Role of a digital clinical decision-support system in management of chronic obstructive pulmonary disease

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Acronyms and Abbreviations

1. COPD: Chronic Obstructive Pulmonary Disease
2. LMIC: Low- and Middle-Income Countries
3. HIC: High-Income Countries
4. FEV1: Forced Expiratory Volume in 1 second
5. FVC: Forced Vital Capacity
6. GOLD: Global Initiative for Chronic Obstructive Lung Disease
7. LLN: Lower Limit of Normal
8. mMRC: Modified Medical Research Council
9. CAT: COPD Assessment Test
10. CDSS: Clinical Decision Support System
11. SABA: Short-Acting β_2 Agonists
12. LABA: Long-Acting β_2 Agonists
13. SAMA: Short-Acting Muscarinic Antagonists
14. LAMA: Long-Acting Muscarinic Antagonists
15. ICS: Inhaled Corticosteroids

Foreword

No thesis is the work of a sole person, and mine certainly is no different. I have had the opportunity to borrow from the intellect and expertise of so many.

To my supervisor Dr Bernt Aarli. I owe him greatly for his help with the statistics. This paper would simply not have come about if not for his support. In him I now have a mould for a future as a clinician-researcher. To my supervisor Dr Tehmina Mustafa. I consider myself fortunate to have worked with a guide of her sharpness and professionalism. That their patience is what made this thesis possible, is the honest truth.

To the patients who participated in the study. A deep sense of gratitude is in order.

To the Centre for International Health, Bergen. It has been an immense pleasure learning from and working with academics from all over the world.

To Uma, my mother, for being my North Star. To Vijay, my father, for his stoic wisdom.

To that desolate, century-old cabin on the mountains in Myrkdalen. For I penned the first words of this thesis amidst the deep, unforgiving snow.

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Background

Chronic Obstructive Pulmonary Disease (COPD) is a preventable and modifiable disease, characterised by irreversible (or poorly reversible) airflow limitation, and persistent respiratory symptoms due to airway and/or alveolar abnormalities [1]. Prolonged/significant exposure to noxious particles or gases (primarily from cigarette smoking) are usually the causative factors [2].

Pathogenesis of COPD

Noxious particles, particularly from cigarette smoke, evoke a protective inflammatory response in the lungs [3]. Prolonged exposure to such stimulants however, results in an amplified response, resulting in destruction of lung tissue. In addition to this, there is a disruption of corrective mechanisms that limit such destruction [4]. In general, the structural changes that occur because of inflammatory destruction persist even after cessation of smoking (or removal of noxious stimuli) [5].

The smoke/irritants and the inflammatory response independently lead to a higher oxidative burden (imbalance between oxidants and antioxidants) [6]. The consequence is the activation of proteases and inactivation of antiproteases, resulting in a protease asymmetry [7]. Of note is the deactivation of α1 anti-trypsin (AAT). Individuals with genetic AAT deficiency, who also smoke, are at particular risk of emphysema [8]. Inflammatory changes result in exudate production and remodelling (narrowing) of small-airways (< 2mm) [9]. In addition to this, loss of lung elasticity

stems from destruction of alveolar walls and attachments. Air trapping is the end-result, and the diseased patient experiences the characteristic shortness of breath. These changes correlate to decrease in Inspiratory Capacity and Vital Capacity, accompanied by an increased Total Lung Capacity, Functional Residual Capacity, and Residual Volume, which are indicative of hyperinflation [10, 11].

Chronic productive cough is another archetypal feature in COPD, and it is brought about by a combination of poor ciliary function and increased production of mucus [12]. The hypersecretion is explained by squamous metaplasia, increased numbers of goblet cells [13], and increased size of bronchial submucosal glands[14] in response to chronic irritation. Squamous metaplasia [15] of epithelial cells also results in an abnormal mucociliary escalator and difficulty in expectorating.

Diagnosis

In any patient over 35 years of age presenting with either shortness of breath, chronic cough (dry/productive), recurrent lower respiratory infections and/or exposures to risk factors (smoking, occupational etc.,), a possible diagnosis of COPD should be considered. Diagnosis is only the first step in the work-up of the patient; a complete evaluation involves grading of disease severity, an evaluation of symptoms and how the disease impacts the patient's life, and an evaluation of past and future-risk of exacerbations.

A good history elicited from the patient paves the way for diagnosis. Dyspnoea on exertion, smoking status, and production of phlegm are independent predictors of COPD [16]. Recurrent

respiratory infections [17], occupational [18] and other exposures [19] to noxious stimuli form important components of the patient anamnesis. While there exist no pathognomonic signs of COPD [20], clinical examination can increase the pre-spirometry probability of the diagnosis [21]. Wheezing [22], forced expiratory time of more than 9s [20, 23], maximum laryngeal height≤ 4cm [21, 22] and prolonged expiration [20] have independent diagnostic value. Late signs of the disease include hyperinflation of the chest [24], adventitious lung sounds[25], use of accessory muscles for breathing and intercostal recessions [26], and cachexia[27].

While radiology by no means is diagnostic, a flattened diaphragm, narrow cardiac silhouette, and hyperlucent lung fields on the chest radiograph are indicative of emphysema [28], and increased bronchovascular markings is a non-specific sign of chronic bronchitis. A baseline chest radiograph at the initial assessment of a COPD patient is also recommended as a screen for lung cancer [29]. Additionally, there is some evidence to suggest that radiographic emphysema on the baseline low-dose computer tomography (LDCT) screen is an independent predictor of lung cancer diagnosis, and helps guide management decisions [30].

Serological tests as a screening tool are limited to testing for alpha 1-antitrypsin deficiency in populations with high incidence of the disease [31]. Eosinophil counts have predictive value in the efficacy of inhaled corticosteroids (ICS) in the management of COPD; patients with higher levels of eosinophils are seen to have a better treatment response with ICS [32].

The mainstay for diagnosis is spirometry. While body plethysmography and gas diffusion tests can be a part of an investigative work-up, the presence of a persistent post-bronchodilator

FEV1/FVC <0 is diagnostic of COPD in individuals with an exposure history [1]. Disease severity grading is given by cut-off values of FEV1 in percent of the predicted value.

