

# Annotation guidelines for the COPD corpus

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# 1 Introduction

The annotation task involves *entity annotation*. Entities are text spans that denote concepts of interest; the task consists of identifying and marking up entities, and assigning semantic labels to them, corresponding to entity categories.

In the following sections, for each entity category, we describe both the scope (i.e., the range of entities within each category that should be considered for annotation) and the span (i.e., the exact extent of text that should be marked up to represent entities with the category). Wherever possible, these descriptions are made as precise as possible, presenting illustrative examples of what should be *included* and *excluded* from the annotation scopes and spans.

In the examples provided, information that should be included within annotated text spans is shown inside square brackets, e.g., **[tyrosine]**. Emboldened spans correspond to the entities in focus in the specific examples; other entities of the same type in the same sentence that are related to the focussed examples may also be shown enclosed in square brackets, but are not emboldened.

Information that should be excluded from the annotated spans is crossed through, e.g., ~~[antimicrobial compounds]~~.

Particular words or phrases within a text span that should be annotated, and which help to illustrate a particular guideline or point, may be underlined.

## 2 General Guidelines

### 2.1 Annotation scope

✓Include:

- All mentions of entities belonging to the categories defined in the sections below. Even if the same entity is mentioned multiple times in a document, each individual mention should be annotated.

[Smoking] seems to increase the incidence of [TB] and prevalence of [COPD] is high where [smoking] is highly prevalent

- Instances of abbreviations/acronyms as well as full forms of entities. Where an abbreviation/acronym follows a full form, both the acronym and full form should be annotated as separate entities.

[Chronic obstructive pulmonary disease] ([COPD]), a common, costly and preventable disease and is the fourth leading cause of death globally

The [oxygen therapy] was guided by the [ABG] report and [oxygen saturation] ([SaO<sub>2</sub>]) measured using a [pulse oximeter].

- Members of an entity class may vary from being general to specific. Where a sentence includes both a general member of the class and one or more

enumerated specific instances, **both** the general class (underlined in the example below) and the more specific classes should be annotated.

**[Tiotropium]** is a longer acting **[anticholinergic agent]** that is approximately 10-fold more potent than **[ipratropium bromide]**.

- Longer entities many include other shorter entities that are embedded or “nested” within them; the longer and shorter entities may or may not belong to different semantic categories. Both the longer, enclosing entities AND the embedded entities should **ALWAYS** be annotated, as long as they belong to one of the semantic categories introduced in the sections below, and they fall within the specified annotation scope.

In the example below, there are two text spans corresponding to the *Medical Condition* category, i.e., *lung cancer* and *mild COPD*. However, each of these has an embedded concept that should also be annotated, i.e., the word *lung* within *lung cancer* corresponds to an anatomical entity, while *mild* within *mild COPD* describes a quality of the medical condition.

Similarly, the risk of **[lung] cancer** is increased in **[mild] COPD**.

## 2.2 Annotation span

✓Include:

- Only include words that form an integral part of the entity name within the annotation span.
- Entities on either side of a slash (e.g., as alternatives/variations of a entity) should be annotated as two separate entities.

Increased exposure may cause or worsen didanosine-related clinical toxicities, including pancreatitis, **[symptomatic hyperlactatemia]/[lactic acidosis]**, and peripheral neuropathy

✗Exclude:

- Definite or indefinite articles (e.g. *a*, *the*) that may occur at the beginning of phrases

Thus, [bupropion] should be avoided in patients with **[a-seizure disorder]** (Schroeder 2005).

Major limitations in **[the EBC]** include the plethora of potential markers that cannot be reliably or easily analyzed in these highly diluted samples

- Coordinating conjunctions, such as *and* or *or*. Each entity mentioned within a coordinated phrase should usually be annotated separately.

