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A Structured Review of Electronic Coding Algorithms for Chronic Obstructive Pulmonary Disorder (COPD) and Acute Exacerbations of COPD (AECOPD) Using Administrative Claims and Electronic Health Records

Final Report

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List of Acronyms

AECOPD	Acute Exacerbations of Chronic Obstructive Pulmonary Disease
ATC	Anatomical Therapeutic Chemical
BEST	Biologics Effectiveness and Safety
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CMS	Centers for Medicare and Medicaid Services
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Datalink
DME	Durable Medical Equipment
DMSS	Defense Medical Surveillance System
ED	Emergency Department
EHR	Electronic Health Record
EMR	Electronic Medical Record
FDA	Food and Drug Administration
GEM	General Equivalence Mapping
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HCPCS	Healthcare Common Procedure Coding System
HES	Hospital Episode Statistics
HIRD	HealthCore Integrated Research Database
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-AM	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
LOINC	Logical Observation Identifiers Names and Codes
LRTI	Lower Respiratory Tract Infection
MDI	Metered Dose Inhalers
MeSH	Medical Subject Headings
NDC	National Drug Code
NPV	Negative Predictive Value
OCS	Oral Corticosteroid Prescription
OR	Odds Ratio
PICO	Population, Intervention, Comparator, Outcome
PPV	Positive Predictive Value
SABDs	Short-Acting Bronchodilators

SES	Socioeconomic Status
SMEs	Subject Matter Experts

A Summary

The United States (U.S.) Food and Drug Administration (FDA) Biologics Effectiveness and Safety (BEST) Initiative conducted a literature review (through July 2020) to identify validated coding algorithms for ascertaining cases of chronic obstructive pulmonary disease (COPD) and acute exacerbations of COPD (AECOPD) in large administrative healthcare databases. The studies selected for this targeted review used billing codes in claims or electronic health record (EHR) databases to derive electronic coding algorithms.

A total of 24 relevant studies were reviewed and are included in the report, with two COPD and three AECOPD studies based in the U.S. providing performance measures (e.g., positive predictive value [PPV], negative predictive value [NPV], sensitivity and/or specificity) for algorithms that sought to identify cases of COPD and AECOPD, respectively. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 491.xx (chronic bronchitis), 492.x (emphysema), and 496 (chronic airway obstruction, not elsewhere classified) were used in all ICD-9-CM COPD algorithm studies. Meanwhile, AECOPD algorithm codes were more variable, yet consistently included ICD-9-CM 491.21 (obstructive chronic bronchitis with [acute] exacerbation), however the algorithms tended to perform with consistently low sensitivities. Only four out of 24 studies included in the report used International Classification of Diseases, Tenth Revision (ICD-10) codes and all were conducted outside the U.S.

Of the 15 COPD algorithm studies reviewed in the report, seven were conducted in the U.S. Of these, only two studies were focused on validating COPD algorithms and both were developed using regression-based modelling. In one COPD study which used spirometry test results to validate logistic regression-based models, the highest performing model incorporated albuterol and ipratropium meter-dosed inhaler (MDI) prescriptions, outpatient and inpatient ICD-9-CM codes, and age, which performed with an area under the curve of 0.79.[1] In the other U.S. study the spirometry-based Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition was used to validate a model comprised of age, sex, comorbidities, along with healthcare utilization resources, which was found to accurately predict 73.5% of COPD patients.[2]

The scope of the literature review for informing COPD algorithm development was expanded to studies outside the U.S. A validated Canadian study using traditional chart review applied an ICD-10 algorithm to identify COPD cases in administrative claims data resulting in a moderate PPV (57.5%), with high sensitivity (85%) and specificity (78.4%).[3] This study formed the basis of the COPD algorithm in this report and has also been used previously in a U.S. Medicaid study of comorbidities within the COPD population.[4]

Of the nine AECOPD algorithm studies included in the report, seven were based in the U.S. Of these, three studies conducted validations using predictive modelling and traditional code list-based approaches as part of AECOPD algorithm development, which resulted in consistently low sensitivity measures. One study developed a predictive model to identify patients at risk of severe AECOPD using both COPD and respiratory failure codes, as well as antibiotic and corticosteroid prescriptions; validation against claims-based codes for AECOPD resulted in a PPV of 48.1%, sensitivity of 17.3% and NPV of 90%.[5] In another study using the traditional approach of validated claims-based codes via chart review, AECOPD and respiratory failure code algorithms derived a high PPV range between 81-97%, though the sensitivity was very low (12–25%).[6] A third study used only ICD-9 codes 491.2x, 492.8, and 496 to predict AECOPD, which resulted in a high PPV (97%) based on chart review validation.[7] However, this study was conducted in a small population (n= 200 patients) with limited external validity.

The findings from this literature review were leveraged to develop a comprehensive code-based algorithm for identifying COPD and AECOPD. Codes were mapped from ICD-9-CM to International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) via forward–backward mapping, using

General Equivalence Mappings (GEMs) for reference.[i] Input from clinical subject matter experts (SMEs) informed the development and refinement of the algorithm.

The COPD algorithm developed and described in this study includes codes for chronic bronchitis (ICD-9-CM 491.xx; ICD-10-CM J41.x, J42), emphysema (ICD-9-CM 492.0, 492.8; ICD-10-CM J43.x), chronic obstructive asthma (ICD-9-CM 493.2x), bronchiectasis (ICD-9-CM 494.0, 494.1; ICD-10-CM J47.0, J47.1), chronic airway obstruction (ICD-9-CM 496), and COPD (ICD-10-CM J44.x). Note that a few conditions list only an ICD-9-CM or ICD-10-CM code family; this is due to changes in code description between ICD-9-CM and ICD-10-CM, and not due to the exclusion of the ICD-10-CM equivalent of ICD-9-CM codes included in the algorithm. The AECOPD algorithm includes codes for acute bronchitis (ICD-9-CM 466.xx, 490; ICD-10-CM J20.9, J21.x), chronic bronchitis with acute exacerbation (ICD-9-CM 491.2x, 493.22; ICD-10-CM J41.0, J44.0, J44.1), bronchiectasis with acute exacerbation (ICD-9-CM 494.1; ICD-10-CM J47.0, J47.1), and respiratory failure (ICD-9-CM 518.8x; ICD-10-CM J80, J96.0x, R06.03). Users seeking a more specific algorithm may wish to tailor these lists further.

As an initial step in assessing the feasibility of using the algorithm to identify COPD and AECOPD, the algorithms were applied in the IBM MarketScan® Research Databases (Commercial and Medicare Supplemental), a collection of commercially insured individuals in the U.S., to assess the feasibility of its use. Statistics describing the frequency and proportions of COPD codes included in the algorithm were generated, with results reported below.

B Background

Among other responsibilities, the U.S. FDA is mandated to protect public health by ensuring the safety and efficacy of drugs, biologics and medical devices.[ii] In support of this charge, the FDA Center for Biologics Evaluation and Research (CBER) has a mission to conduct policy and regulatory reviews of biologics and related products, including blood products, vaccines, allergenics, tissues, and cellular and gene therapies. CBER assesses the risks and benefits of new biologic products, as well as previously approved products that have been proposed for new indications. The CBER process emphasizes the pursuit of the maximum public benefit with the minimum risk to public safety associated with each biologic product. The BEST Initiative is a program initiated by CBER with the objective of assessing the safety and effectiveness of biologic products using large datasets of administrative healthcare data.

The objective of this review was to assess and understand the validity of electronic coding algorithms using billing codes for identifying COPD and AECOPD from administrative claims and electronic health records (EHRs). These coding algorithms could draw on a variety of standardized classification systems, including the ICD, the Healthcare Common Procedure Coding System (HCPCS), Current Procedural Terminology (CPT®), National Drug Codes (NDCs) and Logical Observation Identifiers Names and Codes (LOINC).

A structured literature review of coding algorithms for identifying potential cases of COPD and AECOPD using administrative claims and EHR data was conducted, leveraging findings from U.S. and international studies to inform algorithm development. The focus of the review was on algorithms derived from administrative claims data (i.e., claims-based), while algorithms derived from EHRs that used standard billing code sets (i.e., EHR-based) were also considered. The draft algorithm was reviewed by clinical SMEs from IBM (TB, JB), FDA CBER (JC, DT), and Acumen, and testing in the IBM MarketScan Research Databases (Commercial and Medicare Supplemental), a large collection of U.S. administrative insurance claims data accessed using the Treatment Pathways analytic tool. **Sections B1** and **B2 below** provide background on both COPD and AECOPD, respectively. **Section C** summarizes the literature

[i] Additional information about GEMs and the methodology for forward and backward mapping can be found Centers for Medicaid and Medicare Services. (2017). 2018 ICD-10-CM and GEMs. Available at https://www.cms.gov/Medicare/Coding/ICD10/2018-ICD-10-CM-and-GEMs. Researchers used the following website to map ICD-9-CM codes to ICD-10-CM: https://www.icd10data.com.
[ii] US Food and Drug Administration. What We Do. March 28, 2018. https://www.fda.gov/aboutfda/whatwedo/

review methodology and findings; **Section D** provides clinical case definitions for COPD and AECOPD, respectively, which could be of value in further assessing the performance of the proposed algorithms via chart review validation studies; **Sections E** and **F** present the algorithms and their associated assumptions and decisions, respectively; **Section G** presents the approach for and results of the initial application of the algorithms to characterize the population with COPD and AECOPD in a claims database; **Section H** provides discussion and **Section I** provides concluding thoughts.

B1 COPD

COPD affects 24 million adults in the U.S., and medical costs are projected to be near 49 billion U.S. dollars this year.[8] Chronic lower respiratory diseases are the fourth leading cause of death in the U.S.[9] The U.S. Centers for Disease Control and Prevention (CDC) reported that COPD-related death rates per 100,000 declined in men from 57 in 1999 to 44.3 in 2014, while remaining stable at 35 for women during this period. There is considerable geographic variation in COPD-related death rates across the country.[9] In 2014, death rates per 100,000 ranged from 15.3 in Hawaii to 62.8 in Kentucky.[9]

In 2015, COPD prevalence was higher in rural settings (4.7% among adults living in metropolitan areas compared to 8.2% among adults in rural areas), while more Medicare hospitalizations and deaths occur than those in urban areas.[10] COPD risk factors include tobacco smoke, environmental and occupational exposures, respiratory infections, genetics, and asthma. Demographic risk factors include older age and low socioeconomic status (SES). Compared to urban residents, rural dwellers smoke more, have less health insurance and lower SES, which negatively impact COPD management.[10] Other rural respiratory exposures associated with COPD may include mold, organic toxic dust, and nitrogen dioxide.

The GOLD 2019 report defines COPD as a “common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway or alveolar abnormalities, usually caused by significant exposure to noxious particles or gases” (p.4).[11] Spirometry is the most reproducible measurement of airflow limitation and pulmonary function testing that is required for COPD diagnosis in the clinical setting. In the presence of appropriate symptoms and environmental exposures, post-bronchodilator forced expiratory volume in 1 second/ forced vital capacity less than 70% confirms the presence of persistent airflow limitation found in COPD.[11] Though adequately sensitive, peak expiratory flow measurements are not specific enough to be reliably used without including other symptoms.

Despite comprehensive GOLD diagnostic criteria, several studies have found that more than half of COPD patients are misdiagnosed as having asthma due to inadequate spirometry use and primary care provider misdiagnoses.[12-14] COPD pathology is different from asthma. The COPD inflammatory response is driven by airway infiltrating neutrophils which irreversibly destroy the lung parenchyma and create airflow obstruction through dynamic compression.[15] In asthma, airway inflammation involves eosinophil infiltration of airways but not lung parenchyma, resulting in airway hyperresponsiveness.[16] Lung function in asthma typically returns to a normal baseline, whereas it does not in patients with COPD. However, there is also an overlapping syndrome of asthma and COPD and some argue the two conditions may share genetic-based common origins with potential for one disease to evolve into the other.[17-19] In addition, chronic unremitting asthma is represented in the figure below as the portion of asthma that overlaps with both chronic bronchitis and emphysema (Error! Reference source not found.).[20] Asthma and COPD are also two common conditions that can overlap by chance.[21]

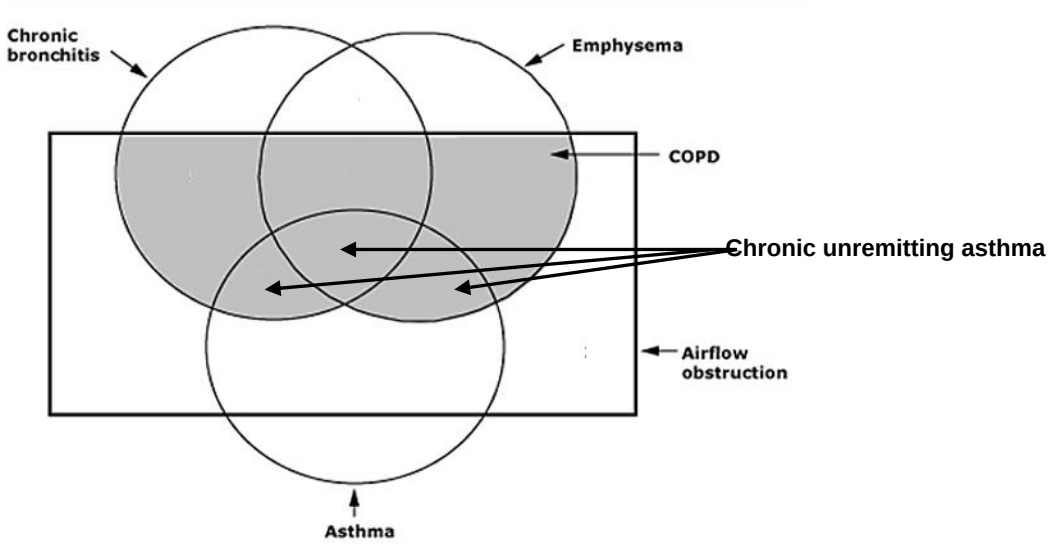

Figure 1. Relationships between chronic bronchitis, emphysema, asthma, and COPD[iii]

B2 AECOPD

AECOPD is defined as an acute worsening of COPD symptoms that result in additional therapy.[22,23] AECOPD involves lung hyperinflation and gas trapping, with reduced expiratory flow, which can result in increased dyspnea, hypercapnia, and hypoxemia.[24,25] According to several studies, over 50% of COPD patients experienced AECOPD within a three-year timespan.[26] Acute exacerbations of COPD are typically not associated with hospital admission.[27] In the East London study, the median exacerbation frequency was 2.5–3 exacerbations per year and nearly 50% of exacerbations went unreported.[28] AECOPD frequency within patients tends to be stable over time, though there is some evidence that an overall decline in lung function can be accompanied by an increase in AECOPD. However, the winter season can increase the incidence of AECOPD by approximately 2-fold compared to the summer, likely due to an increase in respiratory viral infections.[29-31] In a systematic review on COPD and influenza vaccinations, six out of seven studies on vaccine efficacy or effectiveness indicated long-term benefits of seasonal influenza vaccination, such as reduced number of exacerbations, hospitalizations, outpatient visits, all-cause and respiratory mortality.[32] While influenza vaccinations help decrease the risk of AECOPD, the pneumonia vaccine is thought to help prevent bacterial pneumonia, a common cause of COPD exacerbation. GOLD guidelines recommend influenza and pneumonia vaccines for every stage of COPD treatment.[33]

Although AECOPD can be triggered by bacterial and/or viral infections, environmental pollutants, and unknown factors, there are no known causative risk factors associated with AECOPD. Since no diagnostic test is available in the routine clinical setting, an AECOPD is diagnosed when other causes of symptom changes have been excluded. The strongest predictor of future AECOPD is the frequency of exacerbations in the previous year.[34] Chronic bronchitis has been associated with an increased risk and severity of AECOPD.[35]

[iii] Figure adopted from GOLD (2007).[22] Areas shaded in gray represent COPD.

C Literature Review

C1 Methods

The BEST Initiative developed a literature review search strategy based upon a Population, Intervention, Comparator, and Outcome (PICO) framework. The PICO framework for this review can be summarized as follows:

- **Population:** *any population group (human), chronic obstructive pulmonary disease*
- **Intervention:** *any intervention or no intervention*
- **Comparator:** *any comparator, placebo*
- **Outcome:** *chronic obstructive pulmonary disease, and chronic obstructive pulmonary disease acute exacerbations*

The setting for eligible studies was any clinically observable environment that led an individual to seek care.

Briefly, the review process began with conducting systematic searches of existing publications available in the CBER[iv] and Center for Drug Evaluation and Research Sentinel[v] databases (no articles were retrieved from either). Next, a structured review of the academic literature was conducted, using PubMed, and Google Scholar to identify relevant resources. The PubMed search strategy, which is not case-sensitive, is summarized below:

- ***Search 1:*** COPD [MeSH Major Topic] AND diagnos* [Title/Abstract] – **retrieved 6,488 articles**
- ***Search 2:*** COPD [MeSH Major Topic] AND diagnos* [Title/Abstract] AND validation [Title/Abstract] – **retrieved 165 articles**
- ***Search 3:*** COPD [MeSH Major Topic] AND diagnos* [Title/Abstract] AND ICD [Title/Abstract]: **retrieved 87 articles**
- ***Search 4***: COPD [MeSH Major Topic] AND validat* [Title/Abstract] AND ICD [Title/Abstract] – **retrieved 9 results**
- ***Search 5***: COPD acute exacerbation algorithm – **retrieved 90 results**

Similar terms were used in Google Scholar, but additional articles of relevance were not retrieved. A snowballing technique was also applied, wherein the reference lists of relevant studies were scanned for additional publications. Searches were conducted in July 2020 and no publication date restrictions were applied. Only articles available in English were retained.

Since this was not a systematic review, authors did not track the total number of abstracts screened after de-duplication.

All abstracts were reviewed, and 24 articles were reviewed in full text. A Microsoft® Excel spreadsheet was developed to extract relevant data. The data elements collected are provided in **Table 1**. A relevance ranking was assigned based on the judgement of the reviewer and the available information on study location ("Group/Country"), the algorithm specifications ("Algorithm/Criteria"), and the measures of validity and diagnostic accuracy (such as PPV and NPV).

Relevance rankings were assigned based on the following criteria:

[iv] U.S. Food and Drug Administration. Innovation and Regulatory Science. July 10, 2020. https://www.fda.gov/vaccines-blood-biologics/science-research-biologics/innovation-and-regulatory-science
[v] Sentinel. Publications and Presentations. https://www.sentinelinitiative.org/communications/publications

- ***Ranking 1:*** U.S. claims- or EHR-based validation study (i.e., reporting measures of validity and diagnostic accuracy)
- ***Ranking 2:*** U.S. study that reported a claims- or EHR-based coding algorithm but no independent validation OR a non-U.S. validation study
- ***Ranking 3:*** Non-U.S. study that reported a claims- or EHR-based coding algorithm but no independent validation

Table 1. Data elements recorded in the extraction spreadsheet.

Data element
Author
Publication Year
Article Relevance (Ranking 1-3)
Full Citation
Country of Study
Data Source
Years Included
Population Eligibility Criteria
Validation Method
Disease Definition
Algorithm Incidence Rules
ICD-9/ICD-9-CM Codes
ICD-10/ICD-10-CM Codes
Other Codes
PPV % (95% Confidence Interval [CI])
NPV % (95% CI)
Other Performance Measures
Comments

Abbreviations: ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision; PPV, Positive predictive value; NPV, Negative predictive value; 95% CI, 95% confidence interval

C2 Results

Following title and abstract screening, full text review, and data extraction, a total of 24 publications were identified as being of greater relevance for identifying COPD or AECOPD using administrative healthcare datasets. Of these, 15 were relevant to COPD cohort identification and nine were relevant to AECOPD identification. Information from these studies was extracted into **Appendix A**. Each publication reported either measures of diagnostic accuracy associated with EHR-based algorithms (i.e., COPD or AECOPD codes derived from billing codes of admission or discharge medical records) or claims-based algorithms (i.e., COPD or AECOPD codes derived from administrative insurance claims databases). Additional publications identified in the literature review applied a coding algorithm to identify individuals with COPD or cases of AECOPD in administrative claims or EHR/EMR data without validation.

Studies that reported measures of diagnostic accuracy were prioritized, while reports of algorithm applications that did not involve independent validation were also noted to assess the consistency of current approaches. Additional studies identified provided a predictive modelling approach for identifying cases of COPD or AECOPD. Of the 24 studies, 13 were from the U.S., three were from the United Kingdom, two were from Canada, two were from Denmark, and one study each was from Lithuania, Taiwan, and Germany. An additional study was an international systematic review.

We have summarized the literature below by the data source that the coding algorithm was derived from (i.e., insurance reimbursement claims or EHRs), validation with medical charts (i.e., yes or no), and the location of the study (i.e., U.S. or international).

2.a COPD Cohort

i Claims-based Algorithms with Validation

No U.S. validation studies involving a claims-based COPD algorithm were found. Two international claims-based algorithm validation studies were identified.

The best performing algorithm identified in a systematic review for COPD algorithms applied in health systems was from a Canadian study by Gershon and colleagues, which was also used in seven other studies included in the review. Authors conducted a validation study for a COPD cohort identified using administrative claims data.[3,36] An expert panel reviewed 442 medical records of randomly selected adults ≥35 years of age from primary care practices in Ontario to determine a gold standard reference for COPD diagnoses. These reference individuals were then linked to respective health administrative records and compared with predefined claims-based algorithms for COPD. Any inpatient diagnosis with ICD-10 code J41 (chronic bronchitis), J43 (emphysema), or J44 (other COPD), and one physician billing claim as part of Ontario Health Insurance Plan were used. The most sensitive coding algorithm was comprised of ≥1 ambulatory claim or ≥1 hospitalization for COPD, which resulted in a sensitivity of 85.0% (95% CI 77.0–91.0%) and specificity of 78.4% (95% CI 73.6–82.7%). Increasing the number of ambulatory claims resulted in decreased sensitivity and increased specificity. The PPV and NPV for COPD using ≥1 outpatient claim or ≥1 hospitalization was 57.5% (95% CI 49.6–65.1%) and 93.8% (95% CI 90.3–96.4%), respectively.[3]

A cross-sectional study conducted in Taiwan compared claims-based ICD-9-CM COPD codes (491.xx, 492.x, 496) with physician-verified COPD during 2007–2014.[37] A total of 12,127 patients met the criterion of having ≥2 outpatient COPD codes within the span of one year or ≥1 inpatient COPD code in their claims data. Of these potential COPD cases, the diagnosis of COPD was verified by physicians in 7,701 patients (PPV: 63.5%). Three or more outpatient COPD codes or ≥2 inpatient COPD codes increased the PPV to 72.2%. Age ≥65 years and a claim for spirometry were factors most strongly associated with a higher PPV of COPD claim codes. Spirometry testing increased the PPV to 84.6%, though authors did not report what codes were used to identify spirometry.[37]

ii Medical Records-based Algorithms with Validation

No U.S. validation studies involving an EHR-based COPD algorithm were found. Four international studies of EHR-based algorithms with validation were identified.