Table 1. Classification of airway limitation in COPD

GOLD 1	Mild	FEV1≥ 80% predicted
GOLD 2	Moderate	50% ≤ FEV1 < 80% predicted
GOLD 3	Severe	30% ≤ FEV1 < 50% predicted
GOLD 4	Very Severe	FEV 1< 30% predicted

Due to the natural decline of the FEV1/FVC with time, using the FEV1/FVC <0.7 criteria to diagnose COPD leads to a higher rate of diagnoses in the elderly population[33, 34], and a lower rate of diagnosis in younger cohorts [33]. In such cases, usage of lower limit of normal (LLN) may be appropriate. LLN is defined as the FEV1/FVC ratio below the 5^{th} percentile of the healthy reference group[35], according to age and sex.

Questionnaires such as the modified British Medical Research Council Questionnaire (mMRC) [36] and COPD Assessment Test (CAT™) [37]can help indicate the extent of disease severity on the patient's daily life.

MODIFIED MRC DYSPNEA SCALE[a]

PLEASE TICK IN THE BOX THAT APPLIES TO YOU | ONE BOX ONLY | Grades 0 - 4

mMRC Grade 0.	I only get breathless with strenuous exercise.	☐
mMRC Grade 1.	I get short of breath when hurrying on the level or walking up a slight hill.	☐
mMRC Grade 2.	I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.	☐
mMRC Grade 3.	I stop for breath after walking about 100 meters or after a few minutes on the level.	☐
mMRC Grade 4.	I am too breathless to leave the house or I am breathless when dressing or undressing.	☐

Figure 1: The Modified Medical Research Council Dyspnoea Scale. Referenced from [38]

CAT™ ASSESSMENT

For each item below, place a mark (x) in the box that best describes you currently.
Be sure to only select one response for each question.

EXAMPLE: I am very happy	0 (X) 2 3 4 5	**I am very sad**	**SCORE**
I never cough	0 1 2 3 4 5	I cough all the time	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	
I have lots of energy	0 1 2 3 4 5	I have no energy at all	

TOTAL SCORE: ( )

Reference: Jones et al. ERJ 2009; 34 (3); 648-54.
FIGURE 2.3

Figure 2: The COPD Assessment Test (CAT) score. Referenced from [38]

The combination (termed the “ABCD” assessment tool) of Spirometry, symptom severity, and history of exacerbations together forms the holistic assessment of the COPD patient. This approach is vital for prognostication and guides therapeutic decisions[1].

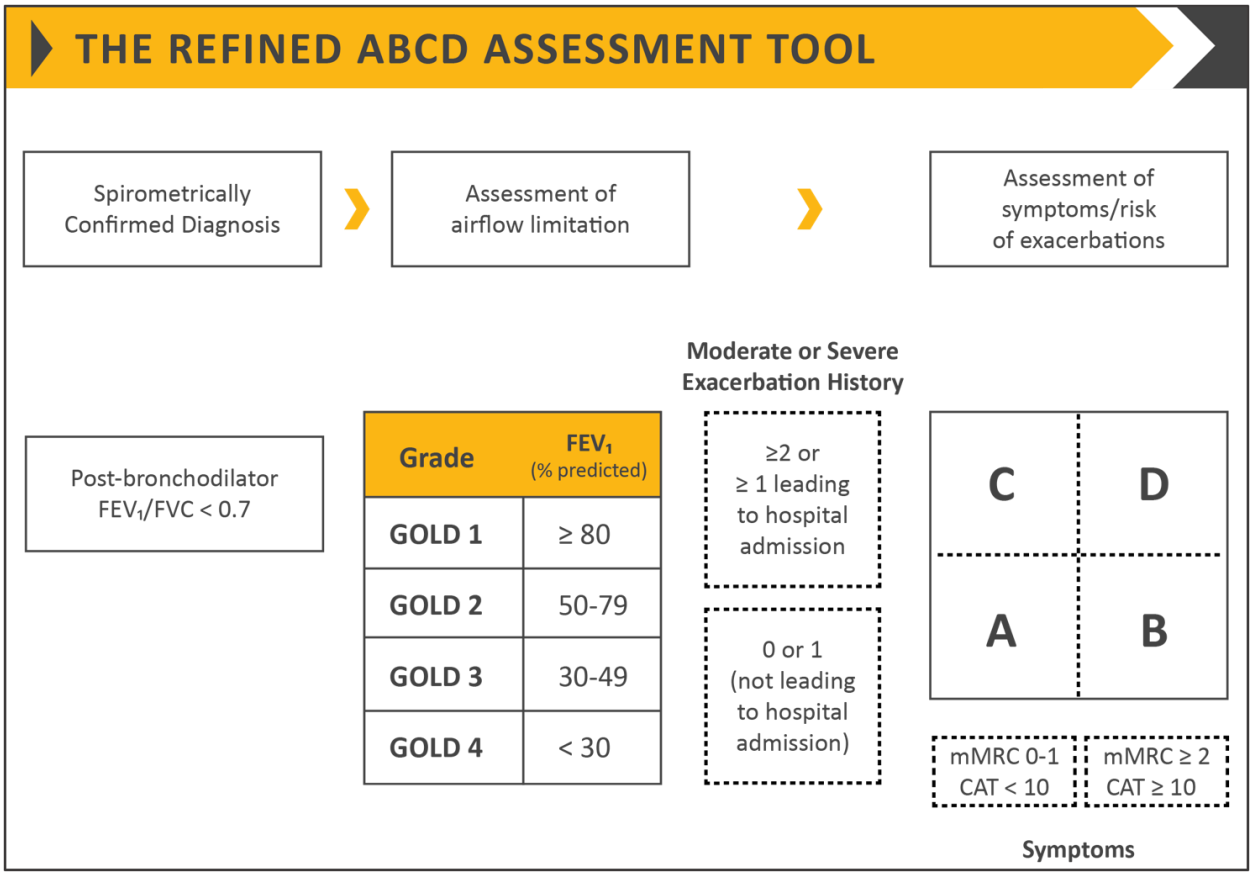

Figure 3: The ABCD assessment tool. Referenced from [38]

Management of stable COPD and exacerbations

Stable COPD is managed based on an individualized assessment of symptoms and risk of future exacerbations. Therapeutic goals are to relieve symptoms and reduce risk of future exacerbations. Both pharmacological and non-pharmacological strategies are vital. Initial management aims to reduce exposure to risk factor(s). Smoking cessation plays an important

role in the management and is offered to all patients. Both the influenza and the pneumococcal vaccine may contribute to reduce the risk of exacerbations. Initial pharmacological therapy is based on the ABCD grading of the patient's illness. Patients are followed-up at regular intervals to evaluate treatment response and to assess adherence.