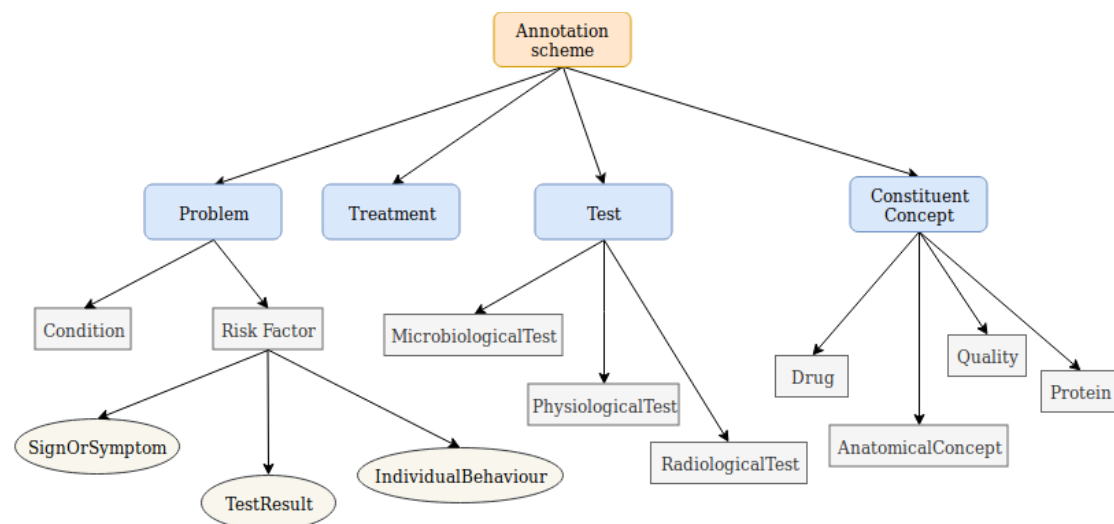
The **[[chronic] inflammation]** evokes an associated increase in airway hyperresponsiveness that leads to recurrent episodes of **[wheezing]**, **[breathlessness]**, **[[chest] tightness]**, and **[coughing]**, particularly at night or in the early morning.

### 3 Category-specific guidelines

In this section, we provide definitions and guidelines for each different entity category.

NOTE: The categories are organised as a hierarchy. When considering which category to assign to an entity, it is always the case that the MOST SPECIFIC category possible should be assigned.

The overall structure of the hierarchy is shown in Figure 1. More detailed information and guidelines for each of the categories is provided in the sections that follow.



**Figure 1: Hierarchical structure of annotation categories**

#### 3.1 Problem

A general category for any COPD indicates of concern, which may be assigned if none of the more specific sub-categories are appropriate.

##### 3.1.1 Annotation scope

✓Include:

- General classes of disorders that do not correspond to specific named conditions. Note that the *Condition* label (see section 3.2) is used for named conditions.

Other known risk factors for COPD include airway hyperresponsiveness,

genetic abnormalities such as alpha-1-antitrypsin deficiency, air pollution, biomass smoke exposure, occupational dusts and chemicals, **[respiratory infections]** especially during childhood, and poor nutrition (Chapman et al 2006).

Other confounding factors include consumption of alcohol, diets with variable amounts of antioxidants, smoking, **[subclinical lung diseases]** which have not been clinically manifested, and differences in the collection of the samples and their storage.

- Problems that relate to subclasses of the Problem hierarchy (i.e., they include more specific annotations belonging to subclasses of *Problem*, such as *Medical Condition* or *Sign or Symptom* embedded within them, but they constitute longer phrases). The examples below concern problems that relate to *Conditions*. In each case, the nested *Condition* entity that is nested within the *Problem* annotation is underlined>.

Compared to continued smokers, **[CVD mortality]** is reduced by over 60% in sustained quitters (Anthonisen et al 2005)

There is overlap not only in the inflammatory profile but also in the oxidant markers, especially in acute asthma and **[COPD exacerbations]**.

High prevalence of **[past pulmonary TB]** was observed and **[active pulmonary TB]** was identified to be an important infective cause of **[AE-COPD]**.

✗Exclude:

- Named conditions, which should be annotated as *Medical Condition* (see section 3.2)

One major limitation of exhaled CO in assessing oxidative stress in **[asthma]** or **[COPD]** is the marked effects of smoking on CO concentrations

- Signs or symptoms of medical conditions, which should be assigned the *SignOrSymptom* category (see section 3.4).

