskeletal Pain ; n (%)	7,847 (36.2%)	11,143 (36.5%)	-0.0062	11,173 (30.4%)	20,027 (31.0%)	-0.0130	19,020 (32.6%)	31,170 (32.7%)	-0.002
OCM - Dorsopathies; n (%)	6,114 (28.2%)	8,136 (26.6%)	0.0359	8,276 (22.5%)	13,884 (21.5%)	0.0241	14,390 (24.6%)	22,020 (23.1%)	0.035
OCM - Gout (acute/chronic) ; n (%)*	143 (0.7%)	251 (0.8%)	-0.0116	278 (0.8%)	437 (0.7%)	0.0116	421 (0.7%)	688 (0.7%)	0.000
OCM - Hyperthyroidism ; n (%)*	136 (0.6%)	171 (0.6%)	0.0000	179 (0.5%)	286 (0.4%)	0.0149	315 (0.5%)	457 (0.5%)	0.000
OCM - Hypothyroidism ; n (%)*	2,033 (9.4%)	2,899 (9.5%)	-0.0034	2,650 (7.2%)	4,532 (7.0%)	0.0078	4,683 (8.0%)	7,431 (7.8%)	0.007
OCM - VTE ; n (%)*	400 (1.8%)	502 (1.6%)	0.0155	663 (1.8%)	1,090 (1.7%)	0.0076	1,063 (1.8%)	1,592 (1.7%)	0.008
OCM - GERD ; n (%)	3,134 (14.4%)	3,995 (13.1%)	0.0378	2,891 (7.9%)	4,522 (7.0%)	0.0343	6,025 (10.3%)	8,517 (8.9%)	0.048
OCM - Cancer ; n (%)	2,248 (10.4%)	2,942 (9.6%)	0.0267	3,071 (8.4%)	4,758 (7.4%)	0.0371	5,319 (9.1%)	7,700 (8.1%)	0.036
OCM - Hypovolemia/volume depletion ; n (%)*	468 (2.2%)	601 (2.0%)	0.0139	622 (1.7%)	1,021 (1.6%)	0.0079	1,090 (1.9%)	1,622 (1.7%)	0.015
OCM - Anemia ; n (%)	2,185 (10.1%)	3,009 (9.8%)	0.0100	2,840 (7.7%)	4,754 (7.4%)	0.0114	5,025 (8.6%)	7,763 (8.2%)	0.014
OCM - Dementia ; n (%)*	777 (3.6%)	968 (3.2%)	0.0221	887 (2.4%)	1,320 (2.0%)	0.0273	1,664 (2.8%)	2,288 (2.4%)	0.025
OCM - Depression ; n (%)	3,467 (16.0%)	4,284 (14.0%)	0.0560	3,580 (9.7%)	5,735 (8.9%)	0.0275	7,047 (12.1%)	10,019 (10.5%)	0.051
ORX - Metformin; n (%)*	2,200 (10.1%)	3,182 (10.4%)	-0.0099	3,134 (8.5%)	5,875 (9.1%)	-0.0212	5,334 (9.1%)	9,057 (9.5%)	-0.014
ORX - 1st and 2nd Generation SUs ; n (%)	1,054 (4.9%)	1,597 (5.2%)	-0.0137	1,837 (5.0%)	3,494 (5.4%)	-0.0180	2,891 (4.9%)	5,091 (5.3%)	-0.018
ORX - Insulins ; n (%)	897 (4.1%)	1,355 (4.4%)	-0.0149	1,551 (4.2%)	2,879 (4.5%)	-0.0147	2,448 (4.2%)	4,234 (4.4%)	-0.010
ORX - Other antidiabetic medications use; n (%)	826 (3.8%)	1,179 (3.9%)	-0.0052	1,704 (4.6%)	3,252 (5.0%)	-0.0187	2,530 (4.3%)	4,431 (4.7%)	-0.019
ORX - PPIs or H2RAs use; n (%)*	5,118 (23.6%)	6,819 (22.3%)	0.0309	7,835 (21.3%)	13,897 (21.5%)	-0.0049	12,953 (22.2%)	20,716 (21.8%)	0.010
ORX - NSAIDs ; n (%)*	3,492 (16.1%)	5,242 (17.1%)	-0.0269	6,115 (16.6%)	11,947 (18.5%)	-0.0500	9,607 (16.4%)	17,189 (18.1%)	-0.045
ORX - Use of opioids ; n (%)*	7,529 (34.7%)	10,709 (35.0%)	-0.0063	13,564 (36.9%)	23,859 (36.9%)	0.0000	21,093 (36.1%)	34,568 (36.3%)	-0.004
ORX - Use of antipsychotics ; n (%)*	992 (4.6%)	1,281 (4.2%)	0.0195	1,445 (3.9%)	2,380 (3.7%)	0.0105	2,437 (4.2%)	3,661 (3.8%)	0.020
ORX - Use of antidepressants ; n (%)	7,865 (36.3%)	10,356 (33.9%)	0.0503	12,794 (34.8%)	21,535 (33.3%)	0.0317	20,659 (35.4%)	31,891 (33.5%)	0.040
ORX - Use of anxiolytics/hypnotics ; n (%)	2,098 (9.7%)	3,001 (9.8%)	-0.0034	3,956 (10.8%)	7,101 (11.0%)	-0.0064	6,054 (10.4%)	10,102 (10.6%)	-0.007
ORX - Use of anticonvulsants ; n (%)*	3,680 (17.0%)	4,802 (15.7%)	0.0352	4,975 (13.5%)	8,461 (13.1%)	0.0118	8,655 (14.8%)	13,263 (13.9%)	0.026
ORX - Use of Benzodiazepines ; n (%)*	3,637 (16.8%)	5,129 (16.8%)	0.0000	8,276 (22.5%)	13,795 (21.3%)	0.0290	11,913 (20.4%)	18,924 (19.9%)	0.012
ORX - Use of dementia meds ; n (%)*	546 (2.5%)	679 (2.2%)	0.0198	871 (2.4%)	1,357 (2.1%)	0.0202	1,417 (2.4%)	2,036 (2.1%)	0.020
ORX - Use of antiparkinsonian meds ; n (%)*	821 (3.8%)	997 (3.3%)	0.0270	1,231 (3.4%)	2,000 (3.1%)	0.0169	2,052 (3.5%)	2,997 (3.1%)	0.022
ORX - Use of oral anticoagulants ; n (%)*	1,035 (4.8%)	1,345 (4.4%)	0.0191	2,074 (5.6%)	3,252 (5.0%)	0.0268	3,109 (5.3%)	4,597 (4.8%)	0.023
ORX - Use of antiplatelet agents ; n (%)*	1,438 (6.6%)	1,582 (5.2%)	0.0594	3,661 (10.0%)	5,416 (8.4%)	0.0554	5,099 (8.7%)	6,998 (7.3%)	0.052
LFS - Obesity; n (%)	1,630 (7.5%)	2,388 (7.8%)	-0.0113	1,578 (4.3%)	2,791 (4.3%)	0.0000	3,208 (5.5%)	5,179 (5.4%)	0.004