Non-pharmacological therapy in COPD

Smoking cessation

Smoking cessation is one of the most efficacious therapeutic interventions. Smoking remains the central risk factor in the development of COPD. Higher amounts of smoking are directly correlated with higher risk for hospitalization [39] and decline in FEV1 [40].

NON-PHARMACOLOGIC MANAGEMENT OF COPD*

PATIENT GROUP	ESSENTIAL	RECOMMENDED	DEPENDING ON LOCAL GUIDELINES
A	Smoking Cessation (can include pharmacologic treatment)	Physical Activity	Flu Vaccination Pneumococcal Vaccination Pertussis Vaccination
B, C and D	Smoking Cessation (can include pharmacologic treatment) Pulmonary Rehabilitation	Physical Activity	Flu Vaccination Pneumococcal Vaccination Pertussis Vaccination

*Can include pharmacologic treatment.

Figure 4: Non-pharmacological management of COPD. Referenced from [38]

Immunization

Influenza vaccination is recommended for all COPD patients [41]. Pneumococcal vaccination is recommended for patients> 65 years, and in younger patients with comorbid cardiac and pulmonary diseases [1].

Pulmonary rehabilitation

The current GOLD report encourages pulmonary rehabilitation to improve dyspnoea, functional capacity, and quality of life[1].

Pharmacological therapy in COPD

The goal of pharmacotherapy is to alleviate symptoms, limit exacerbation frequency and severity, and improve exercise tolerance. In general, medications are administered through inhalers. Below is a summary of the most-frequently used drugs in the treatment of stable COPD [42].

Bronchodilators

Bronchodilators reduce bronchial obstruction by altering the smooth muscle tone of the airways, thus increasing the Forced Expiratory Volume in 1 sec (FEV1). There is good evidence to show that bronchodilators improve exercise performance [43] and are most often prescribed either in

the form of as-needed preparations (short-acting preparations) or regularly (as long-acting preparations) to treat or reduce the frequency of symptoms.

Two major pharmacological classes with a broncho-dilatory effect are used in the treatment of COPD.

1. β_2 adrenoreceptor Agonists

β_2 Agonists relax airway smooth muscles by acting on the β_2 adrenergic receptors, resulting in antagonism to bronchoconstriction [44].

1. Short-Acting β_2 Agonists (SABA): The duration of the effect of SABAs is generally 3-6 hours. Both regular and as-needed SABA use has shown to improve FEV1 and relieve symptoms.
2. Long-Acting β_2 Agonists (LABA): LABAs have a duration of action of 12 hours or more and improve symptoms and patient-related outcomes.

2. Antimuscarinics

Antimuscarinics block muscarinic receptors M1, M2, and M3, leading to antagonizing the contraction of bronchial smooth muscles.

1. Short-Acting Muscarinic Antagonists (SAMA): Ipratropium blocks M2 receptor, inhibiting vagal bronchoconstriction. SAMAs have a longer duration of action than SABAs, but they also have a slower onset of action [44]. SAMA monotherapy has shown to be slightly better than LABA monotherapy [45].
2. Long-Acting Muscarinic Antagonists (LAMA): LAMAs have a prolonged effect on M3 receptor, and hence increasing the duration of the bronchodilator effect[44]. LAMA treatments seem

to improve pulmonary rehabilitation efforts[46], reduce exacerbations and hospitalizations [47].

Anti-inflammatory drugs

Inhaled Corticosteroids (ICS)

While monotherapy with ICS are not indicated in COPD [48], glucocorticoids in combination with LABA have been shown to be more effective than either component alone [49] in the improvement of pulmonary function and in reducing exacerbations in patients with moderate to very severe COD. Of particular importance in the predicted effectiveness of adding ICS to a LABA is the eosinophil count. Patients with low eosinophil counts (eosinophil count< 100 cells/uL) show no improvement to combined treatment of LABA/ICS, while those with higher eosinophils (eosinophil counts> 300 cells/uL) have good treatment responses to the combination [50].

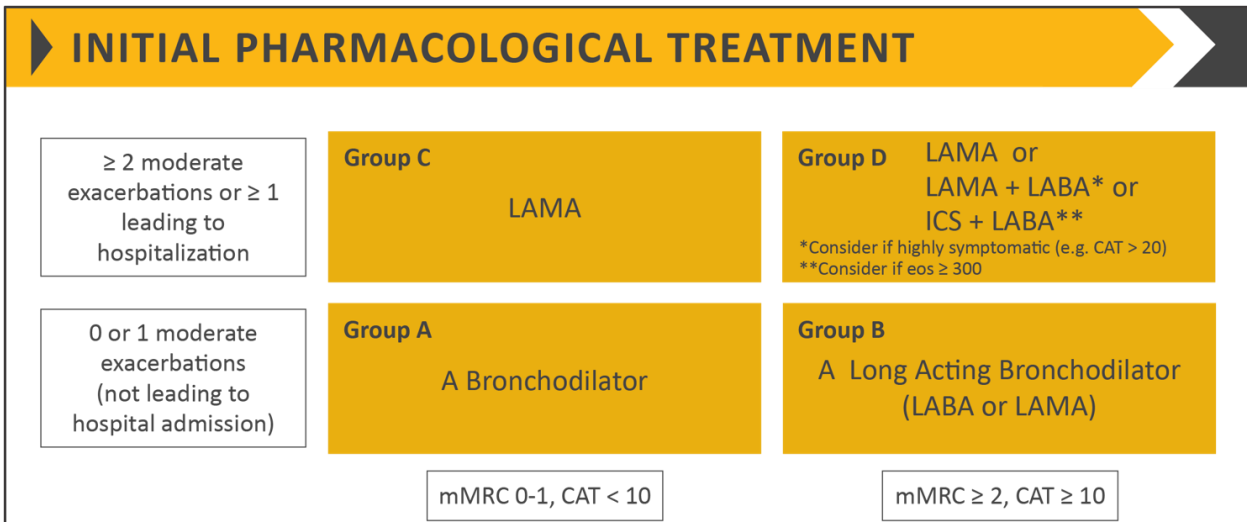

Figure 5: Treatment guidelines according to the A-B-C-D classification of disease severity. Referenced from [38]

Phosphodiesterase-4 Inhibitors (PDE-4Is)

Roflumilast inhibits breakdown of intracellular cyclic AMP (cAMP), thus reducing inflammation. PDE-4Is have no bronchodilator activity. Roflumilast shows some effect on reducing exacerbations and hospital admissions, as well as improving lung function when added to LABAs and ICS [51].