Many pathological conditions in addition to **[airway inflammation]**, can contribute to CO formation

## 3.2 Condition

A disease or medical condition expressed as a noun phrase, which is usually an underlying cause for visible symptoms (the latter of which should be annotated using the category *SignOrSymptom*).

### 3.2.1 Annotation scope

✓Include:

- All named diseases and medical conditions

FeNO has a minor role in evaluating **[COPD]**, but it may have importance in the differentiation of **[asthma]**, **[eosinophilic bronchitis]**, and **[COPD]**.

✗Exclude:

- Signs or symptoms of conditions, which should be annotated using the *SignOrSymptom* category (see section 3.4).

The diagnosis of **[chronic bronchitis]** applies to patients who have a **[chronic productive cough]** for at least three months of the year in two or more successive years.

### 3.2.2 Annotation span

✓Include:

- Adjectives that denote the severity or nature of the condition (such adjectives will normally also be annotated as embedded *Quality* annotations).

Despite these uncertainties, [COPD] with concomitant **[chronic hyper-capnic respiratory failure]** has become one of the major indications for home mechanical ventilation (HMV), at least in Europe (Janssens et al 2003; Lloyd-Owen et al 2005).

In accordance with these findings, in patients with **[very severe ARF]** (pH < 7.25) the rate of NPPV failure was inversely related to the severity of respiratory acidosis (Ambrosino et al 2008).

- Words and phrases that correspond to or pertain to anatomical entities, when these can be considered part of the name of the disease or condition.

This intriguing relationship between smoking, **[pulmonary TB]** and [COPD] merits further study

The mechanisms by which [mild COPD] increase the risk of [CVD] and **[lung cancer]** are still a mystery.

### 3.3 Risk Factor

A phenotype or external factor that can increase a patient's chances of having COPD.

#### 3.3.1 Annotation scope

✓Include:

- Substances or environmental factors that can contribute towards the chances of having COPD.

Internationally there is a substantial variation in death rate due to COPD possibly reflecting **[smoking]** behaviour, type and processing of **[tobacco]**, **[pollution]**, **[climate]**, and **[genetic factors]**.

Inflammation, **[oxidative stress]**, **[DNA mutation]** and shared risk factors are some of the common explanations.

- Altered levels of proteins

**[Alpha-1-antitrypsin (AAT) deficiency]** provides a unique model of COPD, due to the **[loss of a protease inhibitor]** in affected individuals

- Variations in genes

In this cohort, a **[single nucleotide polymorphism within the surfactant protein-B gene]** was associated with elevated systolic pulmonary artery pressure

- Risks concerning diet or food intake

Several studies have demonstrated an association between **[poor nutrition]** and COPD.

- Abnormal or altered patient characteristics/attributes

Furthermore, they should be advised of the importance of avoiding factors that increase the severity of upper-airway obstruction such as sleep deprivation, the use of alcohol, hypnotic agents, and **[increased weight]** (Loube et al 1994; Haynes 2005)

#### 3.3.2 Annotation scope

✓Include:

- Any nouns or adjectives that convey change, alteration or temporal aspects relating to an entity, where such changes or alterations are integral to the description of the risk factor



On the other hand, older smokers with a **[long-term smoking history]** exhibit elevated oxidized glutathione (GSSG) and protein carbonyls in their BAL fluid even in the absence of any lung disease, indicating that lung antioxidant defences have become overwhelmed the prolonged exposure to the [noxious substances] present in [cigarette smoke] (Nagai et al 2006)

The development and progress of COPD is associated with **[increased oxidative stress]** or decreased antioxidant resources (Boots et al 2003).

### 3.4 Sign Or Symptom

An observable irregularity manifested by a patient, as a probable result of injury and/or underlying pathological/disease process, and thus a sign of the disease process, rather than disease or illness in itself.

#### 3.4.1 Annotation scope

✓ Include:

- Nouns and noun phrases corresponding to signs or symptoms

Exertional angina, syncope, or presyncope are distinctly uncommon, with a history of **[cough]**, **[wheezing]**, and respiratory infection often dominating the clinical picture

Other symptoms were strikingly prevalent, including **[pain]** (68%), **[fatigue]** (68%) and **[insomnia]** (55%)

- Abnormality in a physiological function

Importantly, compared with placebo, there was a 29% relative reduction in the number of patients who complained of **[difficulty breathing]**.