A UK validation study of COPD-related diagnostic and procedural codes was conducted, using the Clinical Practice Research Datalink (CPRD) database, with 951 participants registered from 2004–2012.[38] Individuals were selected for ≥1 of eight algorithms to identify people with COPD. General practitioners were sent a questionnaire and additional evidence to support a COPD diagnosis was requested. All information received was reviewed independently by two respiratory physicians whose opinion served as the gold standard. Using an ICD-modified diagnostic code (i.e., Read code[vi]) alone, the PPV was 86.5% (95% CI 77.5–92.3%). When the presence of a spirometry test and specific medication was included; the PPV increased to 89.4% (80.7–94.5%) but reduced case numbers by 10%, suggesting that a small increase in accuracy came at the cost of a larger reduction in sensitivity. Algorithms without specific diagnostic codes were associated with a low PPV (range 12.2–44.4%). Authors suggested that the

[vi] Read codes are a hierarchical coding system of clinical terms based on ICD codes and are used in the UK general practice setting.

presence of a specific COPD diagnostic code alone is sufficient to identify patients with COPD using EHR data. The codes used to indicate spirometry testing and specific medications were not described.[38]

In Canada, a retrospective study was conducted on data from the primary care based EHR/Administrative Data Linked Database.[39] Abstracted charts provided the reference standard based on available physician-diagnoses, COPD medications, smoking history, and spirometry. Three hundred sixty-four patients with COPD were identified in a cohort of 5,889 randomly sampled adults aged ≥35 years (prevalence = 6.2%). The EHR algorithm consisting of ≥3 ICD-9 COPD-related billing codes per year; cumulative patient profile descriptions; tiotropium or ipratropium prescription and a COPD billing code had a sensitivity of 76.9% (95% CI 72.2–81.2%), specificity of 99.7% (95% CI 99.5–99.8%), PPV of 93.6% (95% CI 90.3–96.1%), and NPV of 98.5% (95% CI 98.1–98.8%).[39]

A Danish study identified patients with COPD in EHRs from seven general practices.[40] All general practitioners used EHRs and each patient's record was electronically searchable with all communication in and out of practice electronically. Thirty-two ICD-10 J codes were used to construct coding algorithms. The following Anatomical Therapeutic Chemical (ATC) codes were used for medications: R03AC; R03AK; R03BA; R03BB; R03CC; R03DA; R03DC; and V03AN01. Spirometry was identified by using codes 7113 (expanded lung function test verified by spirometry), 7121 (double lung function test for exertion provoked asthma), or a reversibility test. Administrative data on hospital admissions for lung disease related diagnoses, medications, drugs, and spirometry were combined to develop an algorithm that identified the highest proportion of COPD patients with the fewest criteria. The best performing algorithm (using abstracted charts as the reference standard) had a PPV of 72.2% using three criteria: a) discharged patients with a chronic lung-disease diagnosis at least once during the preceding 5 years; or b) ≥2 lung-medication prescriptions within the preceding 12 months; or c) ≥2 spirometry tests performed during the preceding 12 months.[40]

In Lithuania, a validation study of COPD was conducted for codes identified in ambulatory records from a large primary care center.[41] Digital medical records of current patients (n=228) were screened for ICD-10, Australian Modification (ICD-10-AM) codes J44.0 (chronic obstructive pulmonary disease), J44.1 (chronic obstructive pulmonary disease with acute exacerbation), J44.8 (other specified chronic obstructive pulmonary disease) and J44.9 (chronic obstructive pulmonary disease, unspecified). Spirometry test results were used to validate COPD diagnoses and alignment of disease treatment with clinical guidelines. Spirometry was recorded for 58% of the 228 patients, 75% of whom met the guidelines for COPD diagnosis.

iii Algorithm Application without Validation

Westney and colleagues analyzed U.S. Medicaid claims data to assess the impact of comorbidities in COPD among 291,978 patients who continuously enrolled in Medicaid for 12 months in 2019.[4] This study used the validated algorithm by Gershon consisting of ICD-9-CM diagnostic codes 491.0, 491.1, 491.2, 491.8, 492.x, 493.2, 494.xx, and 496.[3] Patients with COPD were identified if they had ≥1 inpatient claim or ≥2 outpatient claims.

Patients with COPD were identified from the U.S. HealthCore Integrated Research Database (HIRD) using at least one ICD-9-CM code 491.xx, 492.x, or 496 for the outcome of pneumonia (ICD-9-CM codes: 480.xx–486.xx).[42] There was no validation conducted to assess the accuracy of the COPD algorithm.

Abraham and colleagues estimated trends in COPD incidence rates from 2001 to 2013 among active duty U.S. military personnel using the Defense Medical Surveillance System (DMSS).[43] The DMSS is a continuously expanding relational database that documents medical encounters of service members throughout their careers. COPD was defined using ICD-9-CM codes 490 (bronchitis not specified as acute or chronic), 491 (chronic bronchitis), 492 (emphysema), 493 (asthma), 494 (bronchiectasis), 495 (extrinsic allergic alveolitis), and 496 (chronic airway obstruction not otherwise specified). The primary algorithm required ≥2 ambulatory medical encounters recorded with identical ICD-9-CM codes within two years. Another less stringent algorithm required only a single ambulatory medical encounter with a given

ICD-9-CM code. The most specific algorithm required ≥3 ambulatory medical encounters with identical ICD-9-CM codes within two years. Algorithms requiring evidence of persistence of the diagnosis over time resulted in lower COPD rates.[43]

In a German EHR-based study, the predictive value of chronic lower airway disease diagnoses, diagnostic procedures and prescribed treatment for asthma and COPD were assessed.[44] All patients with lower airway symptoms (n = 857) who had attended six general practices between January-June 2003 were included. The following ICD-10 codes for chronic lower airway disease were used: J40 (bronchitis, not specified as acute or chronic), J41 (simple and mucopurulent chronic bronchitis), J42 (unspecified chronic bronchitis), J43 (emphysema), J44 (chronic obstructive pulmonary disease), J45 (asthma), J46 (status asthmaticus), J47 (bronchiectasis). Additionally, J98 (diseases of bronchus, not elsewhere classified) and R05 (cough / bronchial hyperreactivity), J20 (acute bronchitis), J21 (acute bronchiolitis) and J22 (unspecified acute lower respiratory infection) were used. The performed diagnostic procedures and the actual medication for each identified patient were extracted and documented manually. Spirometry was used in 58% of ICD-coded COPD patients.

iv Predictive Modelling

In addition to utilizing an administrative- or claims-based code list defined *a priori* for case identification, predictive modelling or machine learning is another potential tool for identifying conditions.

Himes and colleagues identified factors related to COPD progression among U.S. asthma patients using data extracted from EHR.[45] Cases included those with COPD, determined by at least one of the ICD-9-CM codes for chronic bronchitis, emphysema, or chronic airways obstruction, not otherwise specified (specific ICD-9-CM codes were not listed by study authors). A Bayesian model that included age, sex, race, smoking history, and eight comorbidity variables was developed and applied to predict COPD in an independent set of asthma patients. Predictive validation of the model was done by comparing predicted COPD to observed COPD (based on ICD codes). The model was able to predict COPD with an accuracy of 83.3%.[45]

Cooke and colleagues used spirometry test results to validate logistic regression-based algorithmic models from EHR data of 9573 patients treated at two U.S. Veterans Affairs medical centers between 2003-2007.[1] COPD was defined as: 1) FEV1/FVC <0.70, and 2) FEV1/FVC < lower limits of normal. The FEV1/FVC ratio is a measurement of the amount of air, which can be forcefully exhaled from your lungs. FEV1, or forced expiratory volume in one second, is the volume of breath exhaled with effort in that timeframe. FVC, forced vital capacity, is the full amount of air that can be exhaled with effort in a complete breath. Model inputs included age, outpatient, or inpatient COPD-related ICD-9-CM codes, and the number of metered dose inhalers (MDI) prescribed within one year of spirometry. Patients with any of the following ICD-9-CM codes in the primary position were considered to have a COPD-related visit: 491.xx (chronic bronchitis), 492.x (emphysema), 493.2 (chronic obstructive asthma), and 496. ICD-9-CM code 490 (bronchitis, not specified as acute or chronic) was excluded from the COPD definition due to potential misclassification of acute bronchitis cases. Forty-seven percent had an FEV1/FVC <0.70 which indicates misclassification of COPD based on model inputs in the majority (53%) of patients. The presence of ≥1 outpatient COPD-related visit (i.e., relevant ICD-9-CM assigned) had a sensitivity of 76% and specificity of 67%. The best-performing model included: ≥6 albuterol MDI, ≥3 ipratropium MDI, ≥1 outpatient ICD-9-CM code, ≥1 inpatient ICD-9-CM code, and age, with an area under the curve of 0.79.[1]

In 2010, Mapel and colleagues conducted a study to determine if outpatient pharmacy claims can be used for identification of U.S. COPD patients (≥40 years, one or more outpatient or inpatient claims with ICD-9-CM codes: 491–492, 496).[46] To identify drugs that were related to COPD in the years before the diagnosis, a conditional logistic regression model was built with ICD-9-CM defined COPD status as the dependent variable and sex, age, and medication use as independent variables. To validate the algorithm, it was used in two other databases. The reference standard was at least one inpatient or at least two outpatient claims with a COPD diagnosis in the medical records, based on ICD-9-CM codes. The final algorithm identified patients with a specificity of 70.5% and a sensitivity of 60.6%.

A U.S. study by Macauley and colleagues used logistic regression-based models to predict COPD diagnosis and severity.[2] Patients with a COPD diagnosis using three ICD-9-CM codes and spirometry test results were identified from the Geisinger Health System EHR database linked to healthcare claims (from 2004–2011).[2] Patients were retrospectively selected if they had a recorded COPD diagnosis using ICD-9-CM codes 491, 492 or 496 and EHR results from at least one spirometry test. GOLD-based COPD severity criteria were the primary reference standard, with spirometry test results used to validate 10% of patients. Spirometry test results with claims data available for three months before and following the test were selected. The three-month post-test period was included to capture medication use and treatment following a test, which was believed to be associated with COPD severity. Ninety percent of patients in each severity level were randomly selected to build a logistic regression model, and 10% were used as a validation sample. The final model included age, sex, comorbidities, COPD-related resource utilization, and all-cause healthcare utilization. In the validation sample, the model accurately predicted COPD severity for 62.7% of all patients and accurately predicted COPD relative to the GOLD definition for 73.5% of patients.[2]

2.b AECOPD

i Claims-Based Algorithms with Validation

A U.S. retrospective cohort study at two EDs validated ICD-9-CM codes for AECOPD visits.[7] From 2005 to 2006, ICD-9-CM codes 491.2x (obstructive chronic bronchitis), 492.8 (other emphysema), and 496 in the principal diagnosis position were used to identify AECOPD visits. A random sample of 100 visits by patients aged ≥55 years were selected at each institution for a total of 200 cases adjudicated via chart review by two emergency physicians. The case definition for AECOPD was physician-diagnosed COPD, current respiratory infection, change in cough, or change in sputum. In total, 644 eligible AECOPD visits were identified on basis of ICD-9-CM codes. Of these, 193 (96.5%) visits met the case definition for AECOPD. Most cases were identified using code 491.2x. Most false positives occurred using code 496.[7]

ii Medical Records-based Algorithms with Validation

Stein and colleagues assessed the validity of ICD-9-CM codes for AECOPD at two teaching hospitals in the U.S.[6] Four different code-based algorithms for identifying patients hospitalized for AECOPD were validated with chart review (as a reference standard) using a stratified probability sample of 200 hospitalizations. ICD-9-CM codes used in various algorithms as a primary or secondary discharge diagnosis of AECOPD included: 491.0, 491.1, 491.21, 491.22, 491.8, 491.9, 492.0, 492.8, 493.22, and 496. Primary diagnoses of respiratory failure and secondary discharge diagnosis of the following AECOPD codes were also used: 518.81 (acute respiratory failure), 518.82 (other pulmonary insufficiency, not elsewhere classified), 518.84 (acute and chronic respiratory failure), and 799.1 (respiratory arrest). The reference standard-based prevalence of AECOPD was 7.9%. The sensitivity of all ICD-9-CM based algorithms was low (12–25%) and the NPV was high across algorithms (93–94%). The specificity was 99% for all algorithms, and the PPV was more variable (81–97%).

Using the Danish National Patient Registry, Thomsen and colleagues, assessed the PPV of AECOPD diagnoses, while NPV was calculated using acute pneumonia or respiratory failure discharge diagnoses reported without an accompanying COPD diagnosis.[47] Patients aged ≥30 years with outpatient hospital admission in 2008 were identified. Physicians at 34 hospitals reviewed medical records and validated AECOPD diagnoses using medical history, clinical symptoms, and spirometry test results. Among 1,581 patients a PPV of 92% (95% CI 91–93%) was derived for AECOPD identified by an acute hospitalization episode associated with an ICD-10 J44 (COPD with acute lower respiratory infection) discharge diagnosis code. An NPV of 81% (95% CI 79–83%) was derived for AECOPD, as clinicians concluded that 19% (95% CI 17–21%) of patients discharged with a diagnosis for pneumonia or respiratory failure without mention of COPD had COPD.

In the UK, Rothnie and colleagues validated AECOPD codes using EHR data from 1,385 randomly selected patients within the CPRD between 2004 and 2013.[48] Fifteen algorithms for AECOPD were created using UK-based Read diagnostic codes. AECOPD diagnoses were validated by clinician questionnaire responses that were subsequently reviewed by two respiratory physicians. The response rate was 71.3%. An algorithm using AECOPD diagnostic codes, lower respiratory tract infection (LRTI) codes, and combined antibiotics/oral corticosteroid (OCS) prescription use for 5–14 days had a high PPV (>75%) for identifying AECOPD. Symptom-based algorithms and antibiotic or OCS prescriptions had lower PPVs (60–75%). Combining antibiotic and OCS prescriptions for 5–14 days, or LRTI or AECOPD codes resulted in a PPV of 85.5% and a sensitivity of 62.9%.

In another study using the same database, Rothnie and colleagues examined the Hospital Episode Statistics (HES) administrative claims database to determine the predictive value of AECOPD hospitalization discharge data from 27,182 COPD patients who had a record linked to CPRD.[49] Only inpatient data were used, and ED data were excluded. Nearly 60% of the patients included in the CPRD have been linked to HES. Discharge summaries for recent hospitalizations for AECOPD were used to develop a strategy to identify the recording of hospitalizations for AECOPD in HES. Two algorithms were tested: 1) ICD-10 AECOPD hospitalization code J44.0 (chronic obstructive pulmonary disease with [acute] lower respiratory infection), J44.1 (chronic obstructive pulmonary disease with [acute] exacerbation), J22 (Unspecified acute lower respiratory infection), or J44.9 (chronic obstructive pulmonary disease, unspecified) and 2) any non-hospitalization ICD-10 AECOPD code on the same day as a code for hospitalization due to unspecified reason. Identification of AECOPD hospitalization episodes in HES using the two algorithms had a sensitivity of 87.5% (95% CI 72.4–94.9%). Applying Algorithm 1 as the reference standard in CPRD, resulted in a PPV of 50.2% (95% CI 48.5–51.8%) and a sensitivity of 4.1% (95% CI 3.9–4.3%). Using an AECOPD code with a hospitalization code due to unspecified reason (Algorithm 2) resulted in a PPV of 43.3% (95% CI 42.3–44.2%) and a sensitivity of 5.4% (95% CI 5.1–5.7%).

iii Algorithm Application without Validation

In a U.S. study of managed care administrative claims data, Mapel et al, developed an algorithm to identify AECOPD using ICD-9-CM codes.[50] COPD was identified in 42,565 commercially insured and 8,507 Medicare patients. Criteria for COPD identification was age ≥40 years and any one of the following three algorithms:

1. One inpatient hospitalization or one emergency department visit with a diagnosis of 491.xx (chronic bronchitis), 492.x (emphysema), or 496 listed in any position as a discharge diagnosis
2. Two COPD diagnosis claims listed in any position
3. A COPD-related surgical procedure (e.g., lung volume reduction)

Among this cohort, nearly 200 ICD-9-CM codes were used to define acute exacerbations. More patients with high complexity disease experienced ≥2 acute exacerbations (61.7% commercial; 49.0% Medicare) than those with moderate- (56.9%; 41.6%), or low-complexity disease (33.4%; 20.5%).[50]

Using the U.S. Medicare Advantage Prescription Drug plan database, Dhamane and colleagues assessed AECOPD related healthcare utilization costs from 2008-2010.[51] In this study, a COPD diagnosis was defined as ≥2 medical claims reported at least one day apart within 90 days alongside a primary- or secondary-position COPD ICD-9-CM code (491.xx, 492.x, or 496). Patients with an ICD-9-CM code for cystic fibrosis, pulmonary tuberculosis, or malignant neoplasms were excluded. Also, the following three AECOPD algorithms — organized by severity (from least to greatest) — were used:

- One ED or outpatient medical claim with:
  1. COPD ICD-9-CM code 491.xx, 492.x, or 496 in the primary position OR
  2. Respiratory failure ICD-9-CM code 518.81, 518.83, or 518.84 in the primary position plus a COPD code in the secondary position OR

3. Any AECOPD code (ICD-9-CM 466–466.19, 480–486, 487.0, 490, 493.12, 493.22, 493.92, 494.1, 506.0–506.3, 511.0–511.1, or 518.82) in the primary position and a COPD code in the secondary position

AND ≥1 of the following within seven days of the visit
1) An antibiotic prescription claim relevant to respiratory infections OR
2) An oral corticosteroid prescription claim

- A medical claim for a hospitalization with either:
  1. COPD ICD-9-CM diagnosis code in the primary position OR
  2. Any AECOPD code in the primary position and a COPD code in the secondary position

  AND no respiratory failure diagnosis code in secondary position

- A medical claim for a hospitalization with the following:
  1. COPD ICD-9-CM diagnosis code in the primary position and a respiratory failure diagnosis code in secondary position OR
  2. AECOPD ICD-9-CM diagnosis code in the primary position and a COPD code and a respiratory failure code in the secondary position OR
  3. Respiratory failure ICD-9-CM diagnosis code in the primary position and a COPD code in the secondary position

Of the included 52,459 patients, 44.3% had at least one exacerbation; 26.3%, 9.5%, and 8.5% had one, two, and three exacerbations in the 24-month follow-up period, respectively.

In a study that validated the use of COPD medications as a risk measure for AECOPD, Stanford and colleagues used U.S. administrative claims data between 2006 and 2011 drawn from the Truven MarketScan and Reliant Medical Group databases.[52] COPD status was defined as either an inpatient hospitalization with ICD-9-CM codes 491.xx (chronic bronchitis), 492.x (emphysema), or 496; or two outpatient encounters with a COPD diagnosis occurring within 365 days. Additional inclusion criteria were ≥1 inhaled COPD medication or oral theophylline dispensed during baseline. Moderate exacerbation was defined as a COPD outpatient with ≥1 oral corticosteroid dispensed within seven days of this visit. A severe exacerbation was defined as an inpatient stay with either a primary position COPD diagnosis or a primary diagnosis of respiratory failure (518.81, 518.82, or 518.84) with a secondary diagnosis of COPD.

iv Predictive Modelling

Annavarapu and colleagues, developed a predictive model using Humana claims data to identify patients in the U.S. at risk of severe AECOPD.[5] Patients aged 55–89 years between 2010 and 2013 were included in the study. COPD was identified based on two or more primary position diagnosis codes for COPD (ICD-9-CM 491.xx, 492.x, or 496) on distinct days, with the second claim required to be within 90 days of the first. Patients were excluded from the cohort if they also had a diagnosis codes for malignant neoplasms, cystic fibrosis, fibrosis due to tuberculosis, bronchiectasis, pneumoconiosis, pulmonary fibrosis, pulmonary tuberculosis, sarcoidosis, or asthma. Among this cohort, patients with and without severe AECOPD in the prediction period were compared to identify characteristics associated with severe COPD exacerbations. Patients with non-severe exacerbations were identified using the following algorithm, with diagnosis claims reported in the ED or outpatient setting:

1. COPD diagnosis (ICD-9-CM 491.xx, 492.x, or 496) in the primary position OR
2. Respiratory failure code (ICD-9-CM code 518.81, 518.83, or 518.84) in the primary position with a COPD diagnosis code (above) in the secondary diagnostic position OR
3. At least one AECOPD code (ICD-9-CM codes 466–466.19, 480–486, 487.0, 490, 493.12, 493.22, 493.92, 494.1, 506.0–506.3, 511.0–511.1, or 518.82) in the primary position and a COPD (above) in the secondary diagnostic position
   AND
4. A prescription for a respiratory infection antibiotic within seven days of the visit OR

5. A prescription for an oral corticosteroid within seven days of the visit.

Meanwhile, patients with severe AECOPD were identified using diagnosis codes (1–3) reported in the hospital records. Models were developed to predict the onset of non-severe and severe AECOPD using independent inputs. The best performing model had a PPV of 48.1%, suggesting that one of every two patients identified as being at risk will have AECOPD. The model had a sensitivity of 17.3%, specificity of 97.5%, and NPV of 90.0%. The risk factor with the strongest predictive value for severe AECOPD was a history of severe AECOPD at baseline.

D COPD and AECOPD Clinical Case Definitions

The GOLD 2019 report defines COPD as a "common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway or alveolar abnormalities, usually caused by significant exposure to noxious particles or gases".[11] Spirometry is the most reproducible measurement of airflow limitation and is required for COPD diagnosis in the clinical setting. In the presence of appropriate symptoms and environmental exposures, post-bronchodilator forced expiratory volume in one second/forced vital capacity less than 70% confirms the presence of persistent airflow limitation found in COPD.[11] Though adequately sensitive, peak expiratory flow measurements are not specific enough to be reliably used without including other symptoms.

According to GOLD, COPD may be punctuated by exacerbations (AECOPD) defined as an acute worsening of respiratory symptoms that result in additional therapy. These events are classified as mild (treated with short-acting bronchodilators [SABDs] only), moderate (treated with SABDs plus antibiotics and/or oral corticosteroids), and severe (patients require hospitalizations or visits the ED). However, it was decided that treatment initiation may not be a reliable or valid criterion for the algorithm, as initiation could be patient-initiated and not captured in administrative claims data; this dimension of the definition was excluded from the algorithm as a result.

Should a validation study of the COPD and AECOPD algorithms be executed, these case definitions could be used to inform chart review and adjudication.

E COPD and AECOPD Coding Algorithms

The aim of this review was to develop algorithms to identify COPD and AECOP that could be of potential interest following exposure to a biologic product. To form a comprehensive list of COPD and AECOPD codes for clinical consideration, all ICD codes for COPD and AECOPD were extracted from the articles identified in the literature review (**Appendix A**). As informed by these studies, the workgroup has developed algorithms that include diagnosis codes for a COPD cohort and AECOPD events. To expand the draft code list and reflect current coding practice, ICD-10-CM diagnosis codes were generated from ICD-9-CM codes using forward-backward mapping via the Centers for Medicare and Medicaid Services (CMS) GEMs files. The expanded draft code list, which included ICD-9-CM and ICD-10-CM codes, was subsequently reviewed by clinical SMEs from IBM (TB, JB), FDA CBER (JC, DT), and Acumen. Specific decisions and assumptions related to construction of the algorithm are summarized in **Section F**. Overall, the clinical SMEs recommended the inclusion of additional codes or exclusion of codes from the expanded draft code list based on clinical relevance and optimizing the balance between specificity and sensitivity. As a result, codes that are too general or unrelated to COPD or AECOP and could potentially increase the risk of misclassification were excluded. Codes that were considered but ultimately excluded are listed in **Appendix D**. These codes were not applied as exclusion criteria but were left out of the algorithms to identify COPD and AECOPD.