PFT - Spirometry test only; n (%)	4,594 (21.2%)	3,785 (12.4%)	0.2370	9,392 (25.6%)	10,035 (15.5%)	0.2519	13,986 (23.9%)	13,820 (14.5%)	0.240
PFT - Spirometry test only (Count - 180 days to 31 days before CED) *									
...mean (sd)	0.22 (0.74)	0.13 (0.55)	0.1380	0.23 (0.70)	0.15 (0.53)	0.1289	0.23 (0.72)	0.14 (0.54)	0.141

Appendix B

...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (0.72)	0.00 (0.54)	0.000
PFT - Spirometry test only (Count - 30 days to CED) *									
...mean (sd)	0.18 (0.62)	0.08 (0.41)	0.1903	0.20 (0.60)	0.09 (0.39)	0.2174	0.19 (0.61)	0.09 (0.40)	0.194
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (0.61)	0.00 (0.40)	0.000
PFT - Lung volume, Diffuse capacity, pulmonary stress testing (any); n (%)	2,852 (13.1%)	2,795 (9.1%)	0.1276	4,207 (11.5%)	5,282 (8.2%)	0.1109	7,059 (12.1%)	8,077 (8.5%)	0.119
HCU - Pulmonologist visit (180 to 1 day before CED); n (%)	290 (1.3%)	246 (0.8%)	0.0491	7,544 (20.5%)	8,804 (13.6%)	0.1843	7,834 (13.4%)	9,050 (9.5%)	0.123
HCU - Pulmonologist visit on CED; n (%)	43 (0.2%)	28 (0.1%)	0.0258	1,568 (4.3%)	1,216 (1.9%)	0.1388	1,611 (2.8%)	1,244 (1.3%)	0.106
HCU - Pulmonologist visit (Number of during CAP) *									
...mean (sd)	0.08 (1.11)	0.05 (0.93)	0.0293	0.89 (2.39)	0.49 (1.77)	0.1902	0.59 (2.01)	0.35 (1.55)	0.134
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (2.01)	0.00 (1.55)	0.000
HCU - Number of Internal Medicine/Family Medicine Visits									
...mean (sd)	7.62 (11.28)	6.95 (11.33)	0.0593	6.26 (10.74)	5.66 (9.03)	0.0605	6.76 (10.94)	6.07 (9.83)	0.066
...median [IQR]	4.00 [1.00, 10.00]	3.00 [0.00, 9.00]	0.0885	4.00 [1.00, 8.00]	3.00 [1.00, 7.00]	0.1008	4.00 (10.94)	3.00 (9.83)	0.096
HCU - Number of Cardiologist visits									
...mean (sd)	0.89 (3.16)	0.75 (2.76)	0.0472	0.81 (2.83)	0.67 (2.84)	0.0494	0.84 (2.96)	0.70 (2.81)	0.049
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (2.96)	0.00 (2.81)	0.000
HCU - Number of Emergency Department (ED) visits v3									
...mean (sd)	0.47 (1.31)	0.42 (1.18)	0.0401	0.17 (1.10)	0.16 (1.10)	0.0091	0.28 (1.18)	0.24 (1.13)	0.035
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (1.18)	0.00 (1.13)	0.000
HCU - Old hospitalization (-180 days to -31 days before CED) ; n (%)	1,883 (8.7%)	2,196 (7.2%)	0.0555	4,861 (13.2%)	7,875 (12.2%)	0.0300	6,744 (11.5%)	10,071 (10.6%)	0.029
HCU - Recent hospitalization (-30 days to CED date) ; n (%)	202 (0.9%)	264 (0.9%)	0.0000	595 (1.6%)	1,252 (1.9%)	-0.0229	797 (1.4%)	1,516 (1.6%)	-0.016
HCU - Number of hospitalizations during CAP									
...mean (sd)	0.11 (0.38)	0.09 (0.35)	0.0547	0.16 (0.43)	0.16 (0.43)	0.0000	0.14 (0.41)	0.14 (0.41)	0.000
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (0.41)	0.00 (0.41)	0.000
HCU - Blood eosinophilia or Serum IgE test order; n (%)*	109 (0.5%)	161 (0.5%)	0.0000	145 (0.4%)	299 (0.5%)	-0.0149	254 (0.4%)	460 (0.5%)	-0.015
HCU - Pneumococcal vaccine; n (%)	2,791 (12.9%)	3,065 (10.0%)	0.0912	2,119 (5.8%)	2,509 (3.9%)	0.0885	4,910 (8.4%)	5,574 (5.9%)	0.097
HCU - Flu vaccine ; n (%)	4,134 (19.1%)	5,214 (17.1%)	0.0520	4,507 (12.3%)	6,971 (10.8%)	0.0469	8,641 (14.8%)	12,185 (12.8%)	0.058
HCU - Bone mineral density ; n (%)	988 (4.6%)	1,210 (4.0%)	0.0296	1,146 (3.1%)	1,659 (2.6%)	0.0301	2,134 (3.7%)	2,869 (3.0%)	0.039
HCU - Pap smear ; n (%)	817 (3.8%)	1,594 (5.2%)	-0.0676	1,625 (4.4%)	4,095 (6.3%)	-0.0845	2,442 (4.2%)	5,689 (6.0%)	-0.082
HCU - Mammogram ; n (%)	2,744 (12.7%)	3,954 (12.9%)	-0.0060	3,874 (10.5%)	7,572 (11.7%)	-0.0382	6,618 (11.3%)	11,526 (12.1%)	-0.025
HCU - Prostate exam for DRE ; n (%)	694 (3.2%)	751 (2.5%)	0.0421	666 (1.8%)	767 (1.2%)	0.0494	1,360 (2.3%)	1,518 (1.6%)	0.051
HCU - Number of Echocardiogram *									
...mean (sd)	0.20 (1.26)	0.17 (1.13)	0.0251	0.22 (0.79)	0.21 (0.80)	0.0126	0.21 (0.99)	0.20 (0.92)	0.010