The functional consequence of these abnormalities is **[expiratory airflow limitation]**.

- Abnormality/change in an anatomical entity

The effectiveness of antimuscarinic drugs depends on the role that cholinergic vagal tone has in the pathophysiology of **[bronchial obstruction]**.

These studies and others have been combined via meta-analyses which reached conflicting conclusions about the efficacy of inhaled corticosteroids in ameliorating the **[decline in lung function]**.

However, the degree of **[intimal thickening]** is proportional to the increase in pulmonary pressure during exercise.

- Change in a patient attribute or characteristic

In order to effectively treat patients with COPD, it is important to understand the physical decline, increased sense of isolation, changes in mood such as depression, [muscle wasting], and **[weight loss]** that can afflict such patients [4].

### 3.4.2 Annotation span

✓ Include:

- Adjectives that describe the nature or severity of the sign or symptom

The role of [mucus hypersecretion] in the development of **[chronic airflow limitation]** is still controversial (Peto et al 1983; Vestbo et al 1996)

Skilbeck et al (1998) found that 95% of a cohort of patients that had been admitted with an exacerbation of COPD in the preceding 6 months were experiencing **[severe breathlessness]**

- Anatomical entities, where these are an integral part of the sign or symptom, or where they indicate the site of the sign or symptom

The pathological hallmarks of COPD are **[inflammation of the peripheral airways]** and **[destruction of lung parenchyma]** or emphysema (Thurlbeck 1991)

## 3.5 Individual Behaviour

Habits of a medical subject or group of subjects that can lead to susceptibility of developing COPD.

### 3.5.1 Annotation scope

✓ Include:

- Phrases that describe a particular type of behaviour of a patient or patient group

Internationally there is a substantial variation in death rate due to COPD possibly reflecting **[smoking behaviour]**, type and processing of tobacco, pollution, climate, and genetic factors

In the developing world, smoking rates are increasing with nearly 40% of adults **[smoking on a daily basis]** in certain jurisdictions (Ezzati and Lopez 2003).

- Phrases that characterise (groups of) patients according their behaviour

A two-fold increased risk of ALI has been observed among **[heavy alcohol consumers]** (more than 60 g of ethanol per day) admitted to the medical ICU and those undergoing lung resection, compared with **[alcohol-free patients]** (Licker, de Perrot et al 2003)

There is limited data on the airway pathology of **[smoking asthmatics]**, since these patients are frequently excluded from experimental studies

In contrast, **[sustained quitters]** lost 14 ml/year in FEV1 (Anthonisen et al 1994).

However, a recent evidence-based practice guideline from the American College of Physicians supports the use of PR for symptomatic severe COPD patients (FEV1 <50% of predicted: strong recommendation) and for symptomatic or **[exercise-limited patients]** with FEV1 50% of predicted (weak recommendation)

### 3.5.2 Annotation span

✓Include:

- Adjectives describing the intensity of the individual behaviour

Furthermore, 28.4% patients with AE-COPD admitted to the medical ICU had evidence of past pulmonary TB and all males among them were **[chronic smokers]**.

- Where individual behaviour is described in terms of characterising a group of patients, annotate the complete phrase that describes the group

It also appears that there are features of both accelerated and suppressed inflammatory responses in **[smokers with asthma]**.

## 3.6 Test or Measure Result

Results or outcomes of examinations, tests and measures.

### 3.6.1 Annotation scope

✓ Include:

- Descriptions of changes in attributes or physiological functions that are measurable

Several studies have shown that **[reduced lung function]** is associated with an increase in a variety of systemic inflammatory markers

The most common symptoms of OSAS patients include chronic loud snoring, excessive daytime sleepiness, personality changes, and **[deterioration of quality of life]**

However, the **[increased pulmonary artery pressure]** is the result, not the cause, of the RV-PA mismatch.

- Descriptions of changes in test results. In this case, the span will usually include an embedded *TestOrMeasure* annotation (see section 3.8).