The workgroup has sought a two-step approach that used COPD-specific codes to identify the population cohort (

Table 2) then identified acute exacerbation codes that could be used in the COPD cohort (**Abbreviation:** DX, ICD-CM diagnosis.
Table 3).

The proposed COPD cohort algorithm can be summarized as follows:

> **INCLUDE: ANY** ("either–or") of the codes listed in **Table 2** regardless of health care setting or coding position (only one code required).

The AECOPD algorithm can be summarized as follows

> **AMONG COPD COHORT – INCLUDE: ANY** ("either–or") of the codes listed in **Abbreviation:** DX, ICD-CM diagnosis.
> **Table 3**, regardless of health care setting or coding position (only one code required) occurring **AFTER** date of first COPD diagnosis.

These algorithms take a general approach to defining COPD and AECOPD and may need to be adjusted or tailored for specific research questions that arise in the future. Annual counts of patients with individual diagnosis codes are provided in **Appendix C**.

Table 2. COPD Cohort Algorithm.

Code	Description	Code Cat	Code Type
491.0	Simple chronic bronchitis	DX	9
491.1	Mucopurulent chronic bronchitis	DX	9
491.20	Obstructive chronic bronchitis without exacerbation	DX	9
491.21	Obstructive chronic bronchitis with (acute) exacerbation	DX	9
491.22	Obstructive chronic bronchitis with acute bronchitis	DX	9
491.8	Other chronic bronchitis	DX	9
491.9	Unspecified chronic bronchitis	DX	9
492.0	Emphysematous bleb	DX	9
492.8	Other emphysema	DX	9
493.20	Chronic obstructive asthma, unspecified	DX	9
493.21	Chronic obstructive asthma with status asthmaticus	DX	9
493.22	Chronic obstructive asthma with (acute) exacerbation	DX	9
494.0	Bronchiectasis without acute exacerbation	DX	9
494.1	Bronchiectasis with acute exacerbation	DX	9
496	Chronic airway obstruction, not elsewhere classified	DX	9
J41.0	Simple chronic bronchitis	DX	10
J41.1	Mucopurulent chronic bronchitis	DX	10
J41.8	Mixed simple and mucopurulent chronic bronchitis	DX	10
J42	Unspecified chronic bronchitis	DX	10
J43.0	Unilateral pulmonary emphysema	DX	10
J43.1	Panlobular emphysema	DX	10
J43.2	Centrilobular emphysema	DX	10
J43.8	Other emphysema	DX	10
J43.9	Emphysema, unspecified	DX	10
J44.0	Chronic obstructive pulmonary disease with (acute) lower respiratory infection	DX	10
J44.1	Chronic obstructive pulmonary disease with (acute) exacerbation	DX	10
J44.9	Chronic obstructive pulmonary disease, unspecified	DX	10
J47.0	Bronchiectasis with acute lower respiratory infection	DX	10
J47.1	Bronchiectasis with (acute) exacerbation	DX	10
J47.9	Bronchiectasis, uncomplicated	DX	10

Abbreviation: DX, ICD-CM diagnosis.

Table 3. AECOPD Algorithm.

Code	Description	Code Cat	Code Type
466.0	Acute bronchitis	DX	9
466.11	Acute bronchiolitis due to respiratory syncytial virus (RSV)	DX	9
466.19	Acute bronchiolitis due to other infectious organisms	DX	9
490	Bronchitis, not specified as acute or chronic	DX	9
491.21	Obstructive chronic bronchitis with (acute) exacerbation	DX	9
491.22	Obstructive chronic bronchitis with acute bronchitis	DX	9
493.22	Chronic obstructive asthma with (acute) exacerbation	DX	9
494.1	Bronchiectasis with acute exacerbation	DX	9
518.81	Acute respiratory failure	DX	9
518.82	Other pulmonary insufficiency, not elsewhere classified	DX	9
518.83	Chronic respiratory failure	DX	9
518.84	Acute and chronic respiratory failure	DX	9
J20.9	Acute bronchitis, unspecified	DX	10
J21.0	Acute bronchiolitis due to respiratory syncytial virus	DX	10
J21.1	Acute bronchiolitis due to human metapneumovirus	DX	10
J21.8	Acute bronchiolitis due to other specified organisms	DX	10
J21.9	Acute bronchiolitis, unspecified	DX	10
J40	Bronchitis, not specified as acute or chronic	DX	10
J41.0	Simple chronic bronchitis	DX	10
J44.0	Chronic obstructive pulmonary disease with (acute) lower respiratory infection	DX	10
J44.1	Chronic obstructive pulmonary disease with (acute) exacerbation	DX	10
J47.0	Bronchiectasis with acute lower respiratory infection	DX	10
J47.1	Bronchiectasis with (acute) exacerbation	DX	10
J47.9	Bronchiectasis, uncomplicated	DX	10
J80	Acute respiratory distress syndrome	DX	10
J96.00	Acute respiratory failure, unspecified whether with hypoxia or hypercapnia	DX	10
J96.01	Acute respiratory failure, with hypoxia	DX	10
J96.02	Acute respiratory failure, with hypercapnia	DX	10
R06.03	Acute respiratory distress	DX	10

Abbreviation: DX, ICD-CM diagnosis.

The algorithms proposed in
Table 2 and **Abbreviation:** DX, ICD-CM diagnosis.
Table 3 and exclusions in **Appendix D** are consistent with approaches identified in the peer-reviewed literature and reflect current coding practices. However, such an approach may impact diagnostic accuracy performance if assessed against the typical case definition for COPD and AECOPD, given differences between clinical diagnostic and administrative claims coding practices.

F Assumptions and Decisions

The algorithms presented in **Section E** were reviewed internally as well as with CBER stakeholders and partners. Decisions and assumptions related to algorithm construction are summarized below. Some of these assumptions may be adjusted for future research questions.

F1 COPD Cohort

- Some publications suggested that, for outpatient diagnosis codes, algorithm performance could be improved by requiring a second or third diagnosis code, a procedural code, or a therapy medication code. However, the performance improvement was likely to be marginal and led to the exclusion of cases, so this has not been proposed herein. Nevertheless, users seeking a more specific algorithm could apply the following:
    - ≥1 inpatient diagnosis code for COPD OR
    - ≥1 outpatient diagnosis code AND ≥1 of
        - ≥1 additional outpatient diagnosis code (i.e., 2 outpatient diagnosis codes required) OR
        - ≥1 procedural code (CPT codes listed in **Appendix E**) OR
        - ≥1 medication/therapy code (NDC/HCPCS codes listed in **Appendix E**)

  Please note the following:
    - Procedures (e.g., chest x-ray) and therapies (e.g., levalbuterol) relevant to COPD are quite general and could be useful for other purposes. Therefore, such an approach may not increase specificity as much as desired, and users may wish to further tailor procedures and therapies of interest.
    - NDC codes were drawn from the FDA NDC Database, last updated July 21, 2020.[vii] HCPCS codes were drawn from the HCPCS website, last updated July 21, 2020.[viii] These codes may not include all relevant codes and may be or become out of date, and users are encouraged to review the most current datasets available prior to use of the algorithm.
    - The inclusion of bronchiectasis (ICD-9-CM 494.0, 494.1; ICD-10-CM J47.0, J47.1, J47.9) was discussed, as this could represent a long-term outcome of COPD. These codes were included to optimize sensitivity, but users seeking a more specific algorithm may wish to exclude them.
- Bronchitis, not specified as acute or chronic (ICD-9-CM 490; ICD-10-CM J40), was excluded since these codes are likely to introduce risk of misclassification and error associated with acute bronchitis. Users seeking a more specific algorithm may wish to use these codes as an exclusion criterion (i.e., actively removing users that also have these codes within a certain time period).
- The GOLD definition excludes some conditions included in the algorithm code list (e.g., chronic bronchitis), due to the requirement for airflow limitation that is due to airway and/or alveolar abnormalities. This distinction is largely reflective of a concern that administrative billing practices may not mirror clinical diagnostic ones.
- All asthma codes have been excluded, except for chronic obstructive asthma, which was viewed to represent COPD with asthma. Users seeking a more specific algorithm may wish to use these codes as an exclusion criterion (i.e., actively removing individuals that also have these codes within a certain time period).
- The restriction of queries based on diagnosis coding position (e.g., principal position codes only), varied across the studies reviewed. Queries presented in **Section G** did not restrict based on coding position, out of concern that queries based solely on primary-position codes could improperly exclude individuals with COPD. Users may adjust this approach to include primary, secondary, or unspecified position codes, but this is likely better done at the statistical planning stage, when a specific research question has been formulated.
- In applications of this algorithm, users may choose to exclude claims-based codes that are associated with "rule-out" diagnoses. For example, a diagnosis code may be associated with a test for COPD, with the results showing that the condition is not present. Another option would be to require at least two codes associated with COPD to be reported on different days.
    - These codes were not excluded in the descriptive analyses conducted using the MarketScan Research Databases (**Section G**). This is because decisions about such an

[vii] The FDA NDC Database is available at https://www.fda.gov/drugs/drug-approvals-and-databases/national-drug-code-directory.
[viii] The HCPCS website is available at https://www.hcpcsdata.com/.

exclusion were viewed as more appropriate in a validation study or subsequent use of the algorithm for an epidemiologic study. The intent of the analyses in **Section G** is to characterize the population associated with codes included in the algorithm, regardless the context in which the code was reported.

F2 AECOPD

- The clinical definition of AECOPD includes the initiation of treatment. However, as treatment may be patient-initiated and reasons for treatments were not recorded in administrative claims data, it is recommended that this NOT be used as an algorithm criterion. Given this recommendation, it is also recommended that users avoid efforts to categorize exacerbations according to severity, as these categorizations may not be reliable only based on administrative claims data.
- As the AECOPD algorithm is intended for application among a COPD cohort, a broad list of codes potentially related to exacerbation have been included. Users seeking a more specific algorithm may limit codes to those that specify COPD with exacerbation. This approach was not taken here out of concern that true AECOPD cases may not be recognized or reported as such by the treating physician.
- Exacerbations related to pneumonia have been excluded from this algorithm given the concern that this could introduce a source of misclassification given the broad range of etiologies associated with pneumonia that are likely to be unrelated to COPD exacerbation. Also, FDA CBER is developing a separate pneumonia-specific algorithm (forthcoming), that users may apply if desired.
- The restriction of queries based on diagnosis coding position (e.g., principal position codes only), varied across the studies reviewed. Queries presented in **Section G** did not restrict based on coding position, out of concern that queries based solely on primary-position codes could improperly exclude true cases of AECOPD. Users may adjust this approach to include primary, secondary, or unspecified-position codes, but this is likely better done at the study planning stage, when a specific research question has been formulated.
- Risk windows used to determine the association of AECOPD with a particular exposure should be determined based on the particular research question and exposure of interest.

G Algorithm Characterization

G1 Methods

To summarize the epidemiology of COPD and AECOPD among a commercially insured population in the U.S., the workgroup used the IBM MarketScan Research Databases (Commercial and Medicare Supplemental), accessed via the Treatment Pathways[ix] online analytic platform, to query and analyze the diagnostic codes included in the two algorithms. To gather the broadest range of cases to support a descriptive analysis, the analyses presented herein did not require exposure to a biologic product and did not restrict codes based on diagnosis position. It is recommended that the proposed algorithm undergo a validation study prior to use, and future analytical studies should also tailor the algorithm specifications according to the study question of interest.

Age- and gender-specific data on MarketScan Research Databases enrollment and counts of individuals receiving a diagnostic code for COPD or AECOPD were extracted. In addition to the code-specific queries described in **Section E** and summarized in **Appendix C**, authors executed queries that aggregated all ICD-9-CM codes, all ICD-10-CM codes, and all codes (ICD-9-CM and ICD-10-CM) for COPD and AECOPD.

[ix] IBM MarketScan Research. Insight for Better Healthcare. https://marketscan.truvenhealth.com/marketscanportal/Portal.aspx

The figures presented below were drawn from a large patient dataset during the study period of January 1, 2014–December 31, 2018. For all analyses, authors queried ICD-9-CM codes for January 1, 2014–September 30, 2015 and ICD-10-CM codes for October 1, 2015–December 31, 2018. This was done out of recognition of the transition to ICD-10-CM on October 1, 2015 and an effort to exclude codes reported in error.

Counts of individual patients that had a diagnosis code related to COPD or AECOPD within a given calendar year, rather than counts of cases, were presented. As such, counts relate to the first diagnosed event for an individual during a given surveillance period (e.g., January 1–December 31, 2014), and individuals could only be counted once per surveillance period. Since we did not estimate the incidence of COPD or AECOPD in the study population, no washout period was applied.

Individuals had to be continuously enrolled to be included in the analysis for a particular year. For example, patients had to be continuously enrolled from January 1 to December 31, 2014, to be included in the "2014" dataset. Age is calculated in Treatment Pathways as if each individual was born on July 1 of their given year of birth. Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e., those under one year old), this population group has been left out of the three charts that depict the proportions of individuals with COPD or AECOPD by age. Infants under one year of age were not excluded from queries of the absolute number of patients receiving a COPD or AECOPD diagnosis.

Queries for the AECOPD were run on the combined cohorts of individuals that had a COPD cohort code and were enrolled for at least one calendar year between January 1, 2014–December 31, 2015 (n=778,545 received ≥1 ICD-9-CM diagnosis between January 1, 2014 and September 30, 2015), January 1, 2015–December 31, 2018 (n=842,174 received ≥1 ICD-10-CM diagnosis between October 1, 2015 and December 31, 2018), and January 1, 2014–December 31, 2018 (n=1,302,316 received ≥1 ICD-9-CM or ICD-10-CM diagnosis in this period). Codes were queried from the day following entry date into the COPD cohort until September 30, 2015 for ICD-9-CM codes and from the day following entry date into the COPD cohort until December 31, 2018 for the ICD-10-CM codes. Annual statistics could not be calculated for AECOPD, as query start date could not be anchored to both entry into the COPD cohort and start of the calendar year.

G2 Results

Table 4 provides a summary of aggregate counts for ICD-9-CM and ICD-10-CM codes, suggesting that approximately 13.6–20.4 individuals per 1,000 individuals included in the MarketScan Research Databases received a code associated with COPD each year. Among a cohort of 46,153,898 patients that combined those continuously enrolled for at least one calendar year between January 1, 2014 and December 31, 2018, 1,302,316 individuals (2.8%) had at least one ICD-9-CM or ICD-10-CM diagnosis code for COPD. Of the codes included in the COPD algorithm, ICD-9-CM 496, and ICD-10-CM J44.9 (chronic obstructive pulmonary disease, unspecified) were by far the most frequently used. Of those receiving at least one COPD diagnosis between 2014 and 2018 (n=1,302,316), 43.2% (n=562,884) and 48.7% (n=634,058) had at least one ICD-9-CM 496 and ICD-10-CM J44.9 code, respectively. Additional code-specific queries are provided in **Appendix C**.

Table 4. Counts of patients with COPD by code set and year.

Code/ Description	Year				
	2014	**2015[a]**	**2016**	**2017**	**2018**
ICD-9-CM	562,458	382,143			
ICD-10-CM		222,034	412,110	328,414	263,000
ICD-9-CM OR ICD-10-CM	562,458	451,931	412,110	328,414	263,000
MarketScan Research Databases Enrollment[b]	28,407,959	22,117,235	21,616,291	19,563,847	19,371,891
Proportion of Patients with COPD per 1,000 Enrolled Population[c]	**19.8**	**20.4**	**19.1**	**16.8**	**13.6**

Abbreviations: COPD, Chronic obstructive pulmonary disease; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification.

[a] In 2015, queries combining ICD-9-CM and ICD-10-CM codes returned lower patient counts than when codes were queried individually. This is because of cases in which both ICD-9-CM and ICD-10-CM codes were reported for the same individual, in the January–September and October–December timeframe, respectively.

[b] Individuals included in this row are those who were enrolled for the full calendar year (January 1–December 31) for 2014, 2015, 2016, 2017, and 2018, respectively.

[c] Proportions were calculated using the counts in the "ICD-9-CM OR ICD-10-CM" row.

Within the COPD cohort, 246,941 (19.0%) had at least one ICD-9-CM code and 414,915 (31.9%) had at least one ICD-10-CM code for AECOPD, respectively; 549,827 (42.2%) had at least one of either ICD-9-CM or ICD-10-CM codes for AECOPD.

The workgroup assessed whether the 2015 transition to ICD-10-CM and any associated changes in coding practices resulted in notable shifts in the frequency of COPD. **Figure 2** illustrates the proportion of the enrolled population with a COPD diagnosis and suggests that the transition may have resulted in a change in the proportion of individuals receiving a COPD diagnosis, as the proportion of patients receiving a COPD diagnosis decreased year-over-year between 2015 and 2018. Independent analyses also indicated a decrease in the proportion of patients receiving a diagnosis for acute bronchitis, Bell's palsy, acute respiratory distress syndrome, and pneumonia in 2018. However, it was also noted that the average age of the enrolled population decreased from 62–63 years between 2014 and 2017 to 60 years in 2018, suggesting that the study population was younger and potentially healthier in 2018. This difference may have been particularly important for COPD, as the average age of first diagnosis appears to be in the early sixties (**Figures 3–5**).

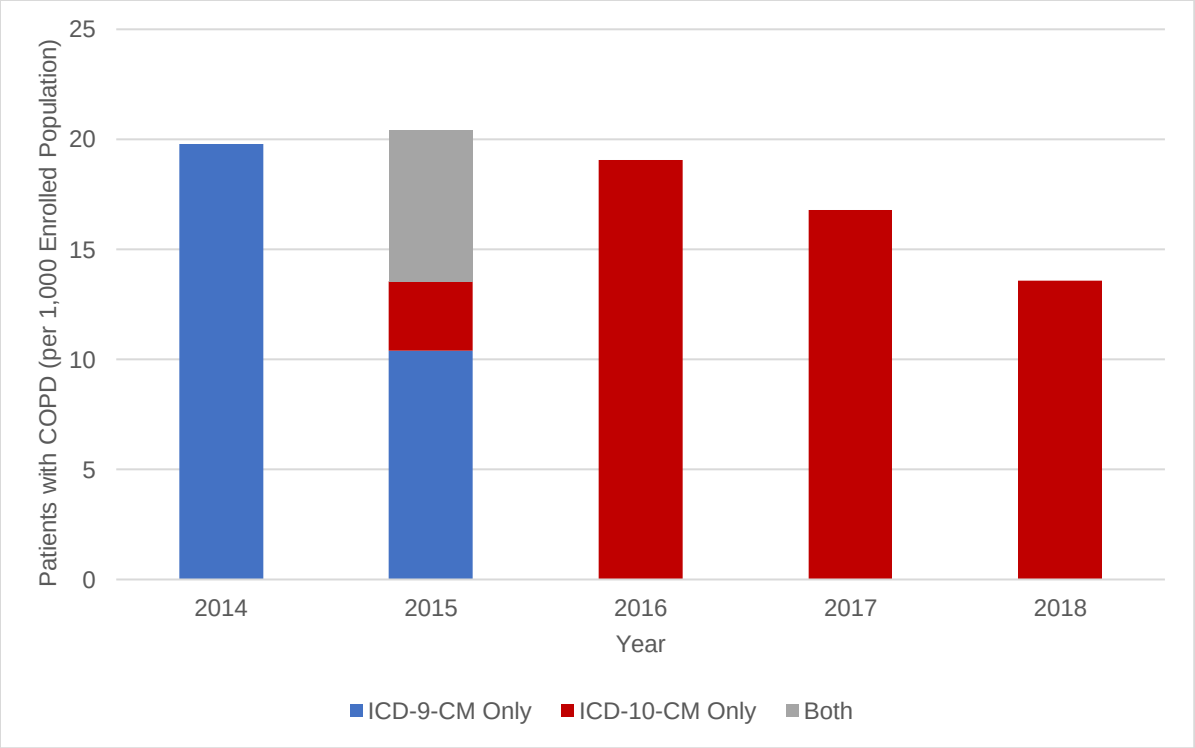

Figure 2. Proportion of patients with COPD per 1,000 enrolled, by year (2014–2018).

Note: In 2015, a patient could receive both an ICD-9-CM and an ICD-10-CM diagnosis, in the January–September and October–December timeframe, respectively.

Figure 3 presents counts of patients with an ICD-9-CM diagnosis for COPD and/or AECOPD stratified by age group. Counts were calculated for the timeframe of January 1, 2014 to September 30, 2015 among the cohort of 33,216,843 patients who were continuously enrolled for at least one calendar year between January 1, 2014 and December 31, 2015. There were 778,545 (2.3%) individuals with at least one diagnosis code for COPD during this period, with an average age at first diagnosis of 62 years. Of this group, 245,320 (31.5%) had at least one AECOPD diagnosis, with an average age at first diagnosis of 65 years.

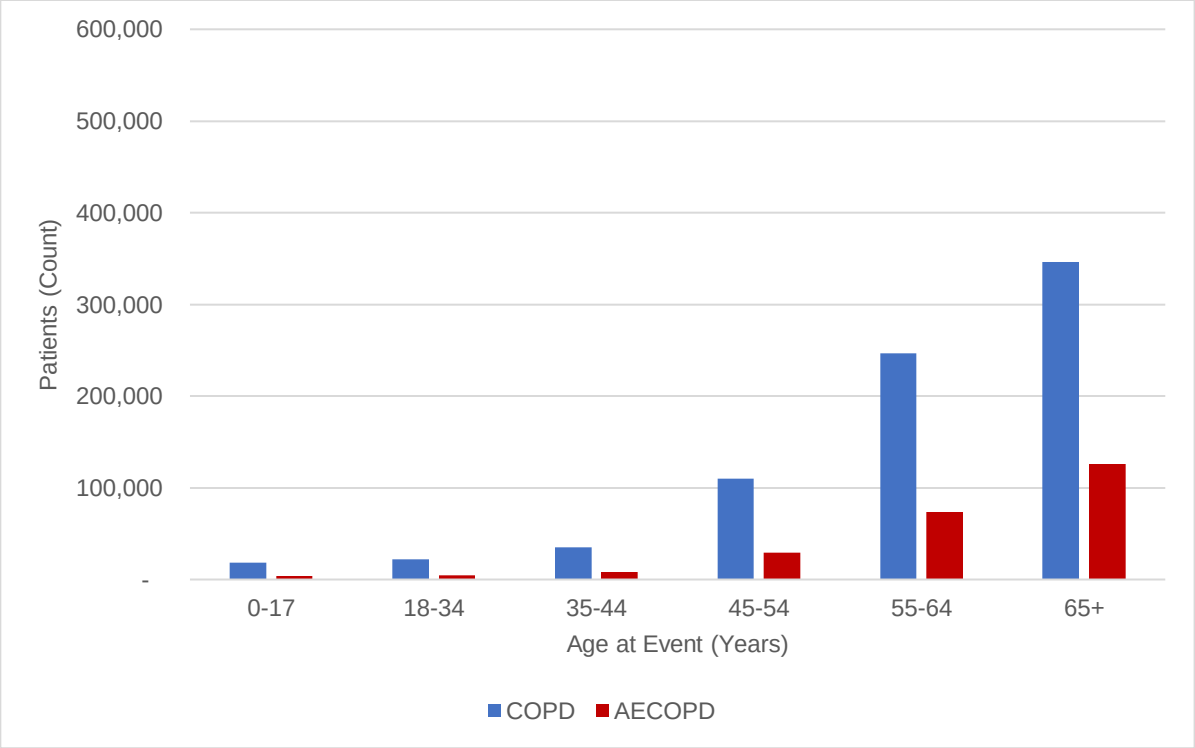

Figure 3. Patients with at least one ICD-9-CM diagnosis code for COPD and/or AECOPD, January 1, 2014–September 30, 2015, stratified by age group.