Rationale for performing this study

Global Burden of COPD

Chronic Obstructive Pulmonary Disease contributes to an enormous share of morbidity and mortality rates worldwide. Disability Adjusted Life Years (DALYs) [52] is an important indicator that measures the burden of a disease. DALYs is a societal measure that takes into account both the Years Lived with Disability metric and the Years of Life Lost metric.

In 2019, COPD was the third-highest cause of all deaths globally, with over 3 million people dying of the disease [53]. This accounted for 6% percent of all the deaths in the world that year [54]. More than 90% of COPD deaths in 2017 occurred in low-middle income nations [55].

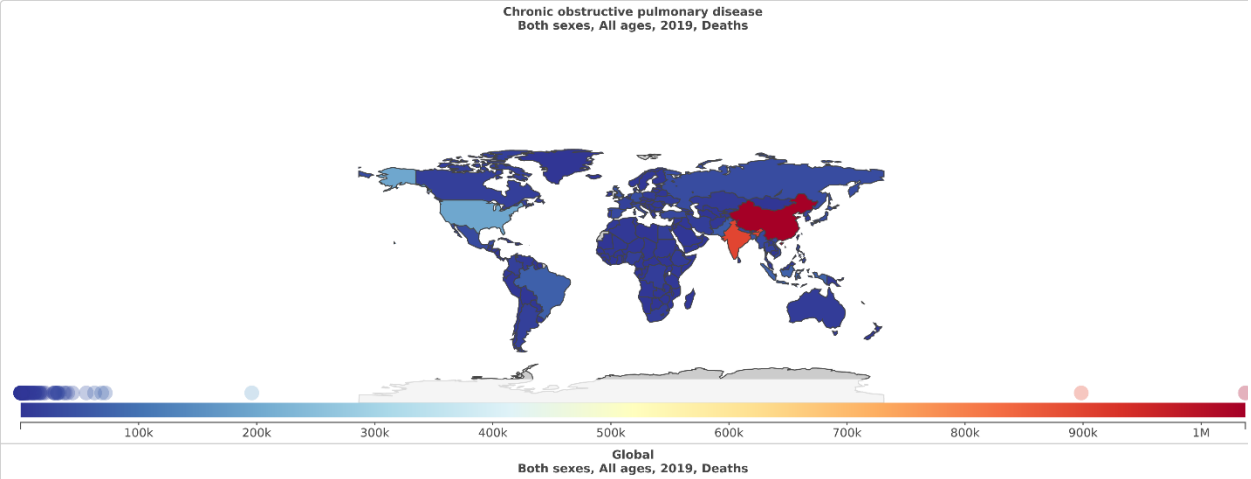

Figure 6:Global Burden of COPD. Countries within the Asian WHO region had the highest mortality in the world. Particularly, India, China, Nepal, and Myanmar were worst affected. Screenshot from[54]

Multiple risk factors, unique to developing nations, act in concert and thus exacting a high toll on these populations. Work-exposures to dusts, vapours, and fumes could be far greater in low-middle income nations as compared to their high-income counterparts.

Challenges in the diagnosis and management of COPD in LMICs

COPD diagnosis begins with a strong suspicion based on symptomatology and history of exposure to risk factors and requires lung-function testing. Younger patients tend to be underdiagnosed [33], and in many resource-restricted parts of the world, access to spirometry is neither adequate nor uniform [56]. Along with these two significant challenges that lead to misdiagnosis of COPD, multiple country-specific and even location-specific factors further complicate the diagnostic process. This section attempts to summarize factors unique to LMICs that lead to high rates of misdiagnosis/underdiagnosis and diagnostic delay.

COPD is unique in terms of the level of mismatch between the morbidity it poses, and the paucity of epidemiological information in LMICs. More than 90% [55] of the COPD related deaths in 2017 were reported from LMICs. Despite such staggering figures relating to mortality (and morbidity) of COPD, health systems in many LMICs have not been effective enough in the communication of disease severity to the general population [57]. Lack of awareness of the disease among the population [58, 59] is a crucial factor in underreporting of symptoms and hence delayed, or in many cases, underdiagnosis of COPD in LMICs. Insidious symptoms such as recurrent cough and chronic sputum production are usually disregarded by patients and are not seen as reasons to seek care [58]. A delay in seeking care eventually results in a delayed diagnosis and often at an advanced stage of COPD. A general lack of awareness of the illness does not only persist among the population but also among treating physicians in LMICs. For instance, COPD was the second-highest cause of death in India in 2017, leading to nearly 1 million deaths that year [60]. A survey in 2013 revealed less than a third of chest physicians and about 90% of general practitioners did not use spirometry [61]. Common responses for not using spirometry were lack of time, poor affordability by patients, and difficulties in using and interpreting test results. Similarly, studies within the sub-Saharan African region show poorly informed healthcare workers who underestimate the severity of smoking and smoke from burning biomass fuels [62].

Availability of infrastructure and resources play an important role in the diagnosis of COPD as well. Even as the burden of communicative diseases on LMICs eases, there is a well-observed epidemiological transition towards higher stress caused by non-communicative chronic diseases [63]. Chronic illnesses pose a special problem for LMICs. The goals of minimizing healthcare costs are at constant odds with optimizing healthcare delivery. Governments must often choose

between competing healthcare needs and this inevitably leads to neglect of certain diseases in a population. Despite contributing to high morbidity and mortality, COPD has arguably received the short end of this stick. Once again, India perhaps demonstrates best the concerning regularity with which COPD slips under the radar in LMICs. In 2018, the Indian government launched a nationwide campaign with (alongside providing insurance to 500 million people) an aim to develop 150,000 Health and Wellness Centres [64]. In the first year, 10,000 of these centres were operational and screened for a multitude of common chronic conditions. COPD was remarkably absent from the screening guidelines[65]. Global estimates regularly point towards a trend of underdiagnosis of COPD in LMICs. A combination of lack of awareness among physicians and the general populace, an already overburdened healthcare system, poor awareness of the condition, and underreporting of symptoms could all partially explain the challenges LMICs face in diagnosing COPD.