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (0.99)	0.00 (0.92)	0.000
HCU - Flexible Sigmoidoscopy or colonoscopy or CT virtual colonoscopy ; n (%)	992 (4.6%)	1,258 (4.1%)	0.0245	1,950 (5.3%)	3,230 (5.0%)	0.0136	2,942 (5.0%)	4,488 (4.7%)	0.014
HCU - Number of Distinct Medication Prescriptions (not generalized to generics)									
...mean (sd)	20.64 (17.20)	20.20 (16.75)	0.0259	19.54 (14.98)	19.61 (15.46)	-0.0046	19.95 (15.84)	19.80 (15.89)	0.009
...median [IQR]	16.00 [9.00, 27.00]	16.00 [9.00, 27.00]	0.0000	16.00 [9.00, 26.00]	16.00 [9.00, 26.00]	0.0000	16.00 (15.84)	16.00 (15.89)	0.000
SES - Copay for pharmacy cost (charges in U.S. $)									
...mean (sd)	32.20 (38.19)	33.47 (36.20)	-0.0341	26.20 (26.21)	26.05 (26.49)	0.0057	28.43 (31.20)	28.43 (29.95)	0.000
...median [IQR]	23.64 [9.89, 41.20]	25.69 [12.25, 43.02]	-0.0551	20.87 [10.38, 35.00]	21.04 [10.00, 35.00]	-0.0065	21.90 (31.20)	22.53 (29.95)	-0.021
SES - Business type									
...Commercial; n (%)	6,697 (30.9%)	13,136 (43.0%)	-0.2527				6,697 (30.9%)	13,136 (43.0%)	-0.253
...Medicare; n (%)	14,992 (69.1%)	17,434 (57.0%)	0.2527				14,992 (69.1%)	17,434 (57.0%)	0.253
SES - Low income indicator ; n (%)	4,586 (21.1%)	4,970 (16.3%)	0.1233				4,586 (21.1%)	4,970 (16.3%)	0.123
SES - Insurance Plan type									
...Comprehensive; n (%)				10,656 (29.0%)	16,804 (26.0%)	0.0672	10,656 (29.0%)	16,804 (26.0%)	0.067
...HMO; n (%)				4,376 (11.9%)	8,310 (12.9%)	-0.0303	4,376 (11.9%)	8,310 (12.9%)	-0.030
...PPO; n (%)				17,092 (46.5%)	30,849 (47.7%)	-0.0240	17,092 (46.5%)	30,849 (47.7%)	-0.024
...Others; n (%)				4,603 (12.5%)	8,690 (13.4%)	-0.0268	4,603 (12.5%)	8,690 (13.4%)	-0.027

* Not included in PS model

Appendix B

PS MATCHED

	OPTUM			MARKETSCAN			POOLED		
	Referent - Tiotropium	Exposure - Salmeterol/Fluticasone	St. Diff	Referent - Tiotropium	Exposure - Salmeterol/Fluticasone	St. Diff	Referent - Tiotropium	Exposure - Salmeterol/Fluticasone	St. Diff
Number of patients	18,017	18,017		31,122	31,122		49,139	49,139	
Calendar Time - Year of Initiation (2004 - 2020)									
...2004-2006; n (%)	1,289 (7.2%)	1,219 (6.8%)	0.0157	5,326 (17.1%)	5,292 (17.0%)	0.0027	6,615 (13.5%)	6,511 (13.3%)	0.006
...2007-2008; n (%)	2,030 (11.3%)	2,065 (11.5%)	-0.0063	5,203 (16.7%)	5,279 (17.0%)	-0.0080	7,233 (14.7%)	7,344 (14.9%)	-0.006
...2009-2011; n (%)	3,594 (19.9%)	3,602 (20.0%)	-0.0025	8,529 (27.4%)	8,599 (27.6%)	-0.0045	12,123 (24.7%)	12,201 (24.8%)	-0.002
...2012-2015; n (%)	5,440 (30.2%)	5,414 (30.0%)	0.0044	9,009 (28.9%)	8,912 (28.6%)	0.0066	14,449 (29.4%)	14,326 (29.2%)	0.004
...2016-2018; n (%)	3,880 (21.5%)	3,887 (21.6%)	-0.0024	3,055 (9.8%)	3,040 (9.8%)	0.0000	6,935 (14.1%)	6,927 (14.1%)	0.000
...2019-Mar. 2020; n (%)	1,784 (9.9%)	1,830 (10.2%)	-0.0100				1,784 (9.9%)	1,830 (10.2%)	-0.010
DMG - Age									
...mean (sd)	67.43 (10.50)	67.84 (11.57)	-0.0371	65.64 (11.34)	66.01 (12.78)	-0.0306	66.30 (11.04)	66.68 (12.35)	-0.032
...median [IQR]	68.00 [60.00, 75.00]	69.00 [60.00, 76.00]	-0.0905	64.00 [58.00, 74.00]	65.00 [57.00, 76.00]	-0.0828	65.47 (11.04)	66.47 (12.35)	-0.085
DMG - Gender									
...Male; n (%)	6,330 (35.1%)	6,304 (35.0%)	0.0021	12,025 (38.6%)	12,000 (38.6%)	0.0000	18,355 (37.4%)	18,304 (37.2%)	0.004
...Female; n (%)	11,687 (64.9%)	11,713 (65.0%)	-0.0021	19,097 (61.4%)	19,122 (61.4%)	0.0000	30,784 (62.6%)	30,835 (62.8%)	-0.004
DMG - Geographic region									
...Northeast; n (%)	1,731 (9.6%)	1,705 (9.5%)	0.0034	4,713 (15.1%)	4,752 (15.3%)	-0.0056	6,444 (13.1%)	6,457 (13.1%)	0.000
...South; n (%)	8,144 (45.2%)	8,102 (45.0%)	0.0040	11,758 (37.8%)	11,766 (37.8%)	0.0000	19,902 (40.5%)	19,868 (40.4%)	0.002
...North Central; n (%)	3,811 (21.2%)	3,855 (21.4%)	-0.0049	10,606 (34.1%)	10,593 (34.0%)	0.0021	14,417 (29.3%)	14,448 (29.4%)	-0.002
...West; n (%)	4,331 (24.0%)	4,355 (24.2%)	-0.0047	4,045 (13.0%)	4,011 (12.9%)	0.0030	8,376 (17.0%)	8,366 (17.0%)	0.000