Abbreviations: COPD; chronic obstructive pulmonary disease, AECOPD; COPD acute exacerbation.

Figure 4 presents counts of patients with an ICD-10-CM diagnosis for COPD and/or AECOPD stratified by age group. Counts were calculated using a cohort of 35,337,738 patients who were continuously enrolled for at least one calendar year between 2015 and 2018 (i.e., January 1–December 31 for at least one of 2015, 2016, 2017, or 2018), which the ICD-10-CM diagnoses were queried for the ICD-10-CM time period (October 1, 2015–December 31, 2018). There were 842,174 (2.4%) with at least one diagnosis for COPD during this period, with an average age at first diagnosis of 63 years. Of this group, 334,801 (39.8%) had at least one AECOPD diagnosis, with an average age at first diagnosis of 65 years. It was noted that, across age groups, a higher proportion of individuals with COPD experienced an exacerbation in the ICD-10-CM query (27.1–45.3% of those with COPD, across age groups) than in the ICD-9-CM query (19.7–36.3% of those with COPD, across age groups). This may be because the longer query period for the ICD-10-CM analyses resulted in a higher proportion of exacerbations among the COPD cohort.

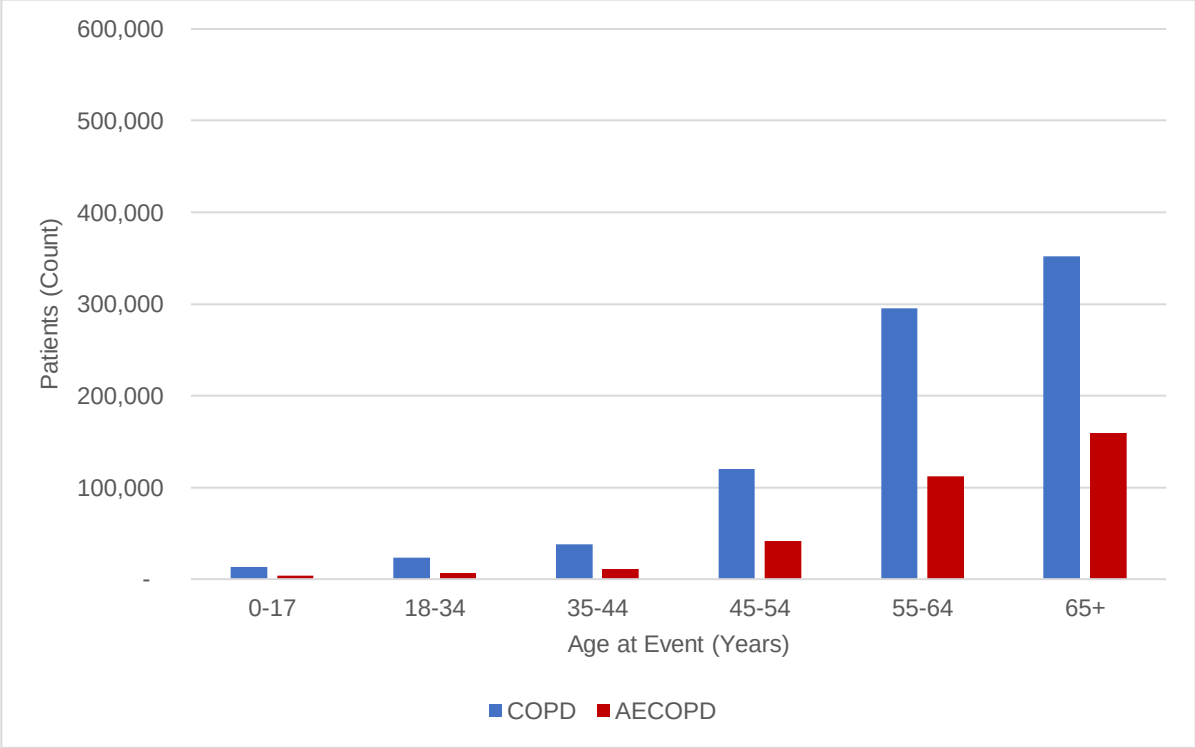

Figure 4. Patients with at least one ICD-10-CM diagnosis code for COPD and/or AECOPD, January 1, 2014–September 30, 2015, stratified by age group.

Abbreviations: COPD; chronic obstructive pulmonary disease, AECOPD; COPD acute exacerbation.

Figure 5 presents counts of patients with either an ICD-9-CM or ICD-10-CM code for COPD and/or AECOPD among a cohort of 46,153,898 individuals who were continuously enrolled for at least one calendar year between 2014 and 2018. Among 1,302,316 individuals (2.8%) who received a diagnosis code for COPD between January 1, 2014, and December 31, 2018, 549,827 (42.2%) also received an AECOPD diagnosis. The average age at first diagnosis was 61 and 64 years for COPD and AECOPD, respectively, and absolute counts were substantially higher for the age groups of 55–64 and 65+ years for both COPD and AECOPD compared to younger age groups.

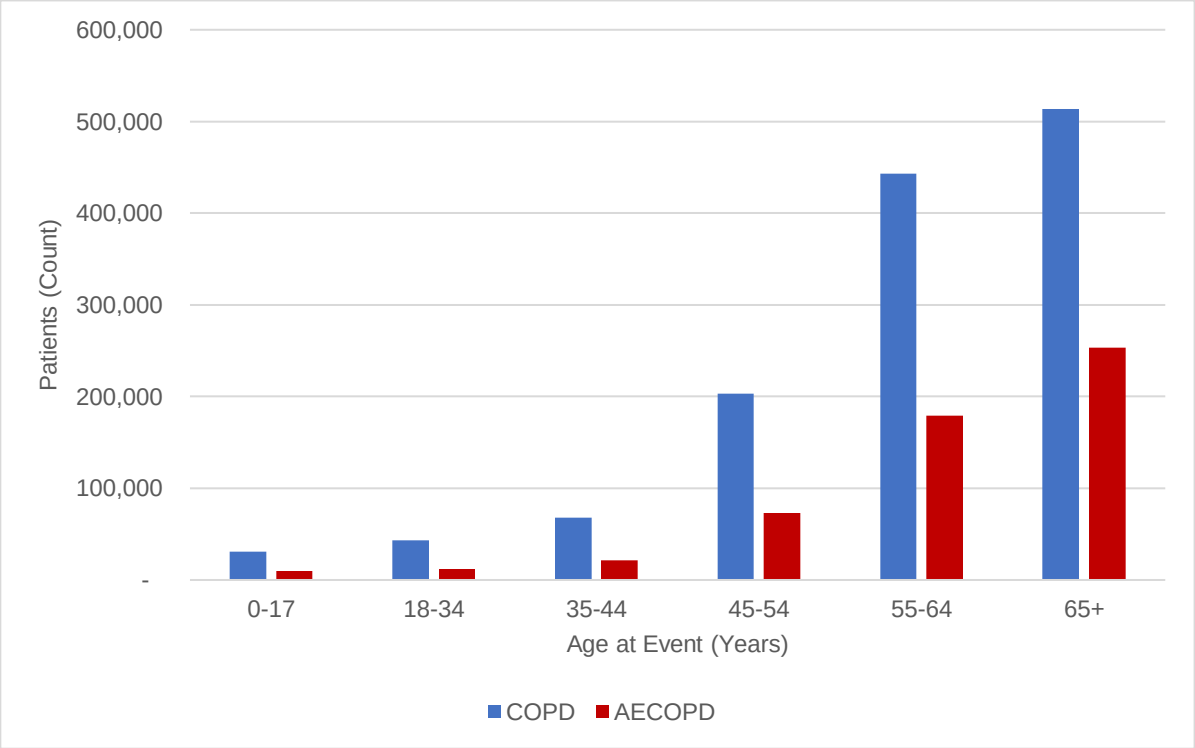

Figure 5. Patients with at least one diagnosis code for COPD and/or AECOPD (ICD-9-CM or ICD-10-CM), January 1, 2014–December 31, 2018, stratified by age group.

Abbreviations: COPD; chronic obstructive pulmonary disease, AECOPD; COPD acute exacerbation.

Figure 6 and **Figure 7** summarize the proportion of the population (aged 1-85+ years) with at least one ICD-9-CM or ICD-10-CM code for COPD and AECOPD, respectively, per 1,000 population enrolled in the MarketScan Research Databases (between January 1, 2014, and December 31, 2018) by age and gender. Patients 85 years of age and older were grouped to minimize the effect of unstable estimates due to the smaller enrolled population sizes available in this age range in the commercially insured population. The 46 million-patient cohort was used for this analysis and individuals were required to be enrolled for at least one calendar year between 2014 and 2018 but were not required to be enrolled for the full five-year period to be included in the calculations. The results suggest that the proportion of patients with COPD and AECOPD increases with age from about 40 years, with similar proportions between males and females until about 70 years of age (at which point both COPD and AECOPD appear to be more common in men).

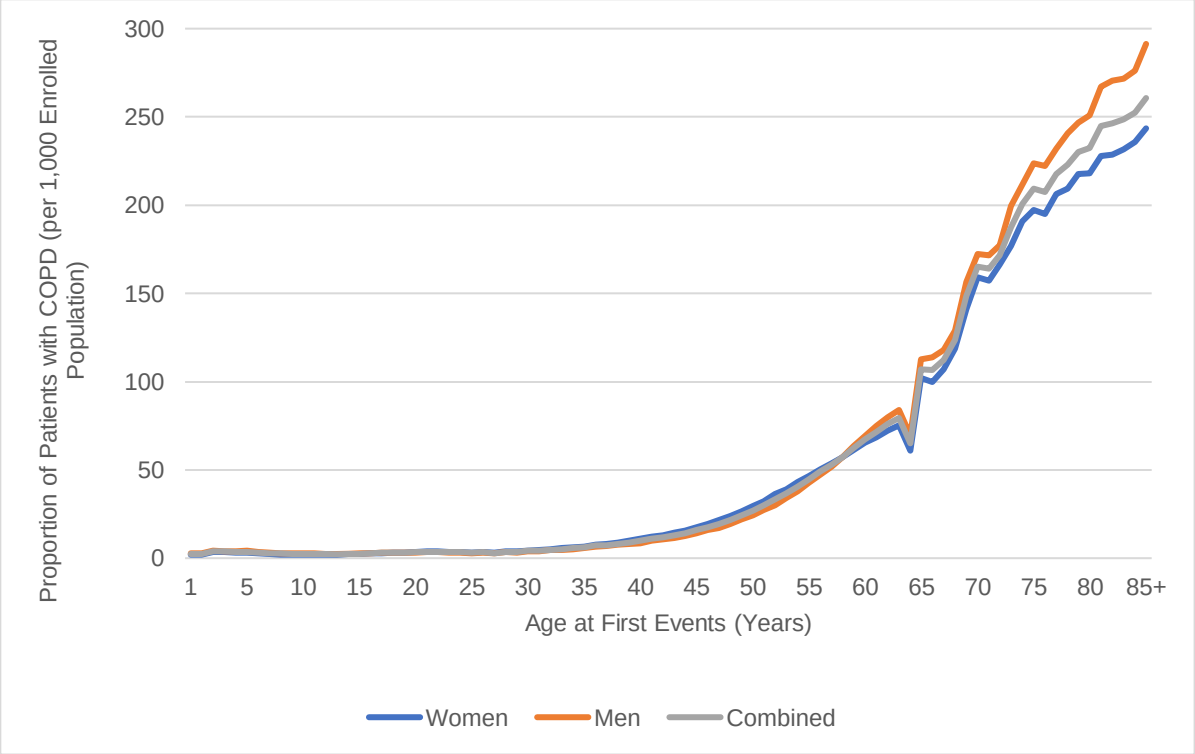

Figure 6. Proportion of patients (1–85+ years)* with at least one diagnosis code for COPD (ICD-9-CM or ICD-10-CM) per 1,000 population, by age and gender (January 1, 2014–December 31, 2018).

*Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e., those under 1 year old), and recognizing that COPD is likely not relevant in infant populations, the proportion of those under 1 year old experiencing COPD is excluded from the chart.

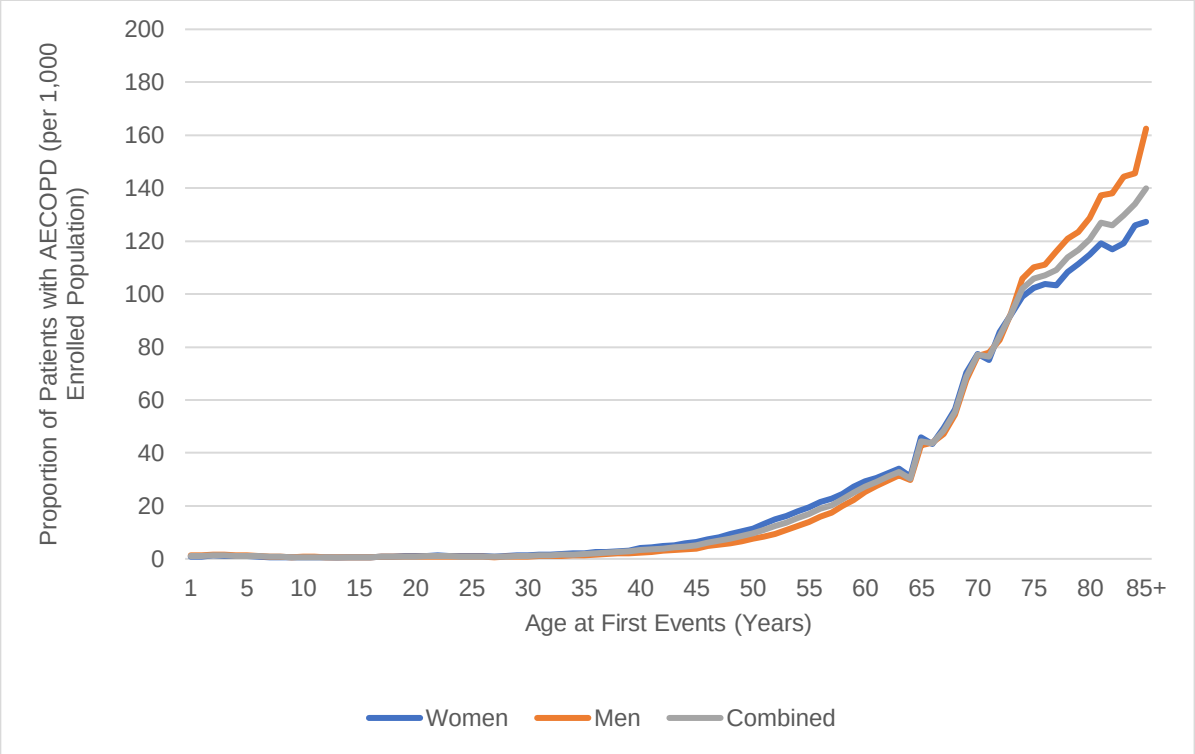

Figure 7. Proportion of patients (1–85+)* with at least one diagnosis code for AECOPD (ICD-9-CM or ICD-10-CM) per 1,000 population, by age and gender (January 1, 2014–December 31, 2018).

*Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e., those under 1 year old), and recognizing that COPD is likely not relevant in infant populations, the proportion of those under 1 year old experiencing AECOPD is excluded from the chart.

The workgroup also assessed whether there was notable variation in the proportion of patients with COPD by calendar year of diagnosis. **Figure 8** presents the annual proportions of patients (aged 1-85+ years) with a diagnosis code for COPD for ages 1–85+ years. Results suggest that proportions were consistent across calendar years, though lower proportions were observed for individuals above 65 years of age in 2018; this may have been due to differences in the enrolled population across the years of study, as it was noted above that the average age of the 2018 enrolled population was 60 years instead of 62–63 years in 2014–2017. It should be noted that the proportions presented in **Figure 8** are substantially lower than those in **Figure 6**, where COPD encounters were queried for the entire 2014–2018 period instead of for a single year.

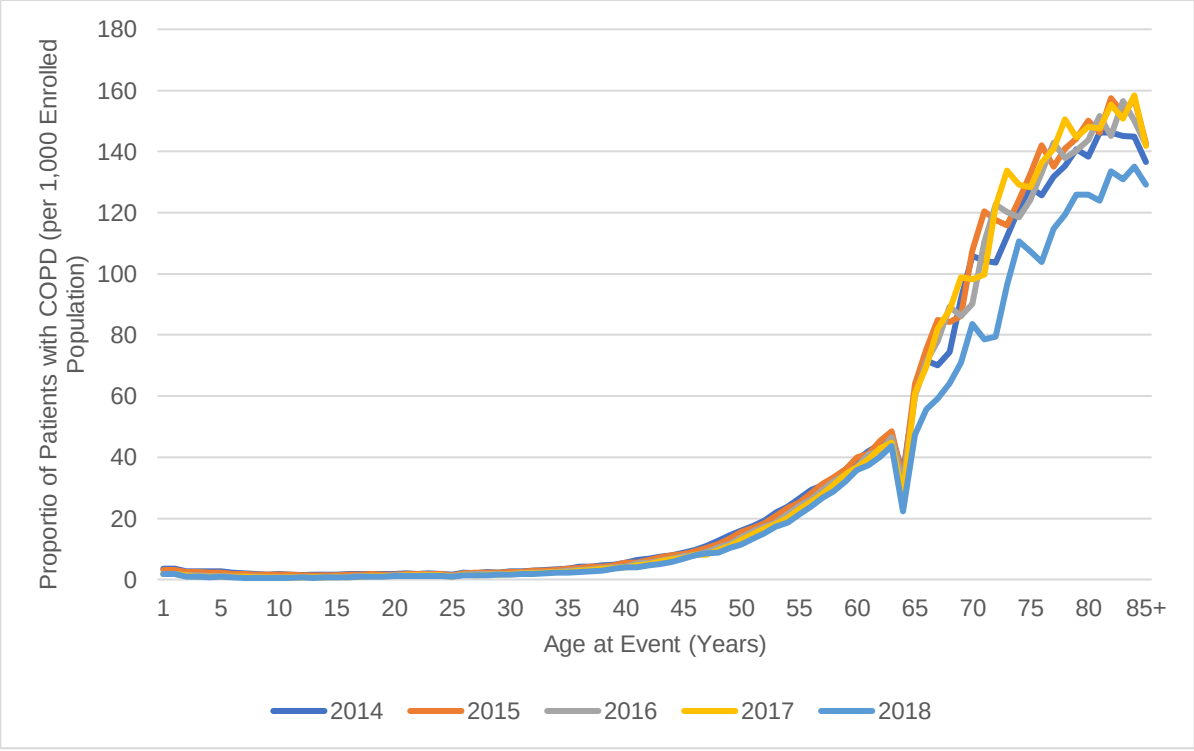

Figure 8. Proportion of patients (1–85+)* with at least one diagnosis code for COPD (ICD-9-CM or ICD-10-CM) per 1,000 population, by age and calendar year (January 1, 2014–December 31, 2018).

*Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e., those under 1 year old), and recognizing that COPD is likely not relevant in infant populations, the proportion of those under 1 year old experiencing COPD has been excluded from the chart and marked as zero.

Analyses were also conducted to test whether there was a temporal association in the occurrence or reporting of COPD according to the time of the year, possibly as a result of an association with weather patterns or vaccination schedules. To test this, enrollment and COPD encounter data for January 1–June 30 and July 1–December 31 were queried for each year. As presented in **Table 5** and **Figure 9**, the proportion of patients experiencing COPD was slightly lower in the second half of the year across the entire study period, with the exception of 2014.

Table 5. Counts and proportions of patients experiencing COPD*, defined by ICD-9-CM and ICD-10-CM codes, stratified by time of year (2014–2018).

Description	Calendar Year				
	2014	2015	2016	2017	2018
January–June patient count	414,317	340,781	315,433	251,004	197,615
July–December patient count	416,467	327,141	288,813	237,466	189,604
January–June enrollment	31,110,014	24,094,695	23,531,649	21,406,675	21,225,754
July–December enrollment	30,867,380	23,759,879	23,759,879	20,866,148	20,866,232
January–June proportion (per 1,000 enrolled)	**13.3**	**14.1**	**13.4**	**11.7**	**9.3**
July–December proportion (per 1,000 enrolled)	**13.5**	**13.8**	**12.2**	**11.4**	**9.1**

* The sum of the proportions presented here exceeds those presented for full calendar years. This is because a patient can be counted in both time periods when queries are run separately, whereas they would only be counted once when the query spans the full year.

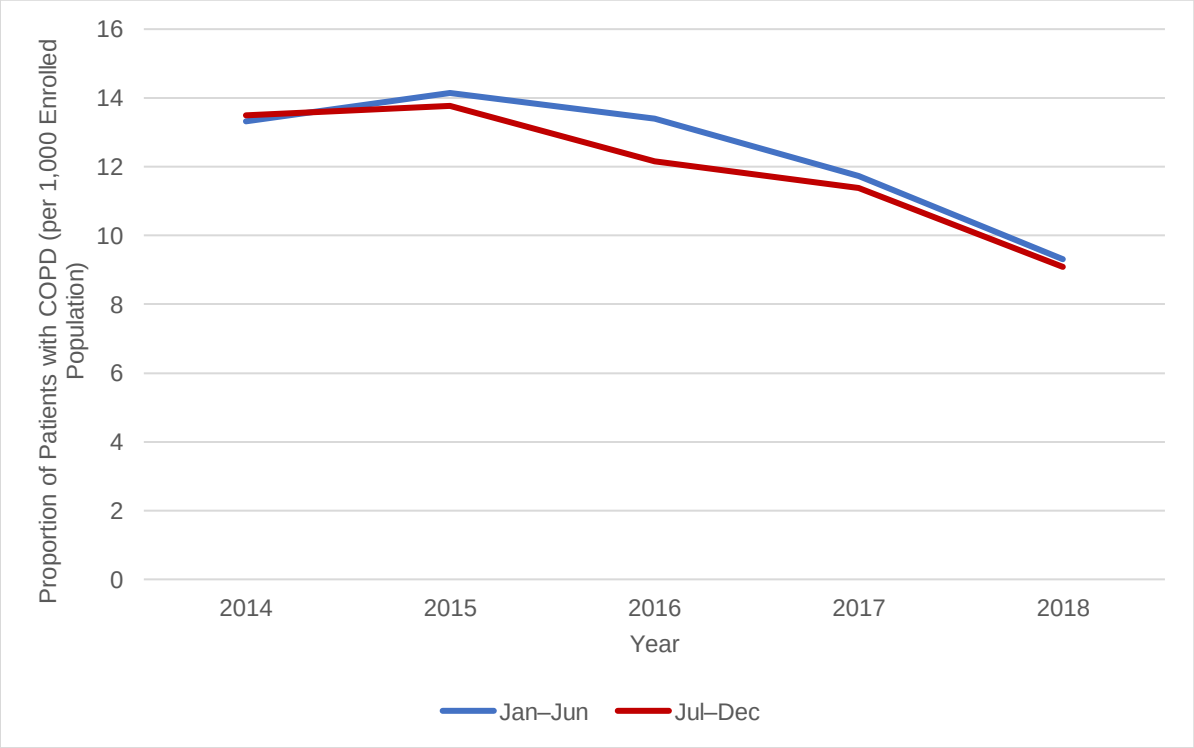

Figure 9. Proportion of patients with at least one diagnosis code for COPD (ICD-9-CM or ICD-10-CM) per 1,000 population, stratified by time of year (2014–2018).