One study found that a 20-session course led to **[improved 6 minute walk distance]** and better quality life compared with a 10-session course.

It is well known that smoking accelerates the **[decline in FEV1]**, while smoking cessation normalizes the rate of decline

- Phrases that include values or levels of test results

It is currently unknown whether the delivery of oxygen in the presence of **[PaO2 values >60 mmHg]** is beneficial in acute exacerbations.

Fujimoto and collaborators (Fujimoto et al 2002) studied pulmonary hemodynamics in 75 patients with mild hypoxemia (**[PaO2 >60 mmHg]**) at rest and either mild (**[FEV1% >50%]**), moderate (**[FEV1% <50% or >35%]**), or severe COPD (**[FEV1% 35%]**) at rest and with exercise.

### 3.6.2 Annotation span

✓Include:

- Units of measurement of test results where they are provided

Total lung capacity is usually not affected (ie, it remains within the lower limits of normal values), although some studies report decreases in cases of very severe obesity (**[body mass index >45 kg/m<sup>2</sup>]**).

LTOT improves survival in stable COPD patients with resting hypoxemia (**[PaO<sub>2</sub> < 55mmHg]**) and is associated with a mild improvement in pulmonary hemodynamics [76, 77]

- Where a test result is expressed as a range of values, include the specified range within the annotated span

The current American Thoracic Society/European Respiratory Society guidelines for management of AAT deficiency suggest consideration in those subjects with **[FEV<sub>1</sub> between 35% and 65% predicted]**.

They showed **[PaO<sub>2</sub> levels ranging from 40 to 60 mmHg]** and coexisting hypercapnia or congestive heart failure (MRC 1981).

### 3.7 Treatment

Any medication, therapy or program for treatment

#### 3.7.1 Annotation scope

✓Include:

- Phases corresponding to groups of drugs

In the 1990s, there was renewed enthusiasm for using **[inhaled corticosteroids]** to modify the natural history of COPD (Sin et al 2005a).

Several studies have addressed the effect of **[bronchodilators]** on lung hyperinflation (Table 2).

- Generic names for drugs

Unless **[salbutamol]** had produced changes in the ability to generate force by

the respiratory muscles, or the elastic properties of the lung, both of which it are unlikely.

Ramirez-Venegas and colleagues (1997) found that the use of **[salmeterol]** reduced not only dyspnea but improved lung function in patients with COPD.

- Processes/procedures used for treatment

Criteria for **[intubation]** were not standardized, and **[noninvasive ventilation]** was infrequently utilized at our hospital during the period of study.

**[Pulmonary rehabilitation]** is designed to reduce symptoms, optimize functional status, increase participation, and reduce health care costs through stabilizing or reversing systemic manifestations of the disease [23].

- Surgical procedures

In a select subgroup of patients who were undergoing evaluation for **[lung volume reduction surgery]** and had both Doppler echocardiography and right heart catheterization, Bach and co-workers (Bach et al 1998) did not find a significant correlation between the actual and estimated sPAP but suggested that this difference was due to a single outlying patient.

In patients with truly end-stage lung disease, treatment of the PHD often provides a temporary, but critically important bridge that allows a patient to survive and remain relatively physiologically intact awaiting **[lung transplantation]**.

- Treatment regimes

One of the cornerstones in smoking cessation is the use of **[nicotine replacement therapy] ([NRT])**.

Based on these considerations the present review focuses on clinically and pathophysiologically important aspects of the two major modalities for the treatment of acute or chronic respiratory failure in COPD: [mechanical ventilation] and **[oxygen therapy]**.

- Different mediums/means used for treatment

There are 6 ways in which [NRT] can be administered: as a **[patch]**, **[gum]**, **[sublingual tablet]**, **[lozenge]**, **[nasal spray]**, or **[inhaler]**.

- Departments or units in a hospital

Toxicity due to excessive [oxygen therapy] in the **[emergency department]** is

still a prevalent problem which could be resolved by increasing patient awareness of the risk (Plant et al 2000a).