Private health sector, defined as all providers who exist outside the formal public sector whose aim is to treat disease, plays an important role in the financing and provision of care in LMICs [66]. The effect of private health sector in LMICs is largely undocumented[66]. Private health sector includes both philanthropic as well as for-profit organisations[67]. While for-profit services are generally used by people with a higher-income and educational level, they are available even in the poorest nations and utilised by low-income groups[68]. Scarcity of public services, cheap healthcare for the low-income population, and easy accessibility have all resulted in more healthcare being provided by the private health-sector. However, the use of private healthcare for the treatment of chronic conditions can result in households being unable to afford to meet other vital requirements[69].

A plethora of other variables is also in play, with the common ones being economic standing, sex, social status, type of illness, and quality of service (both perceived and actual) and so on. Low Socio-Economic Status correlates significantly with poor lung function [70, 71], even after adjusting for smoking and occupational exposure to toxicants. It is also an independent risk factor for the development of COPD [70]. Low SES correlates directly with poor access to healthcare [72]. Poor flexibility in work schedule (a lot of the population in lower SES are daily-wage labourers), inability to afford allopathic medicine, lower education levels and physical barriers such as distance all lead to health-seeking behaviours that do not lend themselves to easy repair.

Women are a subset of the population within LMICs that have been overlooked in the studies that measure COPD prevalence. While tobacco smoking is definitely a risk factor in developing COPD, exposure to biomass fuels seems to play an even more important role amongst women in LMICs [73]. In the non-smoking general population, the prevalence of COPD is estimated to be around 30%. 70% of these non-smoking COPD patients are women [74]. These findings have important ramifications for the development of screening guidelines. Most of the population in LMICs lives in rural conditions and households still use traditional biomass fuels for cooking [75, 76]. Crowded dwellings with poor ventilation further contribute to worsening lung function. Women who were exposed for prolonged periods to wood-burning have also shown to have fewer symptoms at the onset than their tobacco-smoking counterparts [77]. Studies examining health-seeking behaviour indicate that women might choose different pathways than men, especially when it involves cultural customs and norms [78]. Ignoring early COPD symptoms could thus be a common phenomenon in LMICs, especially amongst non-smoking women who have a markedly lighter symptomatic burden [75].

Consultation of various versions of “Traditional Medicine” is an important cause of delay in eventual diagnosis of COPD. A repetitive finding in LMICs is that the general population first confer with the traditional healers or informal healthcare providers for certain symptom clusters[58]. This has to do with the perception of the cause of the symptoms. For instance, symptoms that are believed to have been brought about by cultural or social transgressions are first brought to the attention of cultural healers. There is evidence that suggests women have a higher predilection to this health-seeking behaviour than men[79].

COPD has a long-disease course and LMICs face significant challenges in both the pharmacological and non-pharmacological approaches in the treatment of the disease. Accessibility, affordability, and availability of spirometry is generally poor in LMICs[61]. Previous studies also demonstrate a lack of adequate availability of SABA[80-83], SAMA[83-85], LABA[84, 85], LAMA[85], ICS-Bronchodilator combinations[84, 85]. Additionally, the poor availability and inappropriate usage technique of spacers[86, 87], which are delivery devices for inhalational drugs, contribute to difficulties in managing COPD in LMICs.

LMICs also have high rates of smokers, with 80% of world’s smokers living in LMICs[88]. While smoking rates are on the decline in High-Income Countries (HICs), legislative weaknesses in LMICs have provided a platform for tobacco companies to aggressively promote smoking[89-91], particularly to the adolescent population[92, 93]. Continuing usage of biomass fuels at home[94], high levels of pollution and smoking add to significant disease burden.

Computerized Clinical Decision Support System (CCDSS)

Computerized Clinical Decision Support Systems (CCDSS) constitute any fragment of software that enables an analysis of information pertaining to clinical situations and presents conclusions (guidelines) for the clinician as output information [95, 96]. Clinicians input patient symptoms, result of lab or imaging investigations, and the output generated are the diagnostic and therapeutic recommendations [96, 97]. Computerized decision support systems can broadly be categorized into those that utilize a "knowledge-bank" to assist the physician, and those that utilize statistical and machine learning.

Knowledge-based decision support systems are more traditional, and classically contain a knowledge base, a reasoning interface, and a communications interface.

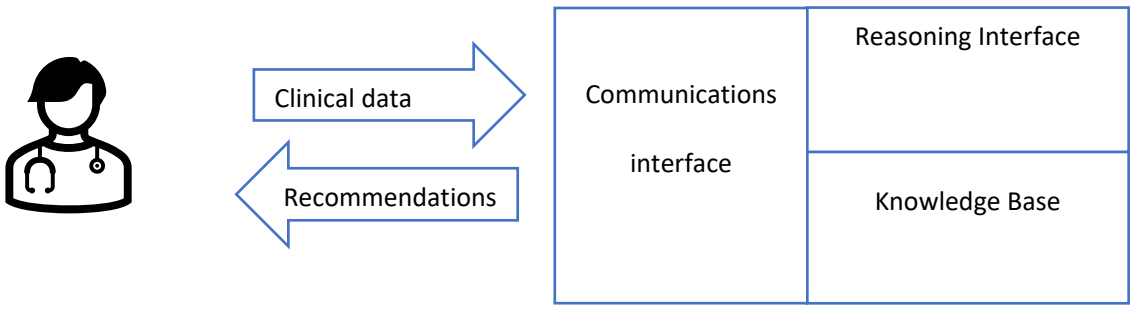

Figure 7: Knowledge-Based CCDSS

The knowledge base consists of well-aggregated data (diagnostic and therapeutic directives derived from literature for instance). The reasoning interface then applies the data from the

knowledge base on to the individual patient's clinical data. The communication interface transports the recommendation to the physician, who ultimately makes a decision. Communication interfaces can either be independent, where the physician has to manually enter patient data, or embedded into the hospital Electronic Medical Record (EMR) system. Decision support systems that are embedded into the hospital EMRs borrow data from the patient's electronic medical record, such as laboratory values, previous diagnoses, current medications and so on.

Nonknowledge based CCDSS still have a communications interface and an analytical interface, but instead of a knowledge base, they use statistical pattern recognition and/or machine learning. Logistic regression is one such example of statistical pattern recognition. Logistic regression is used to predict a binary outcome, based on multiple predictor variables. For instance, a CCDSS based on logistic regression has been used to identify the source, need for intervention, and optimal management strategy in patients presenting with acute gastrointestinal bleeds [98]. Within Artificial Intelligence (AI), machine learning is based on the development and application of algorithms that enable computers to learn through "trained" pattern recognition[99]. There exist multiple machine learning models such as *k*-Nearest Neighbour (kNN) [100, 101], Support Vector Machines (SVM) [102, 103] and Artificial Neural Networks (ANN) [103-105], and they have all been used to design decision support systems.

ANNs were developed to emulate the human thought process [106], and are amongst the most potent branch of machine learning . ANNs consist of nodes (simulation of neurons) that are connected to each other in a weighted manner (corresponding to synapses) [107]. A neural network consists of multiple layers- an input layer, a latent analysis layer, and an output layer.

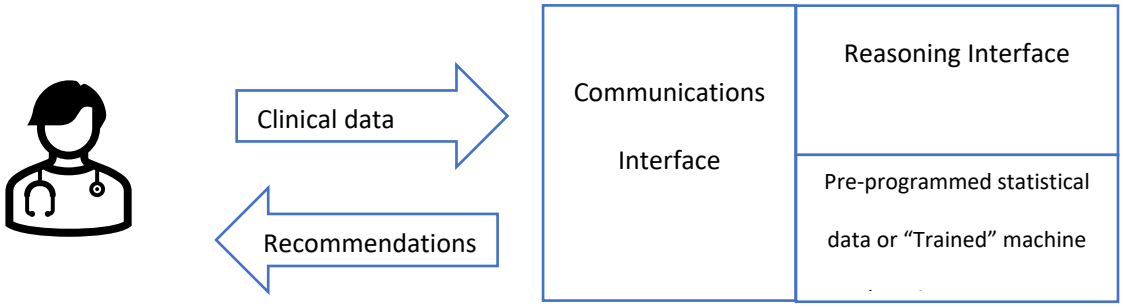

Figure 8: Nonknowledge-Based CDSS

Large amounts of data are fed into the network, and the analysis layer tries to "guess" the connections between the input and the output (for example signs and symptoms against a specific diagnosis) and tests these "guesses" with the output. The end-result is the assignation of "weightage" points for the connections. The network is now said to have been "trained" and can be used on individual cases to determine causal associations.

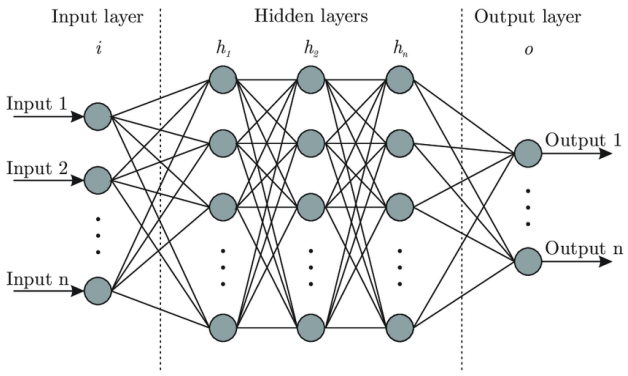

Figure 9: Artificial Neural Network. Image referenced from *[108]*

CCDSS improve diagnostic accuracy, improve treatment safety [109-111], reduce unnecessary diagnostic tests [98, 112, 113], improve the quality of healthcare delivery [112], and lower healthcare costs [112, 114, 115]. While clinical decision support systems have been used yielding good results in the management of asthma [116] and COPD exacerbations [117, 118], there has not been an investigation of stable COPD management at the GP office.

Methodology

Digital Clinical Decision Support Tool: KOLS-kalkulator

The COPD calculator (Kolskalkulator.no) was developed in Bergen in collaboration with the Norwegian Lung and Heart Association. While the calculator has been available online since 2014, this version was tailored to meet our needs to collect study data. The decision support tool is based on the 2019 international GOLD guidelines and the Norwegian COPD guidelines from 2012.

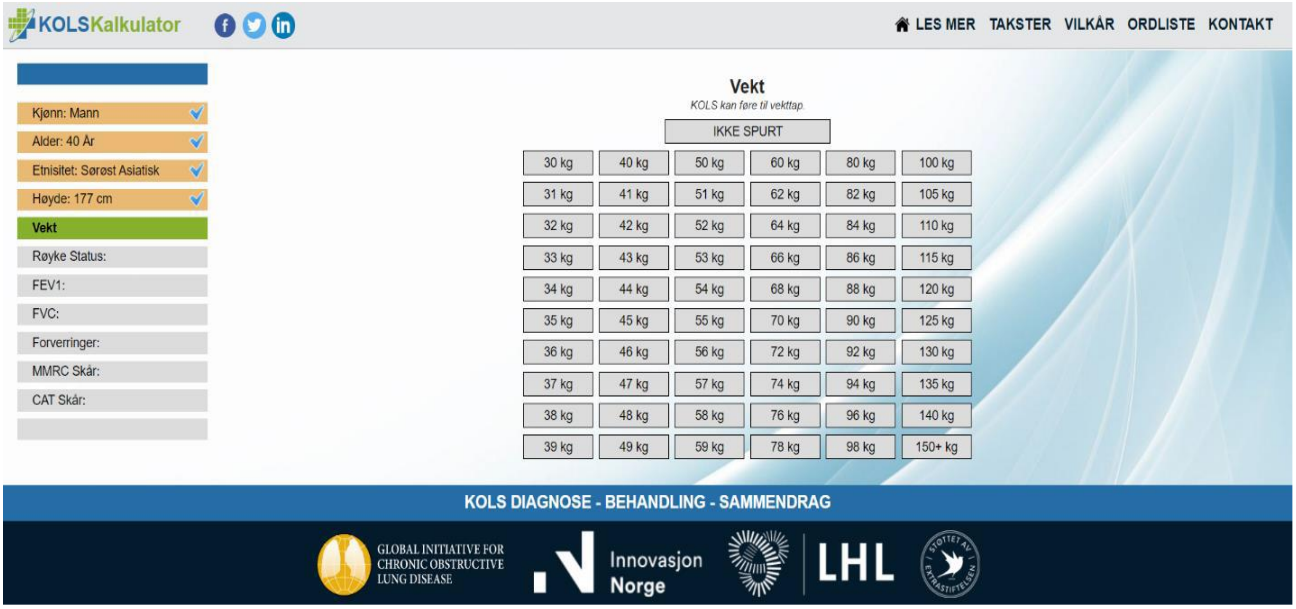

Figure 10: A screenshot from the KOLSKalkulator tool. Based on physician input on various patient parameters, the CDSS returns likelihood of diagnosis, and in case of likely diagnosis, various treatment suggestions.

Based on physician-entered data, the KOLS-kalkulator returned a “Probable diagnosis” in cases where FEV1/FVC ratio was <0.7 or below the lower limit of normal (LLN), and “Diagnosis unlikely” in cases where spirometry pattern was either restrictive or normal. Additionally, GPs received prompt on first-line therapy according to the current ABCD treatment group and a summary of non-pharmacological recommendations in cases where diagnosis was “likely”.

Study Design

This was a randomized controlled pilot study to assess the feasibility of using a digital CDSS to manage COPD patients at the out-patient clinic. Randomized controlled trials are analytical studies where the effect of an intervention is evaluated by measuring outcomes before and

after the intervention has been implemented[119]. Randomized Controlled Trials (RCTS) provide the highest level of evidence of an intervention's efficacy since causal interference can be drawn. Additionally, randomization of study participants allows for the minimization of bias and confounding[120].

Data collection from the patients was done at a single visit in the management course of COPD. This was done to minimize study costs and perform the study in a time-effective manner. While this allowed us to analyze multiple patient variables at the time of data collection, we could not analyze GP behavior over time. COPD is a chronic condition, and our data collection did not include past treatment history of patients, and hence this particular patient visit is not necessarily representative.

Study setting and participants

Bergen municipality (Bergen kommune) is located on the western Norwegian coast. The city had a population of 283.929 at the start of 2020[121], and is served by 238 GP practices. GPs were recruited by personal invitation from the greater Bergen area, using convenience sampling.

A total of 36 GPs were recruited and, using a randomization software, randomized into intervention and control groups in a 1:1 ratio. The GPs in the intervention group used a digital CDSS for decision support. The GPs randomized into the control group continued providing standard care and did not use the decision-support tool. Both groups were asked to include

their next 5-10 patients with COPD, both newly diagnosed and established COPD, to participate in the study. Written, informed consent was obtained from all GPs and patients.

In the control arm, only the transcutaneous oxygen saturation (pulse oximetry reading) and the spirometry measurements (FEV1 and FVC) were recorded. Within the intervention arm, GPs input the following data into the web-calculator tool:

1. Age, sex, weight, height, smoking status, ethnicity
2. Number of moderate/severe COPD exacerbations over the last year
3. The Medical Research Council Dyspnea Scale Questionnaire (MRC score)
4. COPD Assessment Test (CAT score)
5. Spirometry Data (FEV1 and FVC)

In both arms, at the end of the GP consultation, patients were handed an iPad-tablet to answer a few questions.

Figure 11: Screenshot from the iPad questionnaire filled out by the patients at the end of their consultation.

A follow-up questionnaire was sent to the GPs 1 year after conclusion of the study where we asked for the GPs age, sex, when they received their medical license, if they had used the CDSS following the completion of the study, and if that was the case, how useful they found it on a scale from 1-10.

Statistical Analysis

Given that this was a pilot feasibility study, no formal power-calculation on the sample size was performed. All endpoints were included. Statistical analysis was performed in IBM SPSS Statistics, version 26 (SPSS, Inc., Chicago, IL USA). Tests for normality (Wilks-Shapiro test) were performed on continuous data. Parametric tests (Independent analysis T-tests) were performed on data with normal distribution, and non-parametric (Mann-Whitney U and chi-square) tests were performed on data that were not normally distributed.

Results and Extension of Study to LMICs

In the intervention group, no (0%) COPD misdiagnosis occurred, 98% received vaccine recommendations, and all smokers (N=39) received smoking cessation advice. The standard of care group had 23% misdiagnosis ($p< 0.001$), only 67% received vaccine recommendations ($p<0.001$), and 87% smoking cessation advice ($p= 0.022$). While 31% of all patients received medication that was not in keeping with the guidelines, there were no differences between the

two groups. A majority of GPs who responded to the follow-up questionnaire continued to use the KOLS-kalkulator in their practice after the conclusion of the study.

While the use of CCDSS in resource-restrained countries is a relatively new practice, there is still good evidence for its success in the management of both infectious and non-infectious diseases. Out of every 100 inhabitants in developing nations, 65 had an active mobile-broadband coverage and 99 had an active mobile-subscription in 2020 [122]. And indeed mHealth, defined as the practice of medicine and public health through the support of mobile devices [123], has been widely used in LMICs [124-128]. Given the disproportionate disease burden of COPD in LMICs, utilisation of CCDSS could improve patient outcomes.

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Appendices

1. Informed consent for the patients

NOR-COPD CALC STUDIEN

MULIGE FORDELER OG ULEMPER

For gruppen hvor legen bruker det interaktive verktøyet, vil fordelen ved å delta i studien være at tilbakemeldinger fra dataprogrammet gir kvalitetssikring om behandling er i tråd med anbefalinger i norske og internasjonale veiledere. Gruppen behandlet av leger uten bruk av beslutningsstøtteverktøy, vil motta god behandling av leger som er interessert i sykdommen kols og av den grunn har ønsket å delta i studien. Ulemper for deg som pasient er at du må bruke 15 minutter av din tid etter legetimen til å besvare spørsmål på et nettbrett.

FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE SITT SAMTYKKE

Det er frivillig å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Dette vil ikke få konsekvenser for din videre behandling. Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte Bjarte Kjell Nore, tel 906 62 161 / bjarte@kbbmedic.no.

HVA SKJER MED INFORMASJONEN OM DEG?

Opplysningene som registreres om deg skal kun brukes slik som beskrevet i hensikten med prosjektet. Du har rett til innsyn i hvilke opplysninger som er registrert om deg og rett til å få korrigert eventuelle feil i de opplysningene som er registrert. Du har også rett til å få innsyn i sikkerhetstiltakene ved behandling av opplysningene. Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste. Det er kun Bjarte Nore og Bernt B. Aarli som har tilgang til denne listen. Opplysningene om deg vil bli anonymisert eller slettet senest fem år etter prosjektslutt

POTENSIELLE INTERESSEKONFLIKTER

Prosjektleder Bernt Bøgvald Aarli og Prosjektdeltakerne Kjell Bjarte Nore og Kjell Garatun-Tjeldstø har utviklet beslutningsverktøyet som brukes i studien med finansiering fra ExtraStiftelsen med støtte av Landsforeningen for hjerte og lungesyke. Beslutningsverktøyet er en åpen, interaktiv webside som er gratis i bruk. Forskningsprosjektet har mottatt støtte fra legemiddelfirmaet Boehringer Ingelheim. Fra legemiddelselskapet er interessen for prosjektet av vitenskapelig art. Målet er å undersøke om et digitalt beslutningsverktøy kan bidra til mer presis behandling av KOLS. Prosjektet er ikke kommersielt eller salgsfremmende.

FORSIKRING

Du vil være dekket av pasientskadeloven. Det tegnes ikke tilleggsforsikring for deltagere av studien.

GODKJENNING

Regional komité for medisinsk og helsefaglig forskningsetikk har vurdert prosjektet, og har gitt forhåndsgodkjenning REK 2018/947. Etter ny personopplysningslov har dataansvarlig Universitetet i Bergen og prosjektleder Bjarte Nore et selvstendig ansvar for å sikre at behandlingen av dine opplysninger har et lovlig grunnlag. Dette prosjektet har rettslig grunnlag i EUs personvernforordning artikkel 6a og artikkel 9 nr. 2 og ditt samtykke. Du har rett til å klage på behandlingen av dine opplysninger til Datatilsynet.

NOR-COPD CALC STUDIEN

JEG ER VILLIG TIL Å DELTA I PROSJEKTET

Sted og dato

Deltakers signatur

Deltakers navn med trykte bokstaver

Jeg bekrefter å ha gitt informasjon om prosjektet

Sted og dato

Signatur

2. Informed consent for general practitioners

NOR-COPD CALC STUDIEN, 09.03.2021

FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKTET - LEGER

KOLSKALKULATOR STUDIEN

Takk for at du som lege deltok i kolskalkulator studien i 2019. Studiens hadde som formål er å undersøke nytten av et digitalt beslutningsstøttehjelpemiddel i behandling av KOLS-pasienter. Som oppfølging av denne studien ber vi deg besvare et kort spørreskjema.

Overlege Bernt B. Aarli ved Lungeavdelingen, Haukeland Universitetssjukehus og Bjarte Nore ved Bergen legevakt står ansvarlig for studien med Universitetet i Bergen som forskningsansvarlig institusjon.

KOLS er en av våre store folkesykdommer. Imidlertid har retningslinjer for diagnostisering og behandling av kols ikke blitt oppdatert siden de ble publisert i 2012, og det er usikkert i hvilken grad de følges.

HVA INNEBÆRER PROSJEKTET?

I prosjektet ber vi deg besvare 5 spørsmål: Alder, år for autorisasjon, kjønn. Både de som brukte dataverktøyet i studien og de som ikke brukte det vil nå blir spurt om de har brukt dataverktøyet i løpet av 2020 og i så fall om dataverktøyet ble oppfattet som nyttig/unyttig. Mål med denne undersøkelsen er undersøke om det er ulikheter i hvordan denne pasientgruppen blir behandlet i forhold til hvor lenge man har jobbet som lege, og for dem som benyttet det digitale beslutningsstøttehjelpemiddelet, hvorvidt det ble opplevd som nyttig.

MULIGE FORDELER OG ULEMPER

Det tar ca 1 minutt å besvare etteroppfølgingsspørreskjemaet som er avpersonifisert. Deltagelse medfører således svært liten ulempe. Besvarelse av et skjema gir heller ingen fordeler.

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Det er frivillig å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte Bjarte Kjell Nore, tel 906 62 161 / bjarte@kbbmedic.no.

HVA SKJER MED INFORMASJONEN VI FÅR FRA DEG?

Opplysningene som registreres om deg skal kun brukes slik som beskrevet i hensikten med prosjektet. Du har rett til innsyn i hvilke opplysninger som er registrert om deg og rett til å få korrigert eventuelle feil i de opplysningene som er registrert. Du har også rett til å få innsyn i sikkerhetstiltakene ved behandling av opplysningene. Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste. Det er kun Bjarte Nore og Bernt B. Aarli som har tilgang til denne listen. Opplysningene om deg vil bli anonymisert eller slettet senest fem år etter prosjektslutt, med andre ord i 2024.

NOR-COPD CALC STUDIEN, 09.03.2021

POTENSIELLE INTERESSEKONFLIKTER

Prosjektleder Bernt Bøgvald Aarli og Prosjektdeltakerne Kjell Bjarte Nore og Kjell Garatun-Tjeldstø har utviklet beslutningsverktøyet som brukes i studien med finansiering fra ExtraStiftelsen med støtte av Landsforeningen for hjerte og lungesyke. Beslutningsverktøyet er en åpen, interaktiv webside som er gratis i bruk. Forskningsprosjektet har mottatt støtte fra legemiddelfirmaet Boehringer Ingelheim. Fra legemiddelselskapet er interessen for prosjektet av vitenskapelig art. Målet er å undersøke om et digitalt beslutningsverktøy kan bidra til mer presis behandling av KOLS. Prosjektet er ikke kommersielt eller salgsfremmende.

FORSIKRING

Det tegnes ikke tilleggsforsikring for deltagere av studien.

GODKJENNING

Regional komité for medisinsk og helsefaglig forskningsetikk har godkjent prosjektet, REK 2018/947.

Etter ny personopplysningslov har dataansvarlig, Haukeland Universitetssjukehus og prosjektleder