H Discussion

The objective of this structured review was to understand and assess the validity of electronic coding algorithms for identifying COPD and AECOPD from administrative claims and EHRs using billing codes. Of the 15 COPD algorithm studies described in the report, seven were conducted in the U.S. Of these, only two studies included validation, but they were based on predictive modelling. Across studies, a consistent approach of using ICD-9-CM 491.xx, 492.x and 496 to identify COPD was observed. A recent systematic review of COPD algorithms highlighted a Canadian study of particular relevance, which applied an ICD-10 algorithm to identify cases of COPD in administrative data, resulting in a moderate PPV (57.5%), with high sensitivity (85%) and specificity (78.4%) based on chart review.[3,36] This study formed the basis of the COPD algorithm in this report and has also been used previously in a U.S. Medicaid study of comorbidities within the COPD population.[4]

Spirometry test results are a valuable data element that can increase COPD algorithm accuracy. For example, a Taiwanese study improved the PPV for COPD from 72.2% to 84.6% by adding spirometry test results to the original algorithm consisting of ≥2 outpatient codes in 1 year or ≥1 inpatient COPD code.[37] However, bedside spirometry testing is seldom billed in general practice, and so may not be a feasible parameter to include in a claims-based algorithm application. Meanwhile, spirometry testing results would not be available from claims data unless there is a linkage to clinical data. As a result, this measure was not added to the COPD algorithm proposed in this report.

Of the nine AECOPD related studies included in the report, six were based in the U.S. Of these, three studies conducted validation, which resulted in consistently low sensitivity measures. One study developed a predictive model using COPD codes, respiratory failure codes, and antibiotic and corticosteroid prescriptions, resulting in a PPV of 48.1%, sensitivity of 17.3% and NPV of 90%.[5] As affirmed in the GOLD guidelines, the risk factor in this study with the strongest AECOPD predictive value was a history of AECOPD at baseline. In another study, ICD-9-CM codes for AECOPD were assessed from 200 hospitalizations with an AECOPD prevalence of 7.9% derived from two teaching hospitals validated with chart review and a high PPV ranging between 81% and 97% was reported, though sensitivity was very low (12-25%).[2] In another study, an AECOPD algorithm using ICD-9-CM codes 491.2x, 492.8, and 496 had a high PPV of 97% based on chart review.[7] However, this study was conducted using data from EHR in a small population consisting of 644 visits to two teaching hospital EDs, and hence the external validity of this algorithm to large claims databases is unknown.

In a study that assessed methods and data elements used for developing case definitions in EHR databases, diagnostic codes were the most common feature used to define the conditions, and many definitions relied solely on diagnostic codes.[53] It is unclear how diagnostic code-based algorithms would perform differently in EHR compared to claims databases, beyond the differences that already occur within different databases of either EHR or claims. The COPD and AECOPD diagnostic code-based algorithms validated in EHR were assessed as supplemental data to support the completeness of the code lists in this report.

In this study, the proportion per 1,000 of the enrolled population with COPD decreased from 19.8 in 2014 to 13.6 in 2018. Without accounting for multiple COPD risk factors such as older age, lower income, public insurance, and a history of smoking, it is difficult to compare these differences across study years and to prior studies. For example, one of the common inclusion criteria across COPD algorithms identified in the literature is an age requirement of ≥35 years. However, past publications have also reported that COPD prevalence decreased in the U.S. population from 7.2% in 2009, 6.4% in 2015, and 5.1% in 2018.[54,55] Moreover, in 2017, the GOLD guidelines contained substantial revisions, which included prioritizing symptom evaluation and exacerbation history in assessing COPD, whereas previous guidelines focused on spirometry to guide COPD pharmacological treatment decisions.[56,57] It is unknown to what extent these changes in guidelines influenced COPD diagnostic trends.

Both COPD and AECOPD appeared to be most common in older men (≥70 years of age). This is consistent with the traditional perception of COPD as a condition that predominantly affects older men,

due in part to the prevalence of smoking in this population cohort.[58,59] However, a recent systematic review and meta-analysis of the gender-specific prevalence of COPD reported a North American COPD prevalence of 7.30% in women and 8.07% in men, suggesting that this gap may not be as large as previously believed.[59] Meanwhile, it has been suggested that women may be less likely than men to receive a COPD diagnosis for similar levels of impairment and are more susceptible to developing COPD due to the effects of smoking.[60,61]

Results from application of the COPD cohort algorithm in this study indicate that relevant ICD code counts begin to increase in the 35-44 years age group. Further, analyses suggested that the proportion of patients receiving diagnoses for COPD and AECOPD increased with age, especially after approximately 50 years of age. This is consistent with findings of a recent meta-analysis, which reported that COPD prevalence increased with age for both men (3.6% for 15–39 years; 10.1% for 40–69 years; and 27.2% for 70+ years) and women (3.4% for 15–39 years; 6.3% for 40–69 years; 15.9% for 70+ years).[59]

Except for 2014, the proportion of individuals receiving a COPD diagnosis was higher in the first half of the year (January–June) than the second (July–December). This may be due to an increase in AECOPD commonly observed in the winter months, which may be associated with colder weather or circulation of respiratory viruses.[30-32]

I Conclusion

The literature review findings were used to develop an updated algorithm that was revised via consultation with clinical SMEs. Strengths of this study are the development of COPD and AECOPD algorithms using ICD-9-CM and ICD-10-CM coding standards, based on a structured review of coding definitions and active engagement with clinical SMEs. To assess the feasibility of algorithm use, these algorithms were applied in the MarketScan Research Databases, a large administrative claims database, to characterize both COPD and AECOPD in the commercially insured U.S. population and generate descriptive statistics.

The study also includes limitations that should be considered in interpreting findings. First, a limited number of COPD and AECOPD validation studies were identified in the literature (**Appendix A**). Moreover, EHR- or claims-based algorithms were sometimes validated with records that also contain the same diagnostic codes used to develop the algorithm, which can weaken the reliability of the validation.[38] Also, the workgroup sought to provide a broad list of codes potentially related to exacerbation, and the AECOPD algorithm is intended for application among a COPD cohort. Users seeking a more specific algorithm may limit codes to those that specify COPD with exacerbation. This approach was not taken here out of concern that true AECOPD cases may not be recognized or reported as such by the treating physician. Conversely, codes for pneumonia were excluded from the AECOPD algorithm presented herein, out of concern that codes were too general and may not be related to AECOPD; however, an independent pneumonia algorithm has been developed by CBER (publication forthcoming) for users interesting in including pneumonia codes in their study of AECOPD.

Under-ascertainment of individuals with AECOPD is possible, as many cases of AECOPD are not medically attended or reported, suggesting that those presenting for care may not be a representative cohort. Meanwhile, the decision not to exclude rule-out diagnoses — such as would be associated with a test to rule out that COPD was present — likely resulted in an overestimation of the frequency of COPD and AECOPD in algorithm characterization analyses presented in **Section G** and **Appendix C**. The analyses conducted in the MarketScan Research Databases should be viewed as exploratory and generalizable to the U.S. population that is commercially insured, and additional studies among populations with different insurance coverage would be required to validate the results and observations stemming from these queries.

J Acknowledgements

Development of the COPD algorithm and review report benefitted from significant engagement with the FDA CBER team members and their partners. We thank them for their contributions and feedback. Additional feedback on the proposed algorithm and draft report was provided by IBM Watson Health, Acumen (Laurie Feinberg, Nirmal Choradia) and Epi Excellence LLC.

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Appendix A. Literature Review Extracted Results

Tables A1 and **A2,** below include a summary of the data extraction table used to extract papers of relevance to COPD and AECOPD algorithms. The 15 papers summarized in this Table A1 and the 9 papers summarized in Table A2 informed the development of the proposed COPD and AECOPD algorithms, respectively.

Table A1. COPD Cohort Data Extraction Table

Citation	Title	Country	Summary	Disease Definition	Algorithm/Criteria	Validity	Claims-/EHR-based Algorithm[x]
Abraham, 2014	Trends in rates of chronic respiratory conditions among U.S. military personnel, 2001-2013.	U.S.	Estimated trends in COPD rates from 2001 to 2013 among active-duty U.S. military personnel.	COPD was defined using ICD-9 codes 490 (bronchitis not specified as acute or chronic), 491 (chronic bronchitis), 492 (emphysema), 493 (asthma), 494 (bronchiectasis), 495 (extrinsic allergic alveolitis), and 496 (chronic airway obstruction not otherwise specified).	The primary algorithm required ≥ 2 ambulatory medical encounters recorded with identical ICD-9-CM codes within 2 years. Another less stringent algorithm required the appearance of only a single ambulatory medical encounter with a given ICD-9-CM code. The most sensitive algorithm required at least 3 ambulatory medical encounters with identical ICD-9-CM codes within 2 years.	NR	EHR
Cooke, 2011	The validity of using ICD-9 codes and pharmacy records to identify patients with chronic obstructive pulmonary disease.	U.S.	Constructed logistic regression-based algorithmic models from 9,573 patients treated at two Veterans Affairs medical centers between 2003-2007.	COPD was defined as: 1) GOLD criterion: FEV1/FVC <0.70, and 2) LLN criterion: FEV1/FVC < lower limits of normal.	Patients with any of the following primary ICD-9-CM codes were considered to have a COPD-related visit: 491.xx (chronic bronchitis), 492.x (emphysema), 493.2x (chronic obstructive asthma), 496 (chronic airway obstruction, not elsewhere classified).	Bootstrapping (2000 iterations) for internal validation of predictive model	EHR (predictive modelling)

[x] Each publication reported on a either a claims-based (i.e., COPD codes derived from insurance reimbursement claims) or an EHR-based (i.e., COPD codes derived from administrative medical records) algorithm.

Citation	Title	Country	Summary	Disease Definition	Algorithm/Criteria	Validity	Claims-/EHR-based Algorithm[x]
Gershon, 2009	Identifying individuals with physician diagnosed COPD in health administrative databases.	Canada	Validation study for a COPD cohort identified using administrative claims data in Ontario.	The consensus reached by the expert panel was considered the reference standard for COPD diagnosis.	Years >35. Combination of ICD-10 and OHIP codes. Any diagnosis with ICD-10 code for inpatient hospitalization (J41 J43 J44), and one disease code as part of OHIP claim (491 492 496).	The most sensitive algorithm definition was comprised of ≥1 ambulatory claim or ≥1 hospitalization for COPD, which resulted in 85.0% sensitivity (95% CI 77.0–91.0) and 78.4% specificity (95% CI 73.6–82.7). Increasing the number of ambulatory claims required decreased sensitivity and increased specificity. The PPV for COPD using ≥1 outpatient claim or ≥1 hospitalization was 57.5% (95% CI 49.6–65.1%). The NPV for COPD using ≥1 outpatient claim or ≥1 hospitalization was 93.8% (95% CI 90.3–96.4%).	Claims
Gothe, 2019	Algorithms to identify COPD in health systems with and without access to ICD coding: a systematic review.	NA	Systematic review of algorithms to identify COPD in health systems	NA	Most studies used ICD codes, hospitalization, and ambulatory visits to identify COPD patients. Only four studies used methods other than ICD coding. Ambulatory, physician claims and pharmaceutical data were included in 24, 22, and 18 studies, respectively. Five studies used spirometry, two	NA	Literature review

Citation	Title	Country	Summary	Disease Definition	Algorithm/Criteria	Validity	Claims-/EHR-based Algorithm[x]
					used surgery and one used oxygen therapy.		
Himes, 2009	Prediction of chronic obstructive pulmonary disease (COPD) in asthma patients using electronic medical records.	U.S.	Identified factors related to COPD progression among asthma patients using data extracted from EHR.	NA	Cases included those with COPD, determined by at least one of the ICD-9-CM codes for chronic bronchitis, emphysema, or chronic airways obstruction, not otherwise specified (specific ICD-9-CM codes were not listed by study authors).	A Bayesian model that included age, sex, race, smoking history, and 8 comorbidity variables was able to predict COPD with an accuracy of 83.3%.	EHR (predictive modelling)
Ho, 2018	Validity of ICD-9-CM codes to diagnose COPD from National Health Insurance claim data in Taiwan.	Taiwan	A cross-sectional study conducted in Taiwan compared claims-based ICD-9-CM COPD (491.xx, 492.x, 496) codes with those from a medical center during 2007-2014.42 The PPV of these data was assessed with reference to physician-verified COPD.	Physician-verified COPD, when spirometry results were available, COPD staging followed the 2011 GOLD guidelines	At least two outpatient claims within a year or at least one inpatient claim coded for COPD (ICD-9-CM codes 491, 492, and 496) in the first three or five diagnostic codes, respectively	The diagnosis of COPD was verified by physicians in 7,701 (63.5%) subjects. Three or more outpatient codes or ≥2 inpatient codes increased the PPV to 72.2%. Age ≥65 years and a claim for spirometry were factors most strongly associated with the PPV of COPD claim codes. Spirometry testing increased the PPV further to 84.6%.42	Claims

Citation	Title	Country	Summary	Disease Definition	Algorithm/Criteria	Validity	Claims-/EHR-based Algorithm[x]
Kern, 2015	Validation of an administrative claims-based diagnostic code for pneumonia in a U.S.-based commercially insured COPD population.	U.S.	Validation study of pneumonia among patients with COPD identified from the U.S. HealthCore Integrated Research Environment.	NA	At least 1 ICD-9-CM codes 491.xx, 492.x, or 496	No validation of COPD codes/cohort	Claims
Lee, 2017	Identifying individuals with physician-diagnosed chronic obstructive pulmonary disease in primary care electronic medical records: a retrospective chart abstraction study.	Canada	A retrospective study of data from the primary care based EHR/ Administrative Data Linked Database. Abstracted charts provided the reference standard based on available physician-diagnoses, COPD medications, smoking history and spirometry.	Patient identified as "definite COPD" by chart reviewer as reference standard.	a) Physician billing codes for COPD b) Medication prescriptions 1. Tiotropium or ipratropium (or ipratropium/ salbutamol) 2. Tiotropium 3. Ipratropium (or ipratropium/ salbutamol c) Cumulative patient profile (CPP; problem list/past medical history)	The EHR algorithm consisting of ≥3 ICD-9 COPD-related billing codes per year; cumulative patient profile descriptions; tiotropium or ipratropium prescription and a COPD billing code had sensitivity of 76.9% (95% CI 72.2–81.2%), specificity of 99.7% (95% CI 99.5–99.8%), PPV of 93.6% (95% CI 90.3–96.1%), and NPV of 98.5% (95% CI 98.1–98.8%).	EHR/claims (linked)

Citation	Title	Country	Summary	Disease Definition	Algorithm/Criteria	Validity	Claims-/EHR-based Algorithm[x]
Macaulay, 2013	Development and validation of a claims-based prediction model for COPD severity.	U.S.	Identified patients with a COPD diagnosis using three ICD-9-CM codes and spirometry test results identified from the Geisinger Health System EHR database linked to healthcare claims (from 2004–2011).	COPD was defined as 1) GOLD criterion: FEV1/FVC <0.70, and 2) LLN criterion: FEV1/FVC < lower limits of normal.	Patients with any of the following primary ICD-9-CM codes were considered to have a COPD-related visit: 491.xx (chronic bronchitis), 492.x (emphysema), 493.2x (chronic obstructive asthma), 496 (chronic airway obstruction, not elsewhere classified).	In the validation sample, the model accurately predicted COPD severity for 62.7% of all patients and accurately predicted COPD — relative to the GOLD definition — for 73.5% of patients.	EHR (predictive modelling)
Mapel, 2010	Can outpatient pharmacy data identify persons with undiagnosed COPD?	U.S.	Assessed whether outpatient pharmacy claims can be used for identification of COPD.	NR	Patients (≥40 years, one or more outpatient or inpatient claims using ICD-9-CM codes: 491, 492, 496).	The final algorithm identified patients with a specificity of 70.5% and a sensitivity of 60.6%.	Claims (predictive modelling)
Quint, 2014	Validation of chronic obstructive pulmonary disease recording in the Clinical Practice Research Datalink (CPRD-GOLD).	UK	Validated COPD using the Clinical Practice Research Datalink database with 951 participants registered from 2004 -2012. Individuals were selected for ≥1 of eight algorithms to identify people with COPD.	Clinician-verified COPD	The eight algorithms were defined as follows, from the expected most specific to most sensitive construct: 1. Specific COPD code and more than one prescription of a COPD medication and presence of spirometry (COPD Code+spirometry+COPD medication); 2. Specific COPD code and presence of spirometry (COPD Code+spirometry);	Using an ICD-modified diagnostic code (Read codes) alone, the PPV was 86.5% (95% CI 77.5–92.3%). When the presence of a spirometry test and specific medication was included; the PPV increased to 89.4% (80.7–94.5%) but reduced case numbers by	EHR

Citation	Title	Country	Summary	Disease Definition	Algorithm/Criteria	Validity	Claims-/EHR-based Algorithm[x]
					3. Specific COPD code and more than one prescription of a COPD medication (COPD Code+COPD medication) 4. Specific COPD code only (COPD Code only); 5. Non-specific bronchitis code and more than one prescription of a COPD medication (Bronchitis+COPD medication); 6. Non-specific bronchitis code only (Bronchitis only); 7. Respiratory symptoms and presence of spirometry. Respiratory symptoms consisted of persistent cough, sputum production or dyspnoea (Symptoms +spirometry); 8. Respiratory symptom definition only (Symptoms only).	10%. Algorithms without specific diagnostic codes were associated with a low PPV (range 12.2–44.4%). Authors suggested that the presence of a specific COPD diagnostic code alone is sufficient to identify patients with COPD from electronic health records. The codes used to indicate spirometry testing and specific medications were not described.	
Ragaišienė, 2019	Diagnosing COPD in primary care: what has real life practice got to do with guidelines?	Lithuania	Retrospective study of COPD with ambulatory records from a large primary care center.	GOLD criteria	Patients with ambulatory records containing any of the following: ICD-10-AM J J44.0 (chronic obstructive pulmonary disease), J44.1 (chronic obstructive pulmonary disease with acute exacerbation), J44.8 (other specified chronic obstructive pulmonary disease) and J44.9 (chronic obstructive pulmonary disease, unspecified).	Spirometry was recorded for 58% of the 228 patients, 75% the guidelines for COPD diagnosis. After re-analyzing spirometry and correcting the diagnosis, 70% of the patients were determined to be receiving appropriate treatments.	EHR

Citation	Title	Country	Summary	Disease Definition	Algorithm/Criteria	Validity	Claims-/EHR-based Algorithm[x]
Schneider, 2005	Are ICD-10 codes appropriate for performance assessment in asthma and COPD in general practice? Results of a cross sectional observational study.	Germany	Assessed the predictive value of chronic lower airway disease diagnoses, diagnostic procedures and prescribed treatment for asthma and COPD. All patients with lower airway symptoms (n = 857) who had attended six general practices between January-June 2003 were included.	Patients had diagnoses documented with ICD-10 codes grouped into 3 lower airway disease groups (asthma, COPD, other lower airway diseases). In addition, the following diagnostic procedures found in the records were recorded: 1. medical history, 2. medical history plus trial of medication, 3. medical history and performing spirometry, 4. medical history plus single measurement of PEF. The additional performance of bronchial challenge testing and chest X-ray was documented, too.	Relevant ICD-10-diagnosis codes included "chronic lower airway disease": J40 (bronchitis, not specified as acute or chronic), J41 (simple and mucopurulent chronic bronchitis), J42 (unspecified chronic bronchitis), J43 (emphysema), J44 (chronic obstructive pulmonary disease), J45 (asthma), J46 (status asthmaticus), J47 (bronchiectasis). Additionally, the ICD-10-codes J98 (diseases of bronchus, not elsewhere classified) and R05 (cough / bronchial hyperreactivity), and the repeated documentation of ICD-10-codes for "acute lower airway disease": J20 (acute bronchitis), J21 (acute bronchiolitis) and J22 (unspecified acute lower respiratory infection) were considered	NA	EHR
Smidth, 2012	Developing an algorithm to identify people with Chronic Obstructive Pulmonary Disease (COPD) using administrative data.	Denmark	Validation study across seven general practices	GOLD guidelines where spirometry available, otherwise GP confirmation and Patient verification	" Thirty-two ICD-10 J-based codes were used to construct algorithms. The following ATC codes were used for medications: R03AC; R03AK; R03BA; R03BB; R03CC; R03DA; R03DC; V03AN01. Spirometry was identified by using codes: 7113 (expanded lung function test verified by spirometry), 7121 (double lung function test for exertion provoked asthma) or a reversibility test.	The best performing algorithm had a PPV of 72.2 % using three criteria: a) discharged patients with a chronic lung-disease diagnosis at least once during the preceding 5 years; or b) ≥2 lung-medication prescriptions within	EHR

Citation	Title	Country	Summary	Disease Definition	Algorithm/Criteria	Validity	Claims-/EHR-based Algorithm[x]
					Administrative data on hospital admissions for lung disease related diagnoses, medications, drugs, and spirometry were combined to develop an algorithm that identified the highest proportion of COPD patients with the fewest criteria.	the preceding 12 months; or c) ≥2 spirometry tests performed during the preceding 12 months.	
Westney, 2017	Impact of Comorbidities Among Medicaid Enrollees with Chronic Obstructive Pulmonary Disease, United States, 2009.	U.S.	Used Medicaid claims data to assess the impact of comorbidities in COPD among 291,978 patients.	NR	Eligible patients must have been enrolled in Medicaid for 12 months in 2009. This study used the Gershon validated algorithm consisting of ICD-9-CM diagnostic codes 491.0, 491.1, 491.2, 491.8, 492.x, 493.2, 494.xx, and 496, patients with COPD were identified if they had ≥1 inpatient based billed claim or ≥2 outpatient billed claims.	NA	Westney

Abbreviations: COPD, chronic obstructive pulmonary disease; EHR, electronic health record; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-AM, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; NA, not applicable; NR, not reported; NPV, negative predictive value; PPV, positive predictive value

Table A2. AECOPD Data Extraction Table

Citation	Title	Country	Summary	Disease Definition	Algorithm/Criteria	Validity	Claims-/EHR-based Algorithm[xi]
Annavarapu, 2018	Development and validation of a predictive model to identify patients at risk of severe COPD exacerbations using administrative claims data.	U.S.	Developed a predictive model using Humana claims data to identify patients in the U.S. at risk of severe AECOPD. Patients aged 55–89 years between 2010 and 2013 were included in the study.	COPD diagnosis was determined using claims with a COPD-diagnosis code. This operational classification may have resulted in misclassification in some cases, since airflow testing (e.g., forced expiratory volume in 1 second) results were not available to confirm COPD diagnosis.	Patients with non-severe exacerbations were identified using the following algorithm, with diagnosis claims reported in the emergency department or outpatient setting: 1. COPD diagnosis (ICD-9-CM 491.xx, 492.x, or 496) in the primary position OR 2. Respiratory failure code (ICD-9-CM code 518.81, 518.83, or 518.84) in the primary position with a COPD diagnosis code (above) in the secondary diagnostic position OR 3. At least one AECOPD code (ICD-9-CM codes 466–466.19, 480–486, 487.0, 490, 493.12, 493.22, 493.92, 494.1, 506.0–506.3, 511.0–511.1, or 518.82) in the primary position and a COPD (above) in the secondary diagnostic position AND 4. A prescription for a respiratory infection antibiotic within seven days of the visit OR	Predictive modelling: The best performing model had a PPV of 48.1%, suggesting that one of every two patients identified as being at risk will have an AECOPD. The model had a sensitivity of 17.3%, specificity of 97.5%, and NPV of 90.0%. The risk factor with the strongest predictive value for severe AECOPD was a history of severe AECOPD at baseline.	Claims

[xi] Each publication reported on a either a claims-based (i.e., AECOPD codes derived from insurance reimbursement claims) or an EHR-based (i.e., AECOPD codes derived from administrative medical records) algorithm.