DRS - Combined comorbidity score, 180 days									
...mean (sd)	1.37 (1.71)	1.38 (1.78)	-0.0057	1.10 (1.45)	1.10 (1.52)	0.0000	1.20 (1.55)	1.20 (1.62)	0.000
...median [IQR]	1.00 [0.00, 2.00]	1.00 [0.00, 2.00]	0.0000	1.00 [0.00, 2.00]	1.00 [0.00, 2.00]	0.0000	1.00 (1.55)	1.00 (1.62)	0.000
DRS - Frailty Score: Empirical Version (mean)									
...mean (sd)	0.18 (0.06)	0.18 (0.06)	0.0000	0.17 (0.05)	0.17 (0.06)	0.0000	0.17 (0.05)	0.17 (0.06)	0.000
...median [IQR]	0.17 [0.14, 0.21]	0.17 [0.14, 0.21]	0.0000	0.16 [0.13, 0.19]	0.15 [0.13, 0.19]	0.1811	0.16 (0.05)	0.16 (0.06)	0.000
PLM - Smoking ; n (%)	4,968 (27.6%)	4,844 (26.9%)	0.0157	4,977 (16.0%)	4,803 (15.4%)	0.0165	9,945 (20.2%)	9,647 (19.6%)	0.015
PLM - Pneumonia ; n (%)	1,122 (6.2%)	1,104 (6.1%)	0.0042	2,335 (7.5%)	2,288 (7.4%)	0.0038	3,457 (7.0%)	3,392 (6.9%)	0.004
PLM - Oxygen usage; n (%)	1,135 (6.3%)	1,127 (6.3%)	0.0000	2,474 (7.9%)	2,436 (7.8%)	0.0037	3,609 (7.3%)	3,563 (7.3%)	0.000
PLM - Respiratory arrest/dependence on oxygen ; n (%)	452 (2.5%)	452 (2.5%)	0.0000	791 (2.5%)	735 (2.4%)	0.0065	1,243 (2.5%)	1,187 (2.4%)	0.006
PLM - CiPAP/BiPAP use; n (%)	706 (3.9%)	715 (4.0%)	-0.0051	1,569 (5.0%)	1,544 (5.0%)	0.0000	2,275 (4.6%)	2,259 (4.6%)	0.000
PLM - Pulmonary rehabilitation ; n (%)*	49 (0.3%)	36 (0.2%)	0.0200	99 (0.3%)	78 (0.3%)	0.0000	148 (0.3%)	114 (0.2%)	0.020
PLM - Moderate COPD exacerbation - [Count with 365 to 181 days before CED]*									
...mean (sd)	1.27 (2.69)	1.30 (2.75)	-0.0110	0.98 (2.17)	0.97 (2.04)	0.0047	1.09 (2.37)	1.09 (2.33)	0.000
...median [IQR]	0.22 [0.00, 1.35]	0.27 [0.00, 1.40]	-0.0184	0.01 [0.00, 1.00]	0.05 [0.00, 1.00]	-0.0190	0.09 (2.37)	0.13 (2.33)	-0.017
PLM - Moderate COPD exacerbation - [Count 180 to 31 days before CED]*									
...mean (sd)	0.86 (1.93)	0.82 (1.84)	0.0212	0.63 (1.44)	0.62 (1.42)	0.0070	0.71 (1.64)	0.69 (1.59)	0.012
...median [IQR]	0.00 [0.00, 0.95]	0.00 [0.00, 0.93]	0.0000	0.00 [0.00, 0.75]	0.00 [0.00, 0.75]	0.0000	0.00 (1.64)	0.00 (1.59)	0.000
PLM - Moderate COPD exacerbation - [Count with 30 days to CED]*									
...mean (sd)	0.02 (0.10)	0.01 (0.09)	0.1051	0.01 (0.08)	0.01 (0.08)	0.0000	0.01 (0.09)	0.01 (0.08)	0.000
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (0.09)	0.00 (0.08)	0.000
PLM - Moderate exacerbations >=1 in 365 days before CED; n (%)	12,493 (69.3%)	12,555 (69.7%)	-0.0087	19,559 (62.8%)	19,638 (63.1%)	-0.0062	32,052 (65.2%)	32,193 (65.5%)	-0.006
PLM - Moderate exacerbations >=2 in 365 days before CED ; n (%)	7,747 (43.0%)	7,755 (43.0%)	0.0000	11,085 (35.6%)	11,239 (36.1%)	-0.0104	18,832 (38.3%)	18,994 (38.7%)	-0.008
PLM - Severe COPD exacerbation - [Count with 365 to 181 days before CED] *									
...mean (sd)	0.03 (0.18)	0.03 (0.18)	0.0000	0.05 (0.21)	0.05 (0.21)	0.0000	0.04 (0.20)	0.04 (0.20)	0.000
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (0.20)	0.00 (0.20)	0.000
PLM - Severe COPD exacerbation - [Count with 180 to 31 days before CED] *									
...mean (sd)	0.02 (0.14)	0.02 (0.13)	0.0000	0.03 (0.15)	0.03 (0.15)	0.0000	0.03 (0.15)	0.03 (0.14)	0.000
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (0.15)	0.00 (0.14)	0.000
PLM - Severe COPD exacerbation - [Count with 30 days lookback] *									
...mean (sd)	0.00 (0.01)	0.00 (0.01)	0.0000	0.00 (0.01)	0.00 (0.01)	0.0000	0.00 (0.01)	0.00 (0.01)	0.000
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (0.01)	0.00 (0.01)	0.000
PLM - Severe exacerbations >=1 in 365 days before CED; n (%)	1,038 (5.8%)	1,015 (5.6%)	0.0086	2,595 (8.3%)	2,650 (8.5%)	-0.0072	3,633 (7.4%)	3,665 (7.5%)	-0.004
PLM - Severe exacerbations >=2 in 365 days before CED ; n (%)	93 (0.5%)	86 (0.5%)	0.0000	198 (0.6%)	198 (0.6%)	0.0000	291 (0.6%)	284 (0.6%)	0.000
PLM - GOLD C/D Status ; n (%)	5,385 (29.9%)	5,395 (29.9%)	0.0000	9,771 (31.4%)	9,873 (31.7%)	-0.0065	15,156 (30.8%)	15,268 (31.1%)	-0.006