Keeping these factors in mind, the present study was designed to prospectively study the clinical presentation and predictors of outcome in patients with AE-COPD requiring admission to the **[intensive care unit]** (**[ICU]**)

### 3.7.2 Annotation span

✓ Include:

- Method of treatment/drug administration, where provided

Preoperative **[inhaled beta-2 adrenergic agonists]** (ie, [salbutamol]) and **[anticholinergic agents]** (ie, [ipratropium]) should be continued up to the day of surgery in all symptomatic asthmatics and in COPD patients with bronchial hyperreactivity.

A two-week trial of **[oral glucocorticoids]** was proposed to identify patients with a documented spirometric response, assuming that an acute response is predictive of a chronic response (GISCPD 2001).

- Adjectives that characterise the treatment, when they can be considered part of the treatment name

If the symptoms are periodic, **[short-acting bronchodilators]** (eg, [beta-2 agonists] or **[anticholinergics]**) can be used on an as-needed basis.

In the era before the widespread availability of **[long-term oxygen therapy]** ([LTOT]) it was well known that the presence of PH was associated with poor prognosis in COPD.

Similarly, even in the landmark NOT trial [O2 therapy] resulted in an improved survival only in patients whose baseline SVI was >30mL/beat/m<sup>2</sup> (in the **[continuous O2]** group) or PVR was <400dyncm<sup>5</sup> (in the **[nocturnal O2]** group) [78].

### 3.8 Test or Measure

An examination, test or measure of a physiological function, attribute or parameter of a patient.

#### 3.8.1 Annotation scope

✓ Include:

- Physiological functions, when the context indicates that they are being measured or tested

Asthma and cigarette smoking potentiate the effects of each other, leading to impaired asthma control, more severe symptoms (Althuis et al 1999), increased need for rescue medication (Gallefoss and Bakke 2003), accelerated deterioration of **[lung function]** (Lange et al 1998) and reduced short-term therapeutic response to corticosteroids (Chaudhuri et al 2003)

Improvement was found in **[gas exchange]** and [FEV1] associated with a decrease in hospitalizations.

- Names of tests or questionnaires

If applied in defined circumstances, these options can prolong life and/or improve functional capacity, symptoms, and **[health-related quality of life]** (Rabe et al 2007).

Disease-specific questionnaires include the **[Chronic Respiratory Questionnaire][CRQ]** and **[St. Georges Respiratory Questionnaire] ([SGRQ])**

- Diagnostic procedures or tests

At admission, in all the patients full **[haemogram]**, **[serum biochemistry]**; **[urine analysis]** were performed

Diagnosis is hampered by very limited use of **[spirometry]** within primary care because of lack of access and time, cost constraints, inaccurate interpretation of results, and inadequately trained staff

- Measurements and rates of physiological functions and attributes



In controlled ventilation, a reduction of **[inspiratory time]** and **[respiratory frequency]** can increase **[expiratory time]** thus promoting lung deflation with the consequence of a reduction in **[PEEPi]** (Ward et al 2008).

Furthermore, COPD patients may require direct assessment of **[nocturnal desaturation]** by [oximetry], because the degree of hypoxemia during sleep cannot be predicted from measurement of **[arterial oxygen saturation]** in individual awake patients.

Chaouat and colleagues (1995) found that, compared to the OSAS-only group, the overlap population tended to be older, with more common hypoxemia and hypercapnia, higher **[mean pulmonary artery pressures]**, but similar **[body mass index]** (**[BMI]**).

However, it is not easy to predict the extent of this improvement based on an increase in **[forced expiratory volume in one second]** (**[FEV1]**) after a short period of bronchodilatory therapy (Berger and Smith 1988; Hay et al 1992)

### 3.8.2 Annotation span

✓ Include:

- Words that indicate the nature of the measurement

When COPD patients with expiratory flow-limitation need to increase their **[respiratory rate]** to increase minute ventilation, there is potential for inspiratory muscle failure due to DH (Table 1).

Therefore **[total lung capacity]** ([TLC]) does not change significantly during [physical activity] either in normal subjects or in COPD patients (Stubbing et al 1980)

- Anatomical entities that are relevant to determine the exact nature of the measurement or test.