Citation	Title	Country	Summary	Disease Definition	Algorithm/Criteria	Validity	Claims-/EHR-based Algorithm[xi]
					5. A prescription for an oral corticosteroid within seven days of the visit. Patients with severe AECOPD were identified using Criteria #1–3 reported in the hospital setting.		
Dhamane, 2015	COPD exacerbation frequency and its association with health care resource utilization and costs.	U.S.	Assessed AECOPD related healthcare costs from 2008-2010 using the Medicare Advantage Prescription Drug plan database, In this study, a COPD diagnosis was defined as ≥2 medical claims occurring on separate dates within 90 days with a COPD ICD-9-CM code (491.xx, 492.x, or 496) in the primary or secondary position.	NA	The following three AECOPD algorithms — organized by severity (from least to greatest) — were used: • One ER or outpatient medical claim with ≥1 of the following: 1. COPD ICD-9-CM code 491.xx, 492.x, or 496 in the primary position OR 2. Respiratory failure code ICD-9-CM 518.81, 518.83, or 518.84 in the primary position plus a COPD code in the secondary position OR 3. Any AECOPD code (ICD-9-CM 466–466.19, 480–486, 487.0, 490, 493.12, 493.22, 493.92, 494.1, 506.0–506.3, 511.0–511.1, or 518.82) in the primary position and a COPD code in the secondary position AND within 7 days of the visit: AND ≥1 of 1. A respiratory infection based antibiotic prescription OR	No validation	Claims

Citation	Title	Country	Summary	Disease Definition	Algorithm/Criteria	Validity	Claims-/EHR-based Algorithm[xi]
					2. An oral corticosteroid prescription • A medical claim for a hospitalization with either: 1. COPD diagnosis code in the primary position OR 2. Any AECOPD indicative code in the primary position and a COPD code in the secondary position AND no respiratory failure diagnosis code in secondary position • A medical claim for a hospitalization with the following: 1. COPD code in the primary position and a respiratory failure diagnosis code in secondary position OR 2. AECOPD code in the primary position and COPD and a respiratory failure code in the secondary position OR 3. Respiratory failure code in the primary position and COPD code in the secondary position		
Ginde, 2008	Positive predictive value of ICD-9-CM codes to detect acute exacerbation of COPD in the	U.S.	Assessed PPV of AECOPD codes in U.S. emergency departments	Cases were confirmed via chart review by two emergency department The case definition used for AECOPD	ICD-9-CM codes 491.2x (obstructive chronic bronchitis), 492.8 (other emphysema), and 496 (chronic airway obstruction, not elsewhere classified) in the principal diagnosis	Of 200 randomly selected visits these, 193 (96.5%) visits met the case definition for AECOPD. Most cases were identified using code 491.2x.	Claims

Citation	Title	Country	Summary	Disease Definition	Algorithm/Criteria	Validity	Claims-/EHR-based Algorithm[xi]
	emergency department.			was 1) current respiratory infection, 2) change in cough, or 3) change in sputum in a patient with known or new physician diagnosed COPD	field were used to identify AECOPD visits.	Most false positives occurred using code 496 (chronic airway obstruction, not elsewhere classified).	
Mapel, 2011	Identifying and characterizing COPD patients in U.S. managed care. A retrospective, cross-sectional analysis of administrative claims data.	U.S.	Developed an algorithm to identify AECOPD using ICD-9-CM codes.	NR	Criteria for COPD identification was age ≥40 years and any one of the following 3 algorithms: 1. One inpatient hospitalization or one emergency department visit with a diagnosis of 491.xx (chronic bronchitis), 492.x (emphysema), or 496 (chronic airway obstruction) listed in any position as a discharge diagnosis; 2. Two COPD diagnosis claims listed in any position 3. A COPD-related surgical procedure (e.g., lung volume reduction). Nearly 200 ICD-9-CM codes were used to define exacerbation complexity. More patients with high complexity disease experienced ≥2 exacerbations	No validation	Claims
Rothnie, 2016	Validation of the recording of acute	UK	Validated AECOPD codes	AECOPD diagnoses were validated by	Fifteen algorithms for AECOPD were created	An algorithm using AECOPD diagnostic	EHR

Citation	Title	Country	Summary	Disease Definition	Algorithm/Criteria	Validity	Claims-/EHR-based Algorithm[xi]
	exacerbations of COPD in UK Primary Care Electronic Health Records		using EHR data from 1,385 randomly selected patients within the Clinical Practice Research Datalink between 2004 and 2013.47	clinician questionnaire responses that were subsequently reviewed by two respiratory physicians	using UK-based Read diagnostic codes.	codes, lower respiratory tract infection (LRTI) codes, and antibiotics/oral corticosteroid prescription (OCS) use together for 5–14 days had a high PPV (>75%) for identifying AECOPD. Symptom-based algorithms and antibiotic or OCS prescriptions had lower PPVs (60–75%). Combining antibiotic and OCS prescriptions for 5–14 days, or LRTI or AECOPD codes resulted in a PPV of 85.5% and a sensitivity of 62.9%.	
Rothnie, 2016	Recording of hospitalizations for acute exacerbations of COPD in UK electronic health care records.	UK	Assessed the predictive value of AECOPD hospitalization discharge data	NR	Two algorithms were tested: 1) AECOPD hospitalization codes and 2) any non-hospitalization AECOPD code on the same day as a code for hospitalization due to unspecified reason.	Identifying AECOPD hospitalizations in HES had a sensitivity of 87.5%. When compared with HES, AECOPD hospitalization codes resulted in a PPV of 50.2% and a sensitivity of 4.1%. Using a AECOPD code along with a hospitalization code due to unspecified reason resulted in a PPV of 43.3% and a sensitivity of 5.4%.	EHR

Citation	Title	Country	Summary	Disease Definition	Algorithm/Criteria	Validity	Claims-/EHR-based Algorithm[xi]
Stanford, 2016	Validation of a New Risk Measure for Chronic Obstructive Pulmonary Disease Exacerbation Using Health Insurance Claims Data.	U.S.	Sought to validate the use of COPD medications as a risk measure for AECOPD, using data between 2006 and 2011 drawn from the Truven MarketScan and Reliant Medical Group databases.	NA	COPD status was defined as either an inpatient hospitalization with ICD-9-CM codes 491.xx (chronic bronchitis), 492.x (emphysema), or 496 (chronic airway obstruction) or the second of two outpatient encounters with a COPD diagnosis occurring within 365 days. Moderate exacerbation was defined as a COPD outpatient with ≥1 oral corticosteroid dispensed within 7 days of this visit. A severe exacerbation was defined as a primary position COPD-coded inpatient stay or a primary diagnosis of respiratory failure (ICD-9-CM 518.81, 518.82, or 518.84) with a secondary diagnosis of COPD.	No validation	Claims
Stein, 2012	The validity of International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis codes for identifying patients hospitalized for COPD exacerbations.	U.S.	Assessed the validity of ICD-9-CM codes for AECOPD at 2 teaching hospitals in the U.S.	Chart review was used as a reference standard "Reference standard for AE-COPD: 1) physician diagnosis of COPD (documented diagnosis of chronic bronchitis, emphysema, chronic obstructive pulmonary disease, or COPD in	Four different code-based algorithms for identifying patients hospitalized for AECOPD were validated ICD-9-CM codes used in various algorithms as a primary or secondary discharge diagnosis included: 491.0, 491.1, 491.21, 491.22, 491.8, 491.9, 492.0, 492.8, 493.22, and 496. Primary	The reference standard-based prevalence of AECOPD was 7.9%. The sensitivity of all ICD-9-CM based algorithms was very low (12–25%) and the NPV was high across algorithms (93–94%). The specificity was 99% for all algorithms, and the	EHR

Citation	Title	Country	Summary	Disease Definition	Algorithm/Criteria	Validity	Claims-/EHR-based Algorithm[xi]
				the admission note, progress note, or discharge summary from the index hospitalization); 2) presence of cough, dyspnea, or sputum production on presentation; and 3) hospitalization for one of these respiratory symptoms. "	diagnoses of respiratory failure and secondary discharge diagnosis of the following AECOPD codes were also used: 518.81 (acute respiratory failure), 518.82 (other pulmonary insufficiency, not elsewhere classified), 518.84 (acute and chronic respiratory failure).	PPV was more variable (81–97%).	
Thomsen, 2011	Validity and under recording of diagnosis of COPD in the Danish National Patient Registry.	Denmark	Assessed the PPV of AECOPD diagnoses and the NPV of COPD in acute pneumonia or respiratory failure discharge diagnoses using the Danish National Patient Registry. Patients aged ≥30 years with outpatient hospital admission in 2008 were identified.	Physicians at 34 hospitals reviewed medical records and validated COPD diagnoses using medical history, clinical symptoms, and spirometry test results	All acute hospitalization episodes discharged with an ICD-10 J44 diagnostic code (chronic obstructive pulmonary disease with acute lower respiratory infection) among 1,581 patients retrieved.	A PPV of 92% (95% CI 91–93%) was derived for COPD. An NPV of 81% (95% CI 79–83%) was derived from primary or secondary COPD diagnoses combined with a primary diagnosis code J96 (acute respiratory failure) or J13-J18 (pneumonia) during the same hospitalization.	EHR

Abbreviations: EHR, electronic health record; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-AM, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; NA, not applicable; NR, not reported; NPV, negative predictive value; PPV, positive predictive value

Appendix B. Comparison of AECOPD Codes Across Studies

A broad application across studies of diagnosis codes was applied to identify possible cases of acute exacerbation of chronic obstructive pulmonary disease (AECOPD). **Table B1**, below, provides a summary of which diagnosis codes were applied across the studies that were retained and reported the use of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes.

Table B1. Comparison of ICD-9-CM diagnosis codes used to identify potential cases of AECOPD.

ICD-9-CM	Code Description	Annavarapu, 2018	Macaulay, 2013	Kern, 2015	Dhamane, 2015	Standord, 2016	Stein, 2012	Ginde, 2008	Mapel, 2011
491.xx	Chronic bronchitis	X	X	X	X	X	X		X
492.x	Emphysema	X	X	X	X	X	X	X	X
496	Chronic airway obstruction, not elsewhere classified	X	X	X	X	X	X	X	X
Other qualifying codes for exacerbation									
136.3	Pneumocystosis		X						
466-466.19	Acute bronchitis and bronchiolitis	X	X		X				
480-486	Pneumonia	X	X		X				
487.0	Influenza with pneumonia	X	X		X				
490	Bronchitis, not specified as acute or chronic.	X	X		X				
491.21	Obstructive chronic bronchitis with (acute) exacerbation.		X					X	
491.22	Obstructive chronic bronchitis with acute bronchitis.		X					X	
493.02	Extrinsic asthma with (acute) exacerbation								
493.12	Intrinsic asthma with (acute) exacerbation	X			X				
493.22	Chronic obstructive asthma with (acute) exacerbation.	X			X		X		
493.92	Asthma, unspecified type, with (acute) exacerbation.	X			X				
494.1	Bronchiectasis with acute exacerbation	X	X		X				

ICD-9-CM	Code Description	Annavarapu, 2018	Macaulay, 2013	Kern, 2015	Dhamane, 2015	Standord, 2016	Stein, 2012	Ginde, 2008	Mapel, 2011
506.0	Bronchitis and pneumonitis due to fumes and vapors	X	X		X				
506.1	Acute pulmonary edema due to fumes and vapors	X	X		X				
506.2	Upper respiratory inflammation due to fumes and vapors	X	X		X				
506.3	Other acute and subacute respiratory conditions due to fumes and vapors	X	X		X				
507.0	Pneumonitis due to inhalation of food or vomitus		X						
507.1	Pneumonitis due to inhalation of oils and essences		X						
507.8	Pneumonitis due to other solids and liquids		X						
511.0	Pleurisy without mention of effusion or current tuberculosis	X	X		X				
511.1	Pleurisy with effusion, with mention of a bacterial cause other than tuberculosis	X	X		X				
512-512.8	Pneumothorax and air leak.		X						
517.1	Rheumatic pneumonia		X						
518.0	Pulmonary collapse		X						
518.81	Acute respiratory failure.	X	X		X		X		
518.82	Other pulmonary insufficiency, not elsewhere classified	X	X		X		X		
518.83	Chronic respiratory failure	X			X				
518.84	Acute and chronic respiratory failure	X	X		X		X		

Abbreviations: ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification

Appendix C. Counts of Patients with Specific Codes Proposed for the Algorithm

As an initial test of the proposed algorithm, the workgroup ran code-specific queries in a large U.S. administrative claims dataset. Researchers used the MarketScan Research Databases (Commercial, Medicare Supplemental), accessed via the Treatment Pathways online analytic platform, querying the past five full years of available data. Results are presented in **Tables C1** and **C2**. Because the transition between International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification (ICD-9-CM to ICD-10-CM) occurred on October 1, 2015, ICD-9-CM codes were queried for January 1, 2014–September 30, 2015, and ICD-10-CM codes were queried for October 1, 2015–December 31, 2018.

Subtotal rows and total columns may be smaller than the sum of individual cells, because patients with multiple codes in a single year and with more than one of the same diagnosis codes in different years will only be counted once in these rows and columns. As a result, the sum of all "% of Total" cells in a single column may exceed 100%. However, the "Total" column could also be larger than the sum of individual years, as a result of situations where an individual is only enrolled for part of the year that they experience a chronic obstructive pulmonary disease (COPD) event but is then continuously enrolled for a separate year. For example, an individual could be continuously enrolled for a few days, weeks, or months in 2016 and experience a COPD event, then be continuously enrolled for all of 2017. This event would not be captured in the column for the 2016 (as the individual would be excluded from that cohort) but would be captured in the "Total" column.

From the COPD cohort queries, it appears that diagnosis codes for obstructive chronic bronchitis with (acute) exacerbation (ICD-9-CM 491.21; ICD-10-CM J44.1), chronic airway obstruction, not elsewhere classified (ICD-9-CM 496; ICD-10-CM J44.9), and emphysema, unspecified (ICD-10-CM J43.9) were the most frequently used COPD codes. Given this, the inclusion of unspecified codes could introduce risk of bias through the inclusion of conditions other than COPD.

Queries for the COPD acute exacerbation (AECOPD) algorithm were run only on the combined cohort of 1,302,316 individuals that had a COPD cohort code and were enrolled for at least one calendar year between January 1, 2014 and December 31, 2018. Codes were queried from one day following entry into the COPD cohort until September 30, 2015 for ICD-9-CM codes and from one day following entry into the COPD cohort until December 31, 2018 for the ICD-10-CM codes. Results suggest that acute bronchitis (ICD-9-CM 466.0; ICD-10-CM J20.9), bronchitis, not specified as acute or chronic (ICD-10-CM J40) obstructive chronic bronchitis with (acute) exacerbation (ICD-9-CM 491.21; ICD-10-CM J44.0, J44.1), and acute respiratory failure, with hypoxia (ICD-10-CM J96.01) were the most frequently used AECOPD codes.

Table C1. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes proposed for inclusion in the COPD cohort algorithm (January 1, 2014–December 31, 2018).

Code	Code Description	Year										Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)	2018 (Count)	2018 (% of Total		
ICD-9-CM													
491.0	Simple chronic bronchitis	13,455	2.4	8,553	1.9							21,744	1.7
491.1	Mucopurulent chronic bronchitis	4,861	0.9	3,035	0.7							7,883	0.6
491.20	Obstructive chronic bronchitis without exacerbation	45,500	8.1	28,461	6.3							67,297	5.2
491.21	Obstructive chronic bronchitis with (acute) exacerbation	95,614	17.0	61,194	13.5							147,284	11.3
491.22	Obstructive chronic bronchitis with acute bronchitis	21,022	3.7	12,552	2.8							33,997	2.6
491.8	Other chronic bronchitis	4,049	0.7	2,696	0.6							6,670	0.5
491.9	Unspecified chronic bronchitis	22,922	4.1	15,290	3.4							37,612	2.9
492.0	Emphysematous bleb	6,149	1.1	3,722	0.8							10,021	0.8
492.8	Other emphysema	75,742	13.5	50,620	11.2							119,560	9.2
493.20	Chronic obstructive asthma, unspecified	53,478	9.5	34,590	7.7							81,585	6.3
493.21	Chronic obstructive asthma with status asthmaticus	3,691	0.7	**2,272**	0.5							5,751	0.4
493.22	Chronic obstructive asthma with (acute) exacerbation	18,406	3.3	11,147	2.5							29,434	2.3
494.0	Bronchiectasis without acute exacerbation	23,530	4.2	16,519	3.7							35,182	2.7
494.1	Bronchiectasis with acute exacerbation	5,235	0.9	3,317	0.7							7,887	0.6
496	Chronic airway obstruction, not elsewhere classified	404,947	72.0	280,250	62.0							562,884	43.2
ICD-9-CM Subtotal		**562,458**	**100.0**	**382,143**	**84.6**							**787,400**	**60.5**
ICD-10-CM													
J41.0	Simple chronic bronchitis			5,913	1.3	14,915	3.6	12,181	3.7	9,880	3.8	39,475	3.0
J41.1	Mucopurulent chronic bronchitis			1,910	0.4	5,589	1.4	5,003	1.5	4,114	1.6	15,597	1.2
J41.8	Mixed simple and mucopurulent chronic bronchitis			1,010	0.2	2,568	0.6	2,366	0.7	1,701	0.6	6,811	0.5
J42	Unspecified chronic bronchitis			8,500	1.9	23,301	5.7	18,541	5.6	14,862	5.7	60,758	4.7
J43.0	Unilateral pulmonary emphysema			236	0.1	631	0.2	429	0.1	322	0.1	1,616	0.1
J43.1	Panlobular emphysema			1,738	0.4	5,020	1.2	4,882	1.5	3,855	1.5	12,750	1.0
J43.2	Centrilobular emphysema			4,567	1.0	15,526	3.8	15,565	4.7	14,047	5.3	43,106	3.3

Code	Code Description	Year									Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)	2018 (Count)	2018 (% of Total	
J43.8	Other emphysema			3,345	0.7	10,022	2.4	8,388	2.6	6,499	2.5	25,548	2.0
J43.9	Emphysema, unspecified			22,931	5.1	58,560	14.2	45,876	14.0	38,152	14.5	147,022	11.3
J44.0	Chronic obstructive pulmonary disease with (acute) lower respiratory infection			8,682	1.9	23,290	5.7	22,490	6.8	14,707	5.6	68,956	5.3
J44.1	Chronic obstructive pulmonary disease with (acute) exacerbation			35,885	7.9	86,303	20.9	71,854	21.9	53,541	20.4	210,605	16.2
J44.9	Chronic obstructive pulmonary disease, unspecified			174,436	38.6	318,600	77.3	246,524	75.1	189,750	72.1	634,058	48.7
J47.0	Bronchiectasis with acute lower respiratory infection			640	0.1	1,965	0.5	2,092	0.6	1,789	0.7	6,193	0.5
J47.1	Bronchiectasis with (acute) exacerbation			1,787	0.4	4,316	1.0	3,590	1.1	3,169	1.2	10,545	0.8
J47.9	Bronchiectasis, uncomplicated			9,242	2.0	22,163	5.4	18,572	5.7	17,038	6.5	51,808	4.0
ICD-10-CM Subtotal				**222,034**	**49.1**	**412,110**	**100.0**	**328,414**	**100.0**	**263,000**	**100.0**	**847,920**	**65.1**
Total		**562,458**	**100.0**	**451,931**	**100.0**	**412,110**	**100.0**	**328,414**	**100.0**	**263,000**	**100.0**	**1,302,316**	**100.0**

Note: Codes highlighted in yellow represent those that accounted for at least 10% of the overall count among the 2014–2018 cohort

Table C2. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes proposed for inclusion in the AECOPD algorithm (January 1, 2014–December 31, 2018).

Code	Code Description	Total (Count)	Total (% of Total)
ICD-9-CM			
466.0	Acute bronchitis	104,209	19.0
466.11	Acute bronchiolitis due to respiratory syncytial virus (RSV)	944	0.2
466.19	Acute bronchiolitis due to other infectious organisms	3,692	0.7
490	Bronchitis, not specified as acute or chronic.	52,687	9.6
491.21	Obstructive chronic bronchitis with (acute) exacerbation.	104,542	19.0
491.22	Obstructive chronic bronchitis with acute bronchitis.	21,625	3.9
493.22	Chronic obstructive asthma with (acute) exacerbation.	18,201	3.3
494.1	Bronchiectasis with acute exacerbation	5,967	1.1
518.81	Acute respiratory failure	51,261	9.3
518.82	Other pulmonary insufficiency, not elsewhere classified	11,751	2.1
518.83	Chronic respiratory failure	22,297	4.1
518.84	Acute and chronic respiratory failure	21,084	3.8
ICD-9-CM Subtotal		**246,941**	44.9
ICD-10-CM			
J20.9	Acute bronchitis, unspecified	178,009	32.4
J21.0	Acute bronchiolitis due to respiratory syncytial virus	1,290	0.2
J21.1	Acute bronchiolitis due to human metapneumovirus	126	0.0
J21.8	Acute bronchiolitis due to other specified organisms	1,419	0.3
J21.9	Acute bronchiolitis, unspecified	6,208	1.1
J40	Bronchitis, not specified as acute or chronic	98,736	18.0
J41.0	Simple chronic bronchitis	23,349	4.2
J44.0	Chronic obstructive pulmonary disease with (acute) lower respiratory infection	55,676	10.1
J44.1	Chronic obstructive pulmonary disease with (acute) exacerbation	170,523	31.0
J47.0	Bronchiectasis with acute lower respiratory infection	4,517	0.8
J47.1	Bronchiectasis with (acute) exacerbation	8,857	1.6
J47.9	Bronchiectasis, uncomplicated	36,921	6.7
J80	Acute respiratory distress syndrome	13,748	2.5
J96.00	Acute respiratory failure, unspecified whether with hypoxia or hypercapnia	43,273	7.9
J96.01	Acute respiratory failure, with hypoxia	67,724	12.3
J96.02	Acute respiratory failure, with hypercapnia	16,111	2.9
R06.03	Acute respiratory distress	5,216	0.9
ICD-10-CM Subtotal		**414,915**	**75.5**
Total		**549,827**	**100.0**

Note: Codes highlighted in yellow represent those that accounted for at least 10% of the overall count among the 2014–2018 cohort

Appendix D. Codes Excluded from Proposed Algorithm

The diagnosis codes listed in **Table D1** and **Table D2** are proposed for exclusion from the COPD cohort and the AECOPD algorithms, respectively. These codes were initially considered for inclusion based on a literature review and their potential relation to COPD/AECOPD. In consultation with clinical SMEs (TB, JB, JC, DT) these codes – which were not specific to COPD or AECOPD — were ultimately determined to be too general and could potentially increase the risk of misclassification. Further, these codes were not used to identify patients with a relevant COPD diagnosis.

Table D1. Excluded codes potentially relevant to COPD cohort algorithm identified from the literature or GEMs mapping.

Code	Description	Code Category	Code Type
490	Bronchitis, not specified as acute or chronic	DX	9
493.00	Extrinsic asthma, unspecified	DX	9
493.01	Extrinsic asthma with status asthmaticus	DX	9
493.02	Extrinsic asthma with (acute) exacerbation	DX	9
493.10	Intrinsic asthma, unspecified	DX	9
493.11	Intrinsic asthma with status asthmaticus	DX	9
493.12	Intrinsic asthma with (acute) exacerbation	DX	9
493.81	Exercise induced bronchospasm	DX	9
493.90	Asthma, unspecified type, unspecified	DX	9
493.91	Asthma, unspecified type, with status asthmaticus	DX	9
493.92	Asthma, unspecified type, with (acute) exacerbation	DX	9
495.0	Farmers' lung	DX	9
495.1	Bagassosis	DX	9
495.2	Bird-fanciers' lung	DX	9
495.3	Suberosis	DX	9
495.4	Malt workers' lung	DX	9
495.5	Mushroom workers' lung	DX	9
495.6	Maple bark-strippers' lung	DX	9
495.7	Ventilation" pneumonitis	DX	9
495.8	Other specified allergic alveolitis and pneumonitis	DX	9
495.9	Unspecified allergic alveolitis and pneumonitis	DX	9
J40	Bronchitis, not specified as acute or chronic	DX	10
J43.0	Unilateral pulmonary emphysema [MacLeod's syndrome]	DX	10
J45.20	Mild intermittent asthma uncomplicated	DX	10
J45.21	Mild intermittent asthma with (acute) exacerbation	DX	10
J45.22	Mild intermittent asthma with status asthmaticus	DX	10
J45.30	Mild persistent asthma uncomplicated	DX	10
J45.31	Mild persistent asthma with (acute) exacerbation	DX	10
J45.32	Mild persistent asthma with status asthmaticus	DX	10
J45.40	Moderate persistent asthma uncomplicated	DX	10
J45.41	Moderate persistent asthma with (acute) exacerbation	DX	10
J45.42	Moderate persistent asthma with status asthmaticus	DX	10
J45.50	Severe persistent asthma, uncomplicated	DX	10
J45.51	Severe persistent asthma with (acute) exacerbation	DX	10
J45.52	Severe persistent asthma with status asthmaticus	DX	10
J45.901	Unspecified asthma with (acute) exacerbation	DX	10
J45.902	Unspecified asthma with status asthmaticus	DX	10
J45.909	Unspecified asthma uncomplicated	DX	10

Code	Description	Code Category	Code Type
J45.990	Exercise induced bronchospasm	DX	10
J45.991	Cough variant asthma	DX	10
J45.998	Other asthma	DX	10
J67.0	Farmer's lung	DX	10
J67.1	Bagassosis	DX	10
J67.2	Bird fancier's lung	DX	10
J67.3	Suberosis	DX	10
J67.4	Maltworker's lung	DX	10
J67.5	Mushroom-worker's lung	DX	10
J67.6	Maple-bark-stripper's lung	DX	10
J67.7	Air conditioner and humidifier lung	DX	10
J67.8	Hypersensitivity pneumonitis due to other organic dusts	DX	10
J67.9	Hypersensitivity pneumonitis due to unspecified organic dust	DX	10

Abbreviation: DX, ICD-CM diagnosis.

Table D2. Excluded codes potentially relevant to AECOPD algorithm identified from the literature or GEMs mapping.

Code	Description	Code Category	Code Type
136.3	Pneumocystosis	DX	9
480.0	Pneumonia due to adenovirus	DX	9
480.1	Pneumonia due to respiratory syncytial virus	DX	9
480.2	Pneumonia due to parainfluenza virus	DX	9
480.3	Pneumonia due to SARS-associated coronavirus	DX	9
480.8	Pneumonia due to other virus not elsewhere classified	DX	9
480.9	Viral pneumonia, unspecified	DX	9
481	Pneumococcal pneumonia [Streptococcus pneumoniae pneumonia]	DX	9
482.0	Pneumonia due to Klebsiella pneumoniae	DX	9
482.1	Pneumonia due to Pseudomonas	DX	9
482.2	Pneumonia due to Hemophilus influenzae [H. influenzae]	DX	9
482.30	Pneumonia due to Streptococcus, unspecified	DX	9
482.31	Pneumonia due to Streptococcus, group A	DX	9
482.32	Pneumonia due to Streptococcus, group B	DX	9
482.39	Pneumonia due to other Streptococcus	DX	9
482.40	Pneumonia due to Staphylococcus, unspecified	DX	9
482.41	Methicillin susceptible pneumonia due to Staphylococcus aureus	DX	9
482.42	Methicillin resistant pneumonia due to Staphylococcus aureus	DX	9
482.49	Other Staphylococcus pneumonia	DX	9
482.81	Pneumonia due to anaerobes	DX	9
482.82	Pneumonia due to escherichia coli [E. coli]	DX	9
482.83	Pneumonia due to other gram-negative bacteria	DX	9
482.84	Pneumonia due to Legionnaires' disease	DX	9
482.89	Pneumonia due to other specified bacteria	DX	9
482.9	Bacterial pneumonia, unspecified	DX	9
483.0	Pneumonia due to mycoplasma pneumoniae	DX	9
483.1	Pneumonia due to chlamydia	DX	9
483.8	Pneumonia due to other specified organism	DX	9
484.1	Pneumonia in cytomegalic inclusion disease	DX	9
484.3	Pneumonia in whooping cough	DX	9

Code	Description	Code Category	Code Type
484.5	Pneumonia in anthrax	DX	9
484.6	Pneumonia in aspergillosis	DX	9
484.7	Pneumonia in other systemic mycoses	DX	9
484.8	Pneumonia in other infectious diseases classified elsewhere	DX	9
485	Bronchopneumonia, organism unspecified	DX	9
486	Pneumonia, organism unspecified	DX	9
487.0	Influenza with pneumonia	DX	9
491.0	Simple chronic bronchitis	DX	9
491.1	Mucopurulent chronic bronchitis	DX	9
491.20	Obstructive chronic bronchitis without exacerbation	DX	9
491.8	Other chronic bronchitis	DX	9
491.9	Unspecified chronic bronchitis	DX	9
493.02	Extrinsic asthma with (acute) exacerbation	DX	9
493.12	Intrinsic asthma with (acute) exacerbation	DX	9
493.92	Asthma, unspecified type, with (acute) exacerbation.	DX	9
494.0	Bronchiectasis without acute exacerbation	DX	9
506.0	Bronchitis and pneumonitis due to fumes and vapors	DX	9
506.1	Acute pulmonary edema due to fumes and vapors	DX	9
506.2	Upper respiratory inflammation due to fumes and vapors	DX	9
506.3	Other acute and subacute respiratory conditions due to fumes and vapors	DX	9
506.4	Chronic respiratory conditions due to fumes and vapors	DX	9
506.9	Unspecified respiratory conditions due to fumes and vapors	DX	9
507.0	Pneumonitis due to inhalation of food or vomitus	DX	9
507.1	Pneumonitis due to inhalation of oils and essences	DX	9
507.8	Pneumonitis due to other solids and liquids	DX	9
511.0	Pleurisy without mention of effusion or current tuberculosis	DX	9
511.1	Pleurisy with effusion, with mention of a bacterial cause other than tuberculosis	DX	9
511.81	Malignant pleural effusion	DX	9
511.89	Other specified forms of effusion, except tuberculous	DX	9
511.9	Unspecified pleural effusion	DX	9
512.0	Spontaneous tension pneumothorax	DX	9
512.1	Iatrogenic pneumothorax	DX	9
512.2	Postoperative air leak	DX	9
512.81	Primary spontaneous pneumothorax	DX	9
512.82	Secondary spontaneous pneumothorax	DX	9
512.83	Chronic pneumothorax	DX	9
512.84	Other air leak	DX	9
512.89	Other pneumothorax	DX	9
514	Pulmonary congestion and hypostasis	DX	9
517.1	Rheumatic pneumonia	DX	9
518.0	Pulmonary collapse	DX	9
518.1	Interstitial emphysema	DX	9
518.2	Compensatory emphysema	DX	9
518.3	Pulmonary eosinophilia	DX	9
518.4	Acute edema of lung, unspecified	DX	9
518.51	Acute respiratory failure following trauma and surgery	DX	9
518.52	Other pulmonary insufficiency, not elsewhere classified, following trauma and surgery	DX	9
518.53	Acute and chronic respiratory failure following trauma and surgery	DX	9
518.6	Allergic bronchopulmonary aspergillosis	DX	9

Code	Description	Code Category	Code Type
518.7	Transfusion related acute lung injury (TRALI)	DX	9
518.89	Other diseases of lung, not elsewhere classified	DX	9
770.84	Respiratory failure of newborn	DX	9
A22.1	Pulmonary anthrax	DX	10
A37.01	Whooping cough due to Bordetella pertussis with pneumonia	DX	10
A37.11	Whooping cough due to Bordetella parapertussis with pneumonia	DX	10
A37.81	Whooping cough due to other Bordetella species with pneumonia	DX	10
A37.91	Whooping cough, unspecified species with pneumonia	DX	10
B25.0	Cytomegaloviral pneumonitis	DX	10
B44.0	Invasive pulmonary aspergillosis	DX	10
B44.1	Other pulmonary aspergillosis	DX	10
B44.81	Allergic bronchopulmonary aspergillosis	DX	10
B59	Pneumocystosis	DX	10
J11.00	Influenza due to unidentified influenza virus with unspecified type of pneumonia	DX	10
J11.08	Influenza due to unidentified influenza virus with specified pneumonia	DX	10
J12.0	Adenoviral pneumonia	DX	10
J12.1	Respiratory syncytial virus pneumonia	DX	10
J12.2	Parainfluenza virus pneumonia	DX	10
J12.81	Pneumonia due to SARS-associated coronavirus	DX	10
J12.89	Other viral pneumonia	DX	10
J12.9	Viral pneumonia, unspecified	DX	10
J13	Pneumonia due to Streptococcus pneumoniae	DX	10
J14	Pneumonia due to Hemophilus influenzae	DX	10
J15.0	Pneumonia due to Klebsiella pneumoniae	DX	10
J15.1	Pneumonia due to Pseudomonas	DX	10
J15.20	Pneumonia due to staphylococcus, unspecified	DX	10
J15.211	Pneumonia due to Methicillin susceptible Staphylococcus aureus	DX	10
J15.212	Pneumonia due to Methicillin resistant Staphylococcus aureus	DX	10
J15.29	Pneumonia due to other staphylococcus	DX	10
J15.3	Pneumonia due to streptococcus, group B	DX	10
J15.4	Pneumonia due to other streptococci	DX	10
J15.5	Pneumonia due to Escherichia coli	DX	10
J15.6	Pneumonia due to other Gram-negative bacteria	DX	10
J15.7	Pneumonia due to Mycoplasma pneumoniae	DX	10
J15.8	Pneumonia due to other specified bacteria	DX	10
J15.9	Unspecified bacterial pneumonia	DX	10
J16.0	Chlamydial pneumonia	DX	10
J16.8	Pneumonia due to other specified infectious organisms	DX	10
J17	Pneumonia in diseases classified elsewhere	DX	10
J18.0	Bronchopneumonia, unspecified organism	DX	10
J18.1	Lobar pneumonia, unspecified organism	DX	10
J18.2	Hypostatic pneumonia, unspecified organism	DX	10
J18.8	Other pneumonia, unspecified organism	DX	10
J18.9	Pneumonia, unspecified organism	DX	10
J41.0	Simple chronic bronchitis	DX	10
J41.1	Mucopurulent chronic bronchitis	DX	10
J41.8	Mixed simple and mucopurulent chronic bronchitis	DX	10
J42	Unspecified chronic bronchitis	DX	10
J44.9	Chronic obstructive pulmonary disease, unspecified	DX	10
J45.21	Mild intermittent asthma with (acute) exacerbation	DX	10

Code	Description	Code Category	Code Type
J45.31	Mild persistent asthma with (acute) exacerbation	DX	10
J45.41	Moderate persistent asthma with (acute) exacerbation	DX	10
J45.51	Severe persistent asthma with (acute) exacerbation	DX	10
J45.901	Unspecified asthma with (acute) exacerbation	DX	10
J47.9	Bronchiectasis, uncomplicated	DX	10
J68.0	Bronchitis and pneumonitis due to chemicals, gases, fumes and vapors	DX	10
J68.1	Pulmonary edema due to chemicals, gases, fumes and vapors	DX	10
J68.2	Upper respiratory inflammation due to chemicals, gases, fumes and vapors, not elsewhere classified	DX	10
J68.3	Other acute and subacute respiratory conditions due to chemicals, gases, fumes and vapors	DX	10
J68.4	Chronic respiratory conditions due to chemicals, gases, fumes and vapors	DX	10
J68.8	Other respiratory conditions due to chemicals, gases, fumes and vapors	DX	10
J68.9	Unspecified respiratory condition due to chemicals, gases, fumes and vapors	DX	10
J69.0	Pneumonitis due to inhalation of food and vomit	DX	10
J69.1	Pneumonitis due to inhalation of oils and essences	DX	10
J69.8	Pneumonitis due to inhalation of other solids and liquids	DX	10
J81.0	Acute pulmonary edema	DX	10
J81.1	Chronic pulmonary edema	DX	10
J82	Pulmonary eosinophilia, not elsewhere classified	DX	10
J86.9	Pyothorax without fistula	DX	10
J90	Pleural effusion, not elsewhere classified	DX	10
J91.0	Malignant pleural effusion	DX	10
J91.8	Pleural effusion in other conditions classified elsewhere	DX	10
J93.0	Spontaneous tension pneumothorax	DX	10
J93.11	Primary spontaneous pneumothorax	DX	10
J93.12	Secondary spontaneous pneumothorax	DX	10
J93.81	Chronic pneumothorax	DX	10
J93.82	Other air leak	DX	10
J93.83	Other pneumothorax	DX	10
J93.9	Pneumothorax, unspecified	DX	10
J94.1	Fibrothorax	DX	10
J94.2	Hemothorax	DX	10
J94.8	Other specified plural conditions	DX	10
J94.9	Pleural condition, unspecified	DX	10
J95.1	Acute pulmonary insufficiency following thoracic surgery	DX	10
J95.2	Acute pulmonary insufficiency following nonthoracic surgery	DX	10
J95.3	Chronic pulmonary insufficiency following surgery	DX	10
J95.811	Postprocedural pneumothorax	DX	10
J95.812	Postprocedural air leak	DX	10
J95.821	Acute postprocedural respiratory failure	DX	10
J95.822	Acute and chronic postprocedural respiratory failure	DX	10
J95.84	Transfusion-related acute lung injury (TRALI)	DX	10
J96.10	Chronic respiratory failure unspecified whether hypoxia or hypercapnia	DX	10
J96.11	Chronic respiratory failure with hypoxia	DX	10
J96.12	Chronic respiratory failure with hypercapnia	DX	10

Code	Description	Code Category	Code Type
J96.20	Acute and chronic respiratory failure, unspecified whether with hypoxia or hypercapnia	DX	10
J96.21	Acute and chronic respiratory failure, with hypoxia	DX	10
J96.22	Acute and chronic respiratory failure, with hypercapnia	DX	10
J96.90	Respiratory failure, unspecified, unspecified whether with hypoxia or hypercapnia	DX	10
J96.91	Respiratory failure, unspecified, with hypoxia	DX	10
J96.92	Respiratory failure, unspecified, with hypercapnia	DX	10
J98.11	Atelectasis	DX	10
J98.19	Other pulmonary collapse	DX	10
J98.2	Interstitial emphysema	DX	10
J98.3	Compensatory emphysema	DX	10
J98.4	Other disorders of lung	DX	10
P28.5	Respiratory failure of newborn	DX	10
R09.1	Pleurisy	DX	10

Abbreviation: DX, ICD-CM diagnosis.

Appendix E. Procedure and Prescription Codes Relevant to COPD

Users seeking to specify the COPD cohort algorithm further may wish to apply additional criteria to diagnosis codes received in the outpatient setting, as follows:

(≥1 inpatient diagnosis code for COPD OR ≥1 outpatient diagnosis code) AND ≥1 of

- ≥1 additional outpatient diagnosis code (i.e., 2 outpatient diagnosis codes required) OR
- ≥1 procedural code (CPT codes listed in **Table E1**) OR
- ≥1 medication/therapy code (NDC/HCPCS codes listed in **Tables E2** and **E3**)

Based upon observations from the literature and clinical consultation, spirometry and chest x-ray codes were used to define COPD procedures. Prescription codes included albuterol, levalbuterol, ipratropium, budesonide, racemic epinephrine, acetylcysteine, arformoterol and formoterol.

Table E1. Procedural codes relevant to COPD cohort.

Code	Description	Code Category	Code Edition
71010	Radiologic examination, chest; single view, frontal	CPT	4
71015	Radiologic examination, chest; single view, stereo, frontal	CPT	4
71020	Radiologic examination, chest, 2 views, frontal and lateral	CPT	4
71021	Radiologic examination, chest, 2 views, frontal and lateral, with apical lordotic procedure	CPT	4
71022	Radiologic examination, chest, 2 views, frontal and lateral, with oblique projections	CPT	4
71023	Radiologic examination, chest, 2 views, frontal and lateral, with fluoroscopy	CPT	4
71030	Radiologic examination, chest, complete, minimum of 4 views	CPT	4
71034	Radiologic examination, chest, complete, minimum of 4 views, with fluoroscopy	CPT	4
71035	Radiologic examination, chest, special views (e.g., lateral decubitus, Bucky studies).	CPT	4
71045	Radiologic examination, chest; single view	CPT	4
71046	Radiologic examination, chest; 2 views	CPT	4
71047	Radiologic examination, chest; 3 views	CPT	4
71048	Radiologic examination, chest; 4 or more views	CPT	4
94010	Breathing capacity test	CPT	4
94011	Spirometry up to 2 years old	CPT	4
94012	Spirometry w/bronchodilation infants-2 years	CPT	4
94060	Evaluation of wheezing	CPT	4
94070	Evaluation of wheezing	CPT	4
94200	Lung function test	CPT	4
94375	Respiratory flow volume loop	CPT	4
94640	Pressurized or non-pressurized inhalation treatment for acute airway obstruction for therapeutic purposes and/or for diagnostic purposes such as sputum induction with an aerosol generator, nebulizer, metered dose inhaler or intermittent positive pressure breathing device.	CPT	4
94726	Pulmonary function test plethysmograph	CPT	4
94727	Pulmonary function test by gas	CPT	4

Abbreviations: CPT; Current Procedural Terminology

* CPT codes were drawn from https://www.aapc.com/codes/cpt-codes, last updated August 15, 2020. These codes may not include all relevant codes and may be or become outdated. Users should review the most current datasets available prior to use of the algorithm.

Table E2. Procedure codes for treatment relevant to COPD cohort.

Code	Description	Code Category
E0424	Stationary Compressed Gaseous Oxygen System, Rental; Includes Container, Contents, Regulator, Flowmeter, Humidifier, Nebulizer, Cannula or Mask, and Tubing	HCPCS
E0441	Stationary Oxygen Contents, Gaseous, 1 Month's Supply = 1 Unit	HCPCS
E0443	Portable Oxygen Contents, Gaseous, 1 Month's Supply = 1 Unit	HCPCS
E0570	Nebulizer with compression	HCPCS
J0132	Acetylcysteine injection	HCPCS
J7604	Acetylcysteine, inhalation solution, compounded product, administered through durable medical equipment (dme), unit dose form, per gram	HCPCS
J7605	Arformoterol, inhalation solution, FDA approved final product, non-compounded, administered through dme, unit dose form, 15 micrograms	HCPCS
J7606	Formoterol fumarate, inhalation solution, FDA approved final product, non-compounded, administered through dme, unit dose form, 20 micrograms	HCPCS
J7607	Levalbuterol, inhalation solution, compounded product, administered through dme, concentrated form, 0.5 mg	HCPCS
J7608	Acetylcysteine, inhalation solution, FDA-approved final product, non-compounded, administered through dme, unit dose form, per gram	HCPCS
J7609	Albuterol, inhalation solution, compounded product, administered through dme, unit dose, 1 mg	HCPCS
J7610	Albuterol, inhalation solution, compounded product, administered through dme, concentrated form, 1 mg	HCPCS
J7611	Albuterol, inhalation solution, FDA-approved final product, non-compounded, administered through dme, concentrated form, 1 mg	HCPCS
J7612	Levalbuterol, inhalation solution, FDA-approved final product, non-compounded, administered through dme, concentrated form, 0.5 mg	HCPCS
J7613	Albuterol, inhalation solution	HCPCS
J7614	Levalbuterol, inhalation solution, FDA-approved final product, non-compounded, administered through dme, unit dose, 0.5 mg	HCPCS
J7615	Levalbuterol, inhalation solution, compounded product, administered through dme, unit dose, 0.5 mg	HCPCS
J7620	Albuterol, up to 2.5 mg and ipratropium bromide, up to 0.5 mg, FDA-approved final product, non-compounded, administered through dme	HCPCS
J7626	Budesonide, inhalation solution, FDA-approved final product, non-compounded, administered through dme, unit dose form, up to 0.5 mg	HCPCS
J7627	Budesonide, inhalation solution, compounded product, administered through dme, unit dose form, up to 0.5 mg	HCPCS
J7633	Budesonide, inhalation solution, FDA-approved final product, non-compounded, administered through dme, concentrated form, per 0.25 milligram	HCPCS
J7634	Budesonide, inhalation solution, compounded product, administered through dme, concentrated form, per 0.25 milligram	HCPCS
J7640	Formoterol, inhalation solution, compounded product, administered through dme, unit dose form, 12 micrograms	HCPCS
J7644	Ipratropium bromide, inhalation solution, FDA-approved final product, non-compounded, administered through dme, unit dose form, per milligram	HCPCS
J7645	Ipratropium bromide, inhalation solution, compounded product, administered through dme, unit dose form, per milligram	HCPCS

Abbreviations: HCPCS, Healthcare Common Procedure Coding System,
* HCPCS codes were drawn from https://www.hcpcsdata.com/, last updated August 15, 2020. These codes may not include all relevant codes and may be or become outdated. Users should review the most current datasets available prior to use of the algorithm.

Table E3. Prescription codes for treatment relevant to COPD cohort.