PRX - LABA only ; n (%)	93 (0.5%)	99 (0.5%)	0.0000	348 (1.1%)	332 (1.1%)	0.0000	441 (0.9%)	431 (0.9%)	0.000
PRX - LAMA (except tiotropium) inhalers; n (%)	79 (0.4%)	129 (0.7%)	-0.0406	104 (0.3%)	160 (0.5%)	-0.0317	183 (0.4%)	289 (0.6%)	-0.028
PRX - ICS only inhalers ; n (%)	2,225 (12.3%)	2,173 (12.1%)	0.0061	5,212 (16.7%)	5,163 (16.6%)	0.0027	7,437 (15.1%)	7,336 (14.9%)	0.006
PRX - LABA/LAMA inhaler use ; n (%)	114 (0.6%)	80 (0.4%)	0.0284	56 (0.2%)	42 (0.1%)	0.0258	170 (0.3%)	122 (0.2%)	0.020
PRX - Other LABA/ICS combination ; n (%)	916 (5.1%)	892 (5.0%)	0.0046	1,495 (4.8%)	1,469 (4.7%)	0.0047	2,411 (4.9%)	2,361 (4.8%)	0.005
PRX - COPD Maintenance therapy inhalers; n (%)	1,183 (6.6%)	1,169 (6.5%)	0.0040	1,729 (5.6%)	1,698 (5.5%)	0.0044	2,912 (5.9%)	2,867 (5.8%)	0.004
PRX - SAMA inhaler use; n (%)	656 (3.6%)	654 (3.6%)	0.0000	1,405 (4.5%)	1,431 (4.6%)	-0.0048	2,061 (4.2%)	2,085 (4.2%)	0.000
PRX - SABA use; n (%)	8,121 (45.1%)	8,083 (44.9%)	0.0040	13,827 (44.4%)	13,671 (43.9%)	0.0101	21,948 (44.7%)	21,754 (44.3%)	0.008
PRX - SABA/SAMA use; n (%)	2,035 (11.3%)	2,140 (11.9%)	-0.0187	4,133 (13.3%)	4,220 (13.6%)	-0.0088	6,168 (12.6%)	6,360 (12.9%)	-0.009
PRX - Antibiotics treatment (180 days to 31 days before CED); n (%)	6,629 (36.8%)	6,636 (36.8%)	0.0000	12,467 (40.1%)	12,337 (39.6%)	0.0102	19,096 (38.9%)	18,973 (38.6%)	0.006
PRX - Antibiotics treatment (30 days to CED); n (%)	2,690 (14.9%)	2,627 (14.6%)	0.0085	5,514 (17.7%)	5,441 (17.5%)	0.0053	8,204 (16.7%)	8,068 (16.4%)	0.008
PRX - Systemic Corticosteroids (with CPT) use (180 to 31 days before CED); n (%)	5,612 (31.1%)	5,577 (31.0%)	0.0022	9,580 (30.8%)	9,597 (30.8%)	0.0000	15,192 (30.9%)	15,174 (30.9%)	0.000

Appendix B

PRX - Systemic Corticosteroids (with CPT) use (30 days to CED); n (%)	1,016 (5.6%)	940 (5.2%)	0.0177	2,352 (7.6%)	2,284 (7.3%)	0.0114	3,368 (6.9%)	3,224 (6.6%)	0.012
PRX - Roflumilast; n (%) *	40 (0.2%)	31 (0.2%)	0.0000	102 (0.3%)	53 (0.2%)	0.0200	142 (0.3%)	084 (0.2%)	0.020
CVD - Unstable angina/MI; n (%)	468 (2.6%)	464 (2.6%)	0.0000	596 (1.9%)	598 (1.9%)	0.0000	1,064 (2.2%)	1,062 (2.2%)	0.000
CVD - Stable Angina ; n (%)	318 (1.8%)	314 (1.7%)	0.0076	482 (1.5%)	476 (1.5%)	0.0000	800 (1.6%)	790 (1.6%)	0.000
CVD - Any Heart failure (HF) ; n (%)	1,108 (6.1%)	1,131 (6.3%)	-0.0083	1,797 (5.8%)	1,807 (5.8%)	0.0000	2,905 (5.9%)	2,938 (6.0%)	-0.004
CVD - Atrial fibrillation; n (%)	911 (5.1%)	911 (5.1%)	0.0000	1,480 (4.8%)	1,488 (4.8%)	0.0000	2,391 (4.9%)	2,399 (4.9%)	0.000
CVD - Other dysrythmias ; n (%)*	1,256 (7.0%)	1,324 (7.3%)	-0.0116	1,788 (5.7%)	1,841 (5.9%)	-0.0086	3,044 (6.2%)	3,165 (6.4%)	-0.008
CVD - Valve disorder ; n (%)	231 (1.3%)	232 (1.3%)	0.0000	289 (0.9%)	283 (0.9%)	0.0000	520 (1.1%)	515 (1.0%)	0.010
CVD - Implantable cardioverter defibrillator ; n (%)*	51 (0.3%)	59 (0.3%)	0.0000	94 (0.3%)	67 (0.2%)	0.0200	145 (0.3%)	126 (0.3%)	0.000
CVD - CABG/PCI; n (%)	407 (2.3%)	400 (2.2%)	0.0067	375 (1.2%)	359 (1.2%)	0.0000	782 (1.6%)	759 (1.5%)	0.008
CVD - Coronary atherosclerosis and other forms of chronic ischemic heart disease; n (%)	2,082 (11.6%)	2,082 (11.6%)	0.0000	3,397 (10.9%)	3,423 (11.0%)	-0.0032	5,479 (11.2%)	5,505 (11.2%)	0.000
CVD - Stroke/TIA ; n (%)	512 (2.8%)	525 (2.9%)	-0.0060	808 (2.6%)	814 (2.6%)	0.0000	1,320 (2.7%)	1,339 (2.7%)	0.000
CVD - Peripheral Vascular Disease (PVD) or PVD Surgery; n (%)	1,333 (7.4%)	1,330 (7.4%)	0.0000	1,482 (4.8%)	1,478 (4.7%)	0.0047	2,815 (5.7%)	2,808 (5.7%)	0.000
CVD - Hyperlipidemia ; n (%)	7,804 (43.3%)	7,866 (43.7%)	-0.0081	8,374 (26.9%)	8,401 (27.0%)	-0.0023	16,178 (32.9%)	16,267 (33.1%)	-0.004
CVD - Hypertension; n (%)	9,269 (51.4%)	9,370 (52.0%)	-0.0120	11,614 (37.3%)	11,709 (37.6%)	-0.0062	20,883 (42.5%)	21,079 (42.9%)	-0.008
CRX - ACEi or ARB; n (%)	6,749 (37.5%)	6,860 (38.1%)	-0.0124	11,265 (36.2%)	11,481 (36.9%)	-0.0145	18,014 (36.7%)	18,341 (37.3%)	-0.012