The level of inflammation in COPD lungs is greater than that seen in the lungs of smokers without COPD, and the **[number of neutrophils in sputum]** is predictive of **[lung function]** decline

✗ Exclude:

- Any words, phrases or numerical data that indicate the results or outcomes of tests or measurements (such information is included in Test or Measure Result annotations, see section 3.6)

However, there is also a group of patients with **[abnormal spirometry]** but

are otherwise asymptomatic.

They do not properly take into account other important factors of the disease such as a **[low-BMI]**, comorbidities, or frequent exacerbations, all of which may favor a benefit from LTOT (O'Reilly et al 2007)

Such beneficial short-term effects during exercise can also be achieved in milder forms of hypoxemia, which do not reach the critical limit for the definition of hypoxic respiratory failure (**[PaO<sub>2</sub> > 60 mmHg]**) at rest (Dean et al 1992; Fujimoto et al 2002).

### 3.9 Radiological Test

A radiological test for detecting COPD

#### 3.9.1 Annotation scope

✓ Include:

- Any phrases referring to radiological tests, both full forms and acronyms

A careful history and physical examination, accompanied by simple laboratory tests such as pulse oximetry, **[chest radiograph]**, electrocardiogram, complete blood count and spirometry are usually sufficient in excluding other common causes of dyspnea.

These methods include **[nuclear magnetic resonance] ([NMR])** and allow simultaneous detection of hundreds of low molecular weight species within a single fluid sample.

#### 3.9.2 Annotation span

✓ Include:

- Annotated spans may correspond to adjectival forms as well as noun phrases, as long as they refer to radiological tests

The characteristic **[chest radiographic]** findings of PH are enlargement of the central pulmonary arteries causing hilar prominence and rapid tapering of the arteries in the lung periphery.

### 3.10 Physiological Test

A measure that determines a COPD patient's capacity to exercise

### 3.10.1 Annotation scope

✓ Include:

- Any phrases referring to radiological tests, both full forms and acronyms

In a minority of cases, additional tests including **[incremental cardiopulmonary exercise testing]**, echocardiogram and computed tomography (CT) may be necessary

However, in contrast to Patient A, in Patient B, the improved RV function paralleled a relatively marked increase in the **[6MWD]** from 238 m to 320 m, and a fall in NYHA Functional Class from 4 to 3

### 3.11 Microbiological Test

An examination of a COPD- relevant specimen

#### 3.11.1 Annotation scope

✓ Include:

A careful history and physical examination, accompanied by simple laboratory tests such as pulse oximetry, chest radiograph, electrocardiogram, **[complete blood count]** and spirometry are usually sufficient in excluding other common causes of dyspnea.

**[Bacterial isolates]** were grown in 25 (21.6%) patients; in 11 (44%) patients, more than one pathogen was isolated

### 3.12 Constituent Concept

An umbrella type for elementary concepts that may be nested within, or occur within the context of, phenotype description. Usually, this label will not be assigned, and instead one of the four concept types listed below should be used.

### 3.13 Anatomical Concept

A concept corresponding to or pertaining to an anatomical entity

### 3.13.1 Annotation scope

✓ Include:

- Body parts and organs

Other (but more infrequent) symptoms include **[chest]** pain, orthopnea and wheezing.

Clearly, in moderate to severe disease, tiotropium reduces patient symptoms, improves health-related quality of life, reduces exacerbations (Barr et al 2006), decreases dynamic hyperinflation of the **[lungs]** (Maltais et al 2005) and increases exercise tolerance (Casaburi et al 2005)

- Body substances/fluids

**[Sputum]** and **[blood]** culture examination were performed to identify the etiological cause.

GSK-681323 is currently in a 4 week Phase II trial where the efficacy outcome measures include [lung] function, **[sputum]** and **[serum]** biomarkers, including CRP

- Cells

In a comparative study in cigarette smoke-exposed guinea pigs, roflumilast reduced the numbers of **[neutrophils]**, **[lymphocytes]**, and **[eosinophils]**, and reduced protein content in bronchoalveolar lavage fluid whereas treatment with corticosteroids only reduced the number of **[eosinophils]**.