Code	Description	Code Category
0054-0045-44	Ipratropium Bromide	NDC
0054-0046-41	Ipratropium Bromide	NDC
0085-1132-04	Albuterol Sulfate	NDC
0085-2223-01	Mometasone furoate and formoterol fumarate dihydrate	NDC
0085-2223-02	Mometasone furoate and formoterol fumarate dihydrate	NDC
0085-4610-01	Mometasone furoate and formoterol fumarate dihydrate	NDC
0085-4610-02	Mometasone furoate and formoterol fumarate dihydrate	NDC
0085-4610-05	Mometasone furoate and formoterol fumarate dihydrate	NDC
0085-4610-06	Mometasone furoate and formoterol fumarate dihydrate	NDC
0085-7206-01	Mometasone furoate and formoterol fumarate dihydrate	NDC
0085-7206-02	Mometasone furoate and formoterol fumarate dihydrate	NDC
0085-7206-07	Mometasone furoate and formoterol fumarate dihydrate	NDC
0085-7206-08	Mometasone furoate and formoterol fumarate dihydrate	NDC
0093-3174-31	Albuterol Sulfate	NDC
0093-4145-56	Levalbuterol	NDC
0093-4146-56	Levalbuterol	NDC
0093-4147-56	Levalbuterol	NDC
0093-4148-56	Levalbuterol	NDC
0093-6815-55	Budesonide	NDC
0093-6815-73	Budesonide	NDC
0093-6815-76	Budesonide	NDC
0093-6816-55	Budesonide	NDC
0093-6816-73	Budesonide	NDC
0093-6816-76	Budesonide	NDC
0093-6817-73	Budesonide	NDC
0093-7445-01	Budesonide	NDC
0115-1687-74	Budesonide	NDC
0115-1689-74	Budesonide	NDC
0115-9930-78	Levalbuterol Hydrochloride	NDC
0115-9931-78	Levalbuterol Hydrochloride	NDC
0115-9932-78	Levalbuterol Hydrochloride	NDC
0173-0682-20	Albuterol sulfate	NDC
0173-0682-24	Albuterol sulfate	NDC
0186-0370-20	Budesonide and Formoterol Fumarate Dihydrate	NDC
0186-0370-28	Budesonide and Formoterol Fumarate Dihydrate	NDC
0186-0370-60	Budesonide and Formoterol Fumarate Dihydrate	NDC
0186-0372-20	Budesonide and Formoterol Fumarate Dihydrate	NDC
0186-0372-28	Budesonide and Formoterol Fumarate Dihydrate	NDC
0186-0372-60	Budesonide and Formoterol Fumarate Dihydrate	NDC
0186-0916-12	Budesonide	NDC
0186-0917-06	Budesonide	NDC
0186-0917-65	Budesonide	NDC
0186-1988-04	Budesonide	NDC
0186-1989-04	Budesonide	NDC
0186-1990-04	Budesonide	NDC
0254-1007-52	Albuterol Sulfate	NDC
0310-4600-12	Glycopyrrolate and formoterol fumarate	NDC
0310-4600-28	Glycopyrrolate and formoterol fumarate	NDC
0310-4600-39	Glycopyrrolate and formoterol fumarate	NDC

Code	Description	Code Category
0310-7370-20	Budesonide and Formoterol Fumarate Dihydrate	NDC
0310-7372-20	Budesonide and Formoterol Fumarate Dihydrate	NDC
0363-0048-01	Budesonide	NDC
0378-0255-01	Albuterol sulfate	NDC
0378-0572-01	Albuterol sulfate	NDC
0378-4122-01	Albuterol sulfate	NDC
0378-4124-01	Albuterol sulfate	NDC
0378-6991-52	Albuterol sulfate	NDC
0378-6992-52	Albuterol sulfate	NDC
0378-6993-93	Levalbuterol	NDC
0378-7155-01	Budesonide	NDC
0378-7970-52	Ipratropium Bromide	NDC
0378-7970-55	Ipratropium Bromide	NDC
0378-7970-91	Ipratropium Bromide	NDC
0378-7970-93	Ipratropium Bromide	NDC
0378-8270-52	Albuterol Sulfate	NDC
0378-8270-55	Albuterol Sulfate	NDC
0378-8270-91	Albuterol Sulfate	NDC
0378-8270-93	Albuterol Sulfate	NDC
0378-9671-30	Ipratropium Bromide and Albuterol Sulfate	NDC
0378-9671-60	Ipratropium Bromide and Albuterol Sulfate	NDC
0378-9671-93	Ipratropium Bromide and Albuterol Sulfate	NDC
0378-9690-52	Levalbuterol	NDC
0378-9691-52	Levalbuterol	NDC
0378-9692-52	Levalbuterol	NDC
0409-3307-03	Acetylcysteine	NDC
0409-3308-03	Acetylcysteine	NDC
0472-0825-04	Albuterol Sulfate	NDC
0472-0825-16	Albuterol Sulfate	NDC
0487-0201-01	Ipratropium Bromide and Albuterol Sulfate	NDC
0487-0201-02	Ipratropium Bromide and Albuterol Sulfate	NDC
0487-0201-03	Ipratropium Bromide and Albuterol Sulfate	NDC
0487-0201-60	Ipratropium Bromide and Albuterol Sulfate	NDC
0487-0301-01	Albuterol Sulfate	NDC
0487-0301-02	Albuterol Sulfate	NDC
0487-2784-01	Racepinephrine hydrochloride	NDC
0487-5901-99	Racepinephrine hydrochloride	NDC
0487-9501-01	Albuterol Sulfate	NDC
0487-9501-03	Albuterol Sulfate	NDC
0487-9501-25	Albuterol Sulfate	NDC
0487-9501-60	Albuterol Sulfate	NDC
0487-9601-01	Budesonide	NDC
0487-9601-30	Budesonide	NDC
0487-9701-01	Budesonide	NDC
0487-9701-30	Budesonide	NDC
0487-9801-01	Ipratropium Bromide	NDC
0487-9801-02	Ipratropium Bromide	NDC
0487-9801-25	Ipratropium Bromide	NDC
0487-9801-30	Ipratropium Bromide	NDC
0487-9801-60	Ipratropium Bromide	NDC
0487-9901-02	Albuterol Sulfate	NDC
0487-9901-30	Albuterol Sulfate	NDC

Code	Description	Code Category
0487-9904-01	Albuterol Sulfate	NDC
0487-9904-02	Albuterol Sulfate	NDC
0487-9904-25	Albuterol Sulfate	NDC
0517-7504-25	Acetylcysteine	NDC
0517-7510-03	Acetylcysteine	NDC
0517-7604-25	Acetylcysteine	NDC
0517-7610-03	Acetylcysteine	NDC
0517-7630-03	Acetylcysteine	NDC
0536-1112-40	Budesonide	NDC
0536-1112-48	Budesonide	NDC
0574-0805-30	Acetylcysteine	NDC
0574-0815-30	Acetylcysteine	NDC
0574-9850-10	Budesonide	NDC
0574-9855-10	Budesonide	NDC
0591-2510-30	Budesonide	NDC
0591-2927-54	Levalbuterol tartrate	NDC
0591-3467-53	Albuterol Sulfate	NDC
0591-3468-53	Albuterol Sulfate	NDC
0591-3797-30	Albuterol Sulfate	NDC
0591-3797-60	Albuterol Sulfate	NDC
0591-3797-83	Albuterol Sulfate	NDC
0591-3798-30	Ipratropium Bromide	NDC
0591-3798-60	Ipratropium Bromide	NDC
0591-3798-83	Ipratropium Bromide	NDC
0591-3817-39	Ipratropium bromide and albuterol sulfate	NDC
0597-0024-02	Ipratropium bromide and albuterol	NDC
0597-0087-17	Ipratropium bromide	NDC
0781-7515-87	Budesonide	NDC
0781-7516-87	Budesonide	NDC
0781-7517-87	Budesonide	NDC
11822-1700-1	Budesonide	NDC
11822-6000-6	Budesonide	NDC
16714-094-25	Levalbuterol Inhalation Solution	NDC
16714-094-30	Levalbuterol Inhalation Solution	NDC
16714-095-25	Levalbuterol Inhalation Solution	NDC
16714-096-25	Levalbuterol Inhalation Solution	NDC
16714-829-01	Budesonide	NDC
17478-171-30	Levalbuterol Hydrochloride	NDC
17478-172-24	Levalbuterol Hydrochloride	NDC
17478-173-24	Levalbuterol Hydrochloride	NDC
17478-174-24	Levalbuterol Hydrochloride	NDC
17478-660-30	Acetylcysteine	NDC
17856-0740-3	Albuterol Sulfate	NDC
21130-710-06	Budesonide	NDC
24208-398-30	Ipratropium bromide	NDC
24208-399-15	Ipratropium Bromide	NDC
25021-812-30	Acetylcysteine	NDC
35356-166-02	Albuterol sulfate	NDC
36800-113-01	Budesonide	NDC
43598-409-25	Levalbuterol inhalation 1.25mg/3mL	NDC
43598-410-25	Levalbuterol inhalation 0.63mg/3mL	NDC
43598-412-25	Levalbuterol inhalation 0.31mg/3mL	NDC

Code	Description	Code Category
45802-088-01	Albuterol sulfate	NDC
46122-389-76	Budesonide	NDC
47335-706-49	Ipratropium Bromide	NDC
47335-706-52	Ipratropium Bromide	NDC
47335-706-54	Ipratropium Bromide	NDC
47335-743-01	Levalbuterol Inhalation Solution	NDC
47335-743-49	Levalbuterol Inhalation Solution	NDC
47335-743-52	Levalbuterol Inhalation Solution	NDC
47335-746-01	Levalbuterol Inhalation Solution	NDC
47335-746-49	Levalbuterol Inhalation Solution	NDC
47335-746-52	Levalbuterol Inhalation Solution	NDC
47335-753-01	Levalbuterol Inhalation Solution	NDC
47335-753-49	Levalbuterol Inhalation Solution	NDC
47335-753-52	Levalbuterol Inhalation Solution	NDC
49035-703-01	Budesonide	NDC
49502-605-05	Formoterol fumarate dihydrate	NDC
49502-605-30	Formoterol fumarate dihydrate	NDC
49502-605-61	Formoterol fumarate dihydrate	NDC
50090-0516-0	Albuterol Sulfate	NDC
50090-0961-0	Ipratropium bromide	NDC
50090-1329-0	Albuterol Sulfate	NDC
50090-1669-0	Ipratropium Bromide and Albuterol Sulfate	NDC
50090-2566-0	Ipratropium Bromide	NDC
50090-4137-0	Albuterol sulfate	NDC
50090-4185-0	Ipratropium Bromide	NDC
50090-4326-0	Albuterol Sulfate	NDC
50090-4326-1	Albuterol Sulfate	NDC
50090-4491-0	Albuterol Sulfate	NDC
50090-4977-0	Albuterol sulfate	NDC
50383-740-16	Albuterol Sulfate	NDC
50383-741-20	Albuterol Sulfate	NDC
50580-646-01	Budesonide	NDC
50580-646-02	Budesonide	NDC
50580-646-03	Budesonide	NDC
51079-020-03	Budesonide	NDC
51079-657-20	Albuterol	NDC
51407-224-30	Budesonide	NDC
51407-367-01	Albuterol sulfate	NDC
51407-368-01	Albuterol sulfate	NDC
51662-1202-1	Albuterol sulfate	NDC
51662-1202-9	Albuterol sulfate	NDC
51662-1267-1	Albuterol sulfate	NDC
51662-1267-9	Albuterol sulfate	NDC
51662-1499-1	Albuterol sulfate	NDC
51862-580-01	Budesonide	NDC
51862-582-01	Budesonide	NDC
53489-176-01	Albuterol sulfate	NDC
53489-176-02	Albuterol sulfate	NDC
53489-176-03	Albuterol sulfate	NDC
53489-176-05	Albuterol sulfate	NDC
53489-176-10	Albuterol sulfate	NDC
53489-177-01	Albuterol sulfate	NDC

Code	Description	Code Category
53489-177-02	Albuterol sulfate	NDC
53489-177-03	Albuterol sulfate	NDC
53489-177-05	Albuterol sulfate	NDC
53489-177-10	Albuterol sulfate	NDC
55150-259-30	Acetylcysteine	NDC
55154-4350-5	Albuterol Sulfate	NDC
55154-4351-5	Ipratropium Bromide	NDC
55154-4357-5	Ipratropium Bromide and Albuterol Sulfate	NDC
55154-4359-5	Albuterol Sulfate	NDC
55154-4849-5	Budesonide	NDC
55154-5730-5	Acetylcysteine	NDC
55154-5731-5	Acetylcysteine	NDC
55289-045-30	Albuterol sulfate	NDC
55566-1002-1	Budesonide	NDC
55566-1020-1	Budesonide	NDC
59310-117-20	Albuterol sulfate	NDC
59310-117-21	Albuterol sulfate	NDC
59310-540-20	Albuterol Sulfate	NDC
59310-540-21	Albuterol Sulfate	NDC
59310-579-22	Albuterol Sulfate	NDC
59310-580-20	Albuterol Sulfate	NDC
59310-580-21	Albuterol Sulfate	NDC
59651-183-25	Albuterol Sulfate	NDC
59651-184-25	Albuterol Sulfate	NDC
59651-333-01	Albuterol	NDC
59651-333-05	Albuterol	NDC
59651-334-01	Albuterol	NDC
59651-334-05	Albuterol	NDC
60429-264-01	Budesonide	NDC
60429-975-30	Ipratropium Bromide and Albuterol Sulfate	NDC
60429-975-60	Ipratropium Bromide and Albuterol Sulfate	NDC
60505-0820-0	Budesonide	NDC
60505-0821-0	Budesonide	NDC
60505-0826-1	Ipratropium Bromide	NDC
60505-0827-1	Ipratropium bromide	NDC
60505-0839-2	Budesonide	NDC
60505-6129-2	Budesonide	NDC
60505-6129-6	Budesonide	NDC
60505-6129-7	Budesonide	NDC
60505-6194-3	Budesonide	NDC
60687-394-83	Ipratropium Bromide	NDC
60687-395-83	Albuterol Sulfate	NDC
60687-405-83	Ipratropium Bromide and Albuterol Sulfate	NDC
60687-524-83	Budesonide Inhalation	NDC
63187-026-08	Albuterol sulfate	NDC
63187-026-18	Albuterol sulfate	NDC
63187-188-25	Ipratropium Bromide	NDC
63187-204-25	Albuterol Sulfate	NDC
63187-529-30	Ipratropium bromide and albuterol sulfate	NDC
63187-529-60	Ipratropium bromide and albuterol sulfate	NDC
63187-540-85	Albuterol sulfate	NDC
63187-876-15	Levalbuterol tartrate	NDC

Code	Description	Code Category
63187-953-24	Levalbuterol	NDC
63323-690-30	Acetylcysteine	NDC
63323-690-44	Acetylcysteine	NDC
63323-691-30	Acetylcysteine	NDC
63323-692-10	Acetylcysteine	NDC
63323-693-10	Acetylcysteine	NDC
63323-694-04	Acetylcysteine	NDC
63323-694-44	Acetylcysteine	NDC
63323-695-04	Acetylcysteine	NDC
63323-963-30	Acetylcysteine	NDC
63323-963-44	Acetylcysteine	NDC
63402-510-01	Levalbuterol tartrate	NDC
63402-911-08	Arformoterol tartrate	NDC
63402-911-30	Arformoterol tartrate	NDC
63402-911-31	Arformoterol tartrate	NDC
63402-911-64	Arformoterol tartrate	NDC
64980-255-01	Budesonide	NDC
64980-442-01	Albuterol	NDC
64980-442-50	Albuterol	NDC
64980-443-01	Albuterol	NDC
64980-443-50	Albuterol	NDC
65162-778-10	Budesonide	NDC
65162-778-18	Budesonide	NDC
65162-778-30	Budesonide	NDC
65162-778-49	Budesonide	NDC
65649-651-03	Budesonide	NDC
65862-858-03	Albuterol sulfate	NDC
65862-858-25	Albuterol sulfate	NDC
65862-858-30	Albuterol sulfate	NDC
65862-858-60	Albuterol sulfate	NDC
65862-905-03	Ipratropium bromide	NDC
65862-905-25	Ipratropium bromide	NDC
65862-905-30	Ipratropium bromide	NDC
65862-905-60	Ipratropium bromide	NDC
65862-906-03	Ipratropium Bromide and Albuterol Sulfate	NDC
65862-906-30	Ipratropium Bromide and Albuterol Sulfate	NDC
65862-906-60	Ipratropium Bromide and Albuterol Sulfate	NDC
65862-942-03	Levalbuterol	NDC
65862-943-24	Levalbuterol	NDC
65862-944-24	Levalbuterol	NDC
65862-945-24	Levalbuterol	NDC
66220-207-30	Acetylcysteine	NDC
66267-746-06	Albuterol Sulfate	NDC
66689-100-08	Albuterol	NDC
66993-019-68	Albuterol sulfate	NDC
66993-021-27	Levalbuterol Hydrochloride	NDC
66993-022-27	Levalbuterol Hydrochloride	NDC
66993-023-27	Levalbuterol Hydrochloride	NDC
67296-1348-1	Albuterol Sulfate	NDC
68012-309-01	Budesonide	NDC
68012-309-02	Budesonide	NDC
68012-309-30	Budesonide	NDC

Code	Description	Code Category
68071-1525-5	Albuterol Sulfate	NDC
68071-1670-2	Albuterol sulfate	NDC
68071-1737-2	Ipratropium Bromide	NDC
68071-1890-6	Albuterol sulfate	NDC
68071-4048-2	Albuterol Sulfate	NDC
68071-4543-6	Albuterol Sulfate	NDC
68071-4754-2	Albuterol Sulfate	NDC
68071-4777-2	albuterol sulfate	NDC
68071-4940-2	Albuterol Sulfate	NDC
68071-5027-5	Levalbuterol Hydrochloride	NDC
68071-5149-3	Racepinephrine hydrochloride	NDC
68071-5206-2	Albuterol sulfate	NDC
68084-949-25	Albuterol sulfate	NDC
68084-952-25	Albuterol sulfate	NDC
68180-984-30	Budesonide inhalation	NDC
68382-720-01	Budesonide	NDC
68382-720-05	Budesonide	NDC
68382-720-06	Budesonide	NDC
68382-720-10	Budesonide	NDC
68382-720-16	Budesonide	NDC
68382-720-77	Budesonide	NDC
68682-309-30	Budesonide	NDC
68788-0825-4	Albuterol Sulfate	NDC
68788-6845-1	Levalbuterol tartrate	NDC
68788-7229-6	Albuterol sulfate	NDC
68788-7290-3	Budesonide	NDC
68788-7314-3	Budesonide	NDC
68788-7353-2	Albuterol sulfate	NDC
68788-7390-4	Albuterol Sulfate	NDC
68788-7477-2	Albuterol Sulfate	NDC
68788-7573-4	Albuterol Sulfate	NDC
68788-7678-3	Ipratropium Bromide and Albuterol Sulfate	NDC
68788-7702-2	Albuterol Sulfate	NDC
68788-9279-3	ipratropium bromide and albuterol sulfate	NDC
68788-9298-2	Albuterol Sulfate	NDC
68788-9552-2	Albuterol Sulfate	NDC
68788-9552-6	Albuterol Sulfate	NDC
68788-9900-2	Albuterol Sulfate	NDC
69097-142-60	Albuterol Sulfate	NDC
69097-173-53	Ipratropium Bromide and Albuterol Sulfate	NDC
69097-173-64	Ipratropium Bromide and Albuterol Sulfate	NDC
69097-318-87	Budesonide	NDC
69097-319-53	Budesonide	NDC
69097-319-87	Budesonide	NDC
69097-321-53	Budesonide	NDC
69097-321-87	Budesonide	NDC
69097-840-53	Ipratropium Bromide and Albuterol Sulfate	NDC
69238-1344-5	Albuterol	NDC
69238-1345-5	Albuterol	NDC
69339-126-01	Albuterol Sulfate	NDC
69339-127-01	Albuterol Sulfate	NDC
69543-290-10	Albuterol	NDC

Code	Description	Code Category
69543-290-18	Albuterol	NDC
69543-291-10	Albuterol	NDC
69543-291-18	Albuterol	NDC
69842-001-01	Budesonide	NDC
70518-1070-0	Ipratropium Bromide	NDC
70518-1230-0	Albuterol Sulfate	NDC
70518-1237-0	Albuterol Sulfate	NDC
70518-1722-0	Ipratropium bromide and albuterol sulfate	NDC
70518-2243-0	Ipratropium Bromide and Albuterol Sulfate	NDC
70518-2250-0	Ipratropium Bromide and Albuterol Sulfate	NDC
70518-2351-0	Ipratropium Bromide and Albuterol Sulfate	NDC
70518-2413-0	Albuterol Sulfate	NDC
70518-2613-0	Albuterol Sulfate	NDC
70518-2627-0	Ipratropium Bromide and Albuterol Sulfate	NDC
70710-1015-8	Acetylcysteine	NDC
70752-102-12	Albuterol Sulfate	NDC
70771-1075-0	Budesonide	NDC
70771-1075-1	Budesonide	NDC
70771-1075-3	Budesonide	NDC
70771-1075-4	Budesonide	NDC
70771-1075-5	Budesonide	NDC
70771-1075-9	Budesonide	NDC
70771-1412-8	Acetylcysteine	NDC
71205-051-15	Ipratropium Bromide and Albuterol Sulfate	NDC
71205-051-30	Ipratropium Bromide and Albuterol Sulfate	NDC
71205-211-85	Albuterol Sulfate	NDC
71205-441-85	Albuterol sulfate	NDC
71872-7054-1	Albuterol Sulfate	NDC
72124-001-01	Aclidinium bromide and formoterol fumarate	NDC
72124-001-03	Aclidinium bromide and formoterol fumarate	NDC
72189-002-25	Albuterol Sulfate	NDC
72189-016-08	Albuterol Sulfate	NDC
72189-022-25	Albuterol Sulfate	NDC
76204-100-01	Ipratropium Bromide	NDC
76204-100-25	Ipratropium Bromide	NDC
76204-100-30	Ipratropium Bromide	NDC
76204-100-60	Ipratropium Bromide	NDC
76204-200-01	Albuterol Sulfate	NDC
76204-200-25	Albuterol Sulfate	NDC
76204-200-30	Albuterol Sulfate	NDC
76204-200-60	Albuterol Sulfate	NDC
76204-600-01	Ipratropium Bromide and Albuterol Sulfate	NDC
76204-600-05	Ipratropium Bromide and Albuterol Sulfate	NDC
76204-600-12	Ipratropium Bromide and Albuterol Sulfate	NDC
76204-600-30	Ipratropium Bromide and Albuterol Sulfate	NDC
76204-600-60	Ipratropium Bromide and Albuterol Sulfate	NDC
76204-700-01	Levalbuterol Hydrochloride	NDC
76204-700-25	Levalbuterol Hydrochloride	NDC
76204-700-55	Levalbuterol Hydrochloride	NDC
76204-800-01	Levalbuterol Hydrochloride	NDC
76204-800-25	Levalbuterol Hydrochloride	NDC
76204-800-55	Levalbuterol Hydrochloride	NDC

Code	Description	Code Category
76204-900-01	Levalbuterol Hydrochloride	NDC
76204-900-25	Levalbuterol Hydrochloride	NDC
76204-900-55	Levalbuterol Hydrochloride	NDC
76282-640-38	Budesonide	NDC
76282-641-38	Budesonide	NDC
76282-642-38	Budesonide	NDC
76519-1171-0	Albuterol Sulfate	NDC
76519-1175-0	Albuterol Sulfate	NDC

Abbreviations: dme, durable medical equipment; NDC, National Drug Code
* NDC codes were drawn from the FDA NDC Database (https://www.fda.gov/drugs/drug-approvals-and-databases/national-drug-code-directory), last updated August 15, 2020. These codes may not include all relevant codes and may be or become outdated. Users should review the most current datasets available prior to use of the algorithm.