CRX - Mineralocorticoid receptor antagonist ; n (%)	268 (1.5%)	300 (1.7%)	-0.0159	654 (2.1%)	655 (2.1%)	0.0000	922 (1.9%)	955 (1.9%)	0.000
CRX - Loop or Thiazide diuretics; n (%)	3,888 (21.6%)	3,980 (22.1%)	-0.0121	7,188 (23.1%)	7,276 (23.4%)	-0.0071	11,076 (22.5%)	11,256 (22.9%)	-0.010
CRX - Statins and other lipid lowering agents; n (%)	7,327 (40.7%)	7,417 (41.2%)	-0.0102	12,165 (39.1%)	12,317 (39.6%)	-0.0102	19,492 (39.7%)	19,734 (40.2%)	-0.010
CRX - CCB and other antihypertensives; n (%)	3,956 (22.0%)	4,018 (22.3%)	-0.0072	6,868 (22.1%)	6,911 (22.2%)	-0.0024	10,824 (22.0%)	10,929 (22.2%)	-0.005
CRX - Digoxin ; n (%)*	279 (1.5%)	299 (1.7%)	-0.0159	804 (2.6%)	874 (2.8%)	-0.0123	1,083 (2.2%)	1,173 (2.4%)	-0.013
CRX - Nitrates; n (%)*	585 (3.2%)	585 (3.2%)	0.0000	1,392 (4.5%)	1,445 (4.6%)	-0.0048	1,977 (4.0%)	2,030 (4.1%)	-0.005
OCM - Type 1 or 2 DM; n (%)	3,731 (20.7%)	3,818 (21.2%)	-0.0123	5,268 (16.9%)	5,288 (17.0%)	-0.0027	8,999 (18.3%)	9,106 (18.5%)	-0.005
OCM - Occurrence of Diabetic retinopathy/nephropathy/neuropathy; n (%)*	1,023 (5.7%)	1,174 (6.5%)	-0.0334	914 (2.9%)	942 (3.0%)	-0.0059	1,937 (3.9%)	2,116 (4.3%)	-0.020
OCM - Hypertensive nephropathy; n (%)*	557 (3.1%)	600 (3.3%)	-0.0114	379 (1.2%)	377 (1.2%)	0.0000	936 (1.9%)	977 (2.0%)	-0.007
OCM - Hypotension ; n (%)*	300 (1.7%)	292 (1.6%)	0.0079	389 (1.2%)	353 (1.1%)	0.0094	689 (1.4%)	645 (1.3%)	0.009
OCM - Hyperkalemia ; n (%)*	170 (0.9%)	191 (1.1%)	-0.0201	185 (0.6%)	170 (0.5%)	0.0135	355 (0.7%)	361 (0.7%)	0.000
OCM - CKD II, III, or IV; n (%)	994 (5.5%)	1,011 (5.6%)	-0.0044	565 (1.8%)	578 (1.9%)	-0.0074	1,559 (3.2%)	1,589 (3.2%)	0.000
OCM - HD/PD/ESRD; n (%)*	60 (0.3%)	63 (0.3%)	0.0000	129 (0.4%)	161 (0.5%)	-0.0149	189 (0.4%)	224 (0.5%)	-0.015
OCM - Osteoporosis; n (%)	2,105 (11.7%)	2,099 (11.7%)	0.0000	3,085 (9.9%)	3,127 (10.0%)	-0.0033	5,190 (10.6%)	5,226 (10.6%)	0.000
OCM - Sleep apnea ; n (%)	1,533 (8.5%)	1,510 (8.4%)	0.0036	2,639 (8.5%)	2,612 (8.4%)	0.0036	4,172 (8.5%)	4,122 (8.4%)	0.004
OCM - Fractures ; n (%)	792 (4.4%)	795 (4.4%)	0.0000	1,410 (4.5%)	1,453 (4.7%)	-0.0095	2,202 (4.5%)	2,248 (4.6%)	-0.005
OCM - Other Arthritis, Arthropathies and Musculoskeletal Pain ; n (%)	6,547 (36.3%)	6,597 (36.6%)	-0.0062	9,534 (30.6%)	9,658 (31.0%)	-0.0087	16,081 (32.7%)	16,255 (33.1%)	-0.009
OCM - Dorsopathies; n (%)	5,053 (28.0%)	5,104 (28.3%)	-0.0067	7,003 (22.5%)	7,086 (22.8%)	-0.0072	12,056 (24.5%)	12,190 (24.8%)	-0.007
OCM - Gout (acute/chronic) ; n (%)*	121 (0.7%)	143 (0.8%)	-0.0116	238 (0.8%)	227 (0.7%)	0.0116	359 (0.7%)	370 (0.8%)	-0.012
OCM - Hyperthyroidism ; n (%)*	121 (0.7%)	107 (0.6%)	0.0124	145 (0.5%)	142 (0.5%)	0.0000	266 (0.5%)	249 (0.5%)	0.000
OCM - Hypothyroidism ; n (%)*	1,760 (9.8%)	1,783 (9.9%)	-0.0034	2,214 (7.1%)	2,255 (7.2%)	-0.0039	3,974 (8.1%)	4,038 (8.2%)	-0.004
OCM - VTE ; n (%)*	333 (1.8%)	337 (1.9%)	-0.0074	570 (1.8%)	583 (1.9%)	-0.0074	903 (1.8%)	920 (1.9%)	-0.007
OCM - GERD ; n (%)	2,541 (14.1%)	2,518 (14.0%)	0.0029	2,368 (7.6%)	2,363 (7.6%)	0.0000	4,909 (10.0%)	4,881 (9.9%)	0.003
OCM - Cancer ; n (%)	1,869 (10.4%)	1,909 (10.6%)	-0.0065	2,579 (8.3%)	2,626 (8.4%)	-0.0036	4,448 (9.1%)	4,535 (9.2%)	-0.003
OCM - Hypovolemia/volume depletion ; n (%)*	383 (2.1%)	404 (2.2%)	-0.0069	523 (1.7%)	558 (1.8%)	-0.0076	906 (1.8%)	962 (2.0%)	-0.015
OCM - Anemia ; n (%)	1,830 (10.2%)	1,853 (10.3%)	-0.0033	2,414 (7.8%)	2,460 (7.9%)	-0.0037	4,244 (8.6%)	4,313 (8.8%)	-0.007
OCM - Dementia ; n (%)*	639 (3.5%)	763 (4.2%)	-0.0364	751 (2.4%)	916 (2.9%)	-0.0311	1,390 (2.8%)	1,679 (3.4%)	-0.035
OCM - Depression ; n (%)	2,800 (15.5%)	2,815 (15.6%)	-0.0028	2,980 (9.6%)	2,938 (9.4%)	0.0068	5,780 (11.8%)	5,753 (11.7%)	0.003
ORX - Metformin; n (%)*	1,839 (10.2%)	1,854 (10.3%)	-0.0033	2,684 (8.6%)	2,719 (8.7%)	-0.0036	4,523 (9.2%)	4,573 (9.3%)	-0.003
ORX - 1st and 2nd Generation SUs ; n (%)	896 (5.0%)	922 (5.1%)	-0.0046	1,594 (5.1%)	1,545 (5.0%)	0.0046	2,490 (5.1%)	2,467 (5.0%)	0.005
ORX - Insulins ; n (%)	755 (4.2%)	776 (4.3%)	-0.0050	1,328 (4.3%)	1,333 (4.3%)	0.0000	2,083 (4.2%)	2,109 (4.3%)	-0.005
ORX - Other antidiabetic medications use; n (%)	683 (3.8%)	662 (3.7%)	0.0053	1,486 (4.8%)	1,481 (4.8%)	0.0000	2,169 (4.4%)	2,143 (4.4%)	0.000
ORX - PPIs or H2RAs use; n (%)*	4,194 (23.3%)	4,378 (24.3%)	-0.0235	6,598 (21.2%)	6,855 (22.0%)	-0.0194	10,792 (22.0%)	11,233 (22.9%)	-0.022
ORX - NSAIDs ; n (%)*	2,930 (16.3%)	3,002 (16.7%)	-0.0108	5,255 (16.9%)	5,441 (17.5%)	-0.0159	8,185 (16.7%)	8,443 (17.2%)	-0.013
ORX - Use of opioids ; n (%)*	6,320 (35.1%)	6,310 (35.0%)	0.0021	11,650 (37.4%)	11,206 (36.0%)	0.0290	17,970 (36.6%)	17,516 (35.6%)	0.021
ORX - Use of antipsychotics ; n (%)*	815 (4.5%)	809 (4.5%)	0.0000	1,220 (3.9%)	1,219 (3.9%)	0.0000	2,035 (4.1%)	2,028 (4.1%)	0.000
ORX - Use of antidepressants ; n (%)	6,448 (35.8%)	6,479 (36.0%)	-0.0042	10,791 (34.7%)	10,840 (34.8%)	-0.0021	17,239 (35.1%)	17,319 (35.2%)	-0.002
ORX - Use of anxiolytics/hypnotics ; n (%)	1,758 (9.8%)	1,771 (9.8%)	0.0000	3,350 (10.8%)	3,360 (10.8%)	0.0000	5,108 (10.4%)	5,131 (10.4%)	0.000
ORX - Use of anticonvulsants ; n (%)*	3,002 (16.7%)	2,999 (16.6%)	0.0027	4,192 (13.5%)	4,186 (13.5%)	0.0000	7,194 (14.6%)	7,185 (14.6%)	0.000
ORX - Use of Benzodiazepines ; n (%)*	3,043 (16.9%)	2,933 (16.3%)	0.0161	7,066 (22.7%)	6,761 (21.7%)	0.0241	10,109 (20.6%)	9,694 (19.7%)	0.022
ORX - Use of dementia meds ; n (%)*	451 (2.5%)	528 (2.9%)	-0.0247	744 (2.4%)	906 (2.9%)	-0.0311	1,195 (2.4%)	1,434 (2.9%)	-0.031
ORX - Use of antiparkinsonian meds ; n (%)*	686 (3.8%)	657 (3.6%)	0.0106	1,028 (3.3%)	1,055 (3.4%)	-0.0056	1,714 (3.5%)	1,712 (3.5%)	0.000
ORX - Use of oral anticoagulants ; n (%)*	879 (4.9%)	891 (4.9%)	0.0000	1,774 (5.7%)	1,819 (5.8%)	-0.0043	2,653 (5.4%)	2,710 (5.5%)	-0.004
ORX - Use of antiplatelet agents ; n (%)*	1,174 (6.5%)	1,104 (6.1%)	0.0165	3,085 (9.9%)	2,922 (9.4%)	0.0169	4,259 (8.7%)	4,026 (8.2%)	0.018
LFS - Obesity; n (%)	1,298 (7.2%)	1,310 (7.3%)	-0.0039	1,289 (4.1%)	1,290 (4.1%)	0.0000	2,587 (5.3%)	2,600 (5.3%)	0.000
PFT - Spirometry test only; n (%)	3,180 (17.6%)	3,028 (16.8%)	0.0212	7,080 (22.7%)	6,932 (22.3%)	0.0096	10,260 (20.9%)	9,960 (20.3%)	0.015
PFT - Spirometry test only (Count - 180 days to 31 days before CED) *									
...mean (sd)	0.18 (0.66)	0.18 (0.65)	0.0000	0.20 (0.64)	0.22 (0.65)	-0.0310	0.19 (0.65)	0.21 (0.65)	-0.031
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (0.65)	0.00 (0.65)	0.000
PFT - Spirometry test only (Count - 30 days to CED) *									

Appendix B

...mean (sd)	0.14 (0.56)	0.11 (0.48)	0.0575	0.17 (0.55)	0.13 (0.47)	0.0782	0.16 (0.55)	0.12 (0.47)	0.078
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (0.55)	0.00 (0.47)	0.000
PFT - Lung volume, Diffuse capacity, pulmonary stress testing (any); n (%)	1,987 (11.0%)	1,910 (10.6%)	0.0129	3,084 (9.9%)	2,970 (9.5%)	0.0135	5,071 (10.3%)	4,880 (9.9%)	0.013
HCU - Pulmonologist visit (180 to 1 day before CED); n (%)	189 (1.0%)	182 (1.0%)	0.0000	5,646 (18.1%)	5,482 (17.6%)	0.0131	5,835 (11.9%)	5,664 (11.5%)	0.012
HCU - Pulmonologist visit on CED; n (%)	24 (0.1%)	24 (0.1%)	0.0000	949 (3.0%)	932 (3.0%)	0.0000	973 (2.0%)	956 (1.9%)	0.007
HCU - Pulmonologist visit (Number of during CAP) *									
...mean (sd)	0.06 (0.94)	0.07 (0.94)	-0.0106	0.75 (2.21)	0.70 (2.11)	0.0231	0.50 (1.85)	0.47 (1.77)	0.017
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (1.85)	0.00 (1.77)	0.000
HCU - Number of Internal Medicine/Family Medicine Visits									
...mean (sd)	7.48 (11.28)	7.62 (11.09)	-0.0125	6.14 (9.32)	6.16 (9.74)	-0.0021	6.63 (10.08)	6.70 (10.26)	-0.007
...median [IQR]	4.00 [1.00, 10.00]	4.00 [1.00, 10.00]	0.0000	4.00 [1.00, 8.00]	3.00 [1.00, 8.00]	0.1049	4.00 (10.08)	3.37 (10.26)	0.062
HCU - Number of Cardiologist visits									
...mean (sd)	0.86 (3.19)	0.86 (2.82)	0.0000	0.79 (2.82)	0.79 (3.36)	0.0000	0.82 (2.96)	0.82 (3.17)	0.000
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (2.96)	0.00 (3.17)	0.000
HCU - Number of Emergency Department (ED) visits v3									
...mean (sd)	0.46 (1.29)	0.47 (1.25)	-0.0079	0.17 (1.12)	0.16 (0.95)	0.0096	0.28 (1.19)	0.27 (1.07)	0.009
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (1.19)	0.00 (1.07)	0.000
HCU - Old hospitalization (-180 days to -31 days before CED) ; n (%)	1,508 (8.4%)	1,514 (8.4%)	0.0000	4,137 (13.3%)	4,095 (13.2%)	0.0029	5,645 (11.5%)	5,609 (11.4%)	0.003
HCU - Recent hospitalization (-30 days to CED date) ; n (%)	166 (0.9%)	166 (0.9%)	0.0000	532 (1.7%)	523 (1.7%)	0.0000	698 (1.4%)	689 (1.4%)	0.000
HCU - Number of hospitalizations during CAP									
...mean (sd)	0.11 (0.37)	0.11 (0.37)	0.0000	0.17 (0.43)	0.16 (0.43)	0.0233	0.15 (0.41)	0.14 (0.41)	0.024
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (0.41)	0.00 (0.41)	0.000
HCU - Blood eosinophilia or Serum IgE test order; n (%)*	85 (0.5%)	93 (0.5%)	0.0000	113 (0.4%)	136 (0.4%)	0.0000	198 (0.4%)	229 (0.5%)	-0.015
HCU - Pneumococcal vaccine; n (%)	2,119 (11.8%)	2,112 (11.7%)	0.0031	1,615 (5.2%)	1,601 (5.1%)	0.0045	3,734 (7.6%)	3,713 (7.6%)	0.000
HCU - Flu vaccine ; n (%)	3,385 (18.8%)	3,370 (18.7%)	0.0026	3,684 (11.8%)	3,659 (11.8%)	0.0000	7,069 (14.4%)	7,029 (14.3%)	0.003
HCU - Bone mineral density ; n (%)	795 (4.4%)	788 (4.4%)	0.0000	931 (3.0%)	953 (3.1%)	-0.0058	1,726 (3.5%)	1,741 (3.5%)	0.000
HCU - Pap smear ; n (%)	711 (3.9%)	707 (3.9%)	0.0000	1,429 (4.6%)	1,419 (4.6%)	0.0000	2,140 (4.4%)	2,126 (4.3%)	0.005
HCU - Mammogram ; n (%)	2,274 (12.6%)	2,273 (12.6%)	0.0000	3,319 (10.7%)	3,340 (10.7%)	0.0000	5,593 (11.4%)	5,613 (11.4%)	0.000
HCU - Prostate exam for DRE ; n (%)	542 (3.0%)	545 (3.0%)	0.0000	517 (1.7%)	509 (1.6%)	0.0079	1,059 (2.2%)	1,054 (2.1%)	0.007
HCU - Number of Echocardiogram *									
...mean (sd)	0.20 (1.27)	0.19 (1.21)	0.0081	0.23 (0.80)	0.23 (0.84)	0.0000	0.22 (1.00)	0.22 (0.99)	0.000
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (1.00)	0.00 (0.99)	0.000
HCU - Flexible Sigmoidoscopy or colonoscopy or CT virtual colonoscopy ; n (%)	816 (4.5%)	808 (4.5%)	0.0000	1,609 (5.2%)	1,634 (5.3%)	-0.0045	2,425 (4.9%)	2,442 (5.0%)	-0.005
HCU - Number of Distinct Medication Prescriptions (not generalized to generics)									
...mean (sd)	20.27 (17.04)	20.34 (16.67)	-0.0042	19.34 (15.01)	19.39 (15.01)	-0.0033	19.68 (15.78)	19.74 (15.64)	-0.004
...median [IQR]	16.00 [8.00, 27.00]	16.00 [9.00, 27.00]	0.0000	16.00 [9.00, 26.00]	16.00 [9.00, 26.00]	0.0000	16.00 (15.78)	16.00 (15.64)	0.000
SES - Copay for pharmacy cost (charges in U.S. $)									
...mean (sd)	32.00 (38.05)	31.87 (35.15)	0.0035	25.66 (26.01)	25.75 (26.16)	-0.0035	27.98 (30.97)	27.99 (29.77)	0.000
...median [IQR]	23.60 [10.60, 40.25]	24.23 [10.04, 41.52]	-0.0172	20.26 [10.00, 34.37]	20.61 [9.80, 34.59]	-0.0134	21.48 (30.97)	21.94 (29.77)	-0.015
SES - Business type									
...Commercial; n (%)	5,963 (33.1%)	5,735 (31.8%)	0.0278				5,963 (33.1%)	5,735 (31.8%)	0.028
...Medicare; n (%)	12,054 (66.9%)	12,282 (68.2%)	-0.0278				12,054 (66.9%)	12,282 (68.2%)	-0.028
SES - Low income indicator ; n (%)	3,483 (19.3%)	3,604 (20.0%)	-0.0176				3,483 (19.3%)	3,604 (20.0%)	-0.018
SES - Insurance Plan type									
...Comprehensive; n (%)				9,074 (29.2%)	9,146 (29.4%)	-0.0044	9,074 (29.2%)	9,146 (29.4%)	-0.004
...HMO; n (%)				3,810 (12.2%)	3,763 (12.1%)	0.0031	3,810 (12.2%)	3,763 (12.1%)	0.003
...PPO; n (%)				14,372 (46.2%)	14,423 (46.3%)	-0.0020	14,372 (46.2%)	14,423 (46.3%)	-0.002
...Others; n (%)				3,866 (12.4%)	3,790 (12.2%)	0.0061	3,866 (12.4%)	3,790 (12.2%)	0.006

* Not included in PS model