### 3.13.2 Annotation soan

✓ Include:

- Annotations may correspond to adjectives (as well as the more normal noun phrases), where such adjectives refer to or pertain to anatomical entities.

Some studies have used other forms of nutritional supplementation in the context of **[pulmonary]** rehabilitation, albeit with limited benefits.

Causes of pain in COPD include **[subcostal]** pain due to **[diaphragmatic]** and [intercostal muscle] fatigue, [rib] fractures relating to coughing and/or corticosteroid-induced osteoporosis, and **[pleural]** inflammation caused by infection.

- Include adjectives that are used to specify the precise anatomical location

Laaban and colleagues (Laaban et al 1989) compared the measurement of PAP by Doppler echocardiography with **[right heart]** catheterization in 41 patients with stable COPD.

Of the patients with advanced disease studied in the National Emphysema Treatment Trial, only 5% had severe [pulmonary] hypertension (**[pulmonary artery]** pressure > 35 mmHg).

### 3.14 Drug

Names or individual drugs and groups of drugs

Note that annotations of the *Treatment* category also include (but are not limited to) drugs. Where a drug name is encountered (according to the conditions shown below, then it should be annotated as *both* a Treatment AND a Drug

#### 3.14.1 Annotation scope

✓ Include:

- Phases corresponding to groups of drugs

More recently 42 **[nicotinic acetylcholine receptor agonists]** (eg, [varenicline]) have been introduced into the market for smoking cessation (Gonzales et al 2006).

- Names of drugs

**[Varenicline]** appears to be more effective than **[bupropion]** (odds ratio for smoking cessation, 1.66) (Cahill et al 2007).

### 3.15 Protein

A name or a protein or group of proteins

#### 3.15.1 Annotation scope

✓ Include:

- All names of protein, regardless of their form (i.e., both full forms, which may include numbers, and abbreviations/acronyms)

Other known risk factors for COPD include airway hyperresponsiveness, genetic abnormalities such as **[alpha-1-antitrypsin]** deficiency, air pollution, biomass smoke exposure, occupational dusts and chemicals, respiratory infections especially during childhood, and poor nutrition (Chapman et al 2006).

Another method by which the GCR influences inflammatory processes in COPD is the interaction between **[histone deacetylase-2] ([HDAC2])** and **[nuclear factor kappa B] ([Nf-kB])**, a key transcription factor.

- Groups of proteins

Oxidative stress in the lungs results in increased gene expression and production of **[pro-inflammatory cytokines]**.

### 3.16 Quality

Adjectival expressions that serve to modify, qualify or further specify any of the concept types introduced above. Normally (as specified in the *Annotation Span* subsections of the individual concepts), such expressions should be included within span annotated for these concepts. However, they should additionally be annotated as *Quality* annotations.

#### 3.16.1 Annotation scope

✓ Include:

- Adjectives describing the qualities of a medical condition, sign symptom or problem

There is overlap not only in the inflammatory profile but also in the oxidant markers, especially in **[acute]** asthma and COPD exacerbations.

In patients with COPD and **[chronic]** respiratory failure receiving [long-term] oxygen therapy (LTOT), a low level of carbon dioxide tension (PaCO<sub>2</sub>) has even been found to be linked to elevated mortality (Chailleux et al 1996), whereas in another study similar rates of survival were observed in normocapnic (<45 mmHg) and hypercapnic (> 45 mmHg) patients (Aida et al 1998)

- Adjectives describing the severity of a medical condition, sign symptom or problem

The physical examination is completely unremarkable in most patients with **[mild]** COPD

It may predominantly occur in patients with **[very severe]** initial hypercapnia (Moloney et al 2001)

- Adjectives describing the frequency of a medical condition, sign symptom or problem

Thus, LABAs cannot be recommended routinely for mild COPD except in patients who have persistent symptoms despite SABAs or in those who have **[frequent]** exacerbations requiring systemic corticosteroid therapy and/or hospital visit.

- Adjectives that characterise the nature or function of treatments

Third, some of those studies may have used insufficient doses and only a few included **[long-acting]** bronchodilators, and in particular, none included tiotropium (Liesker et al 2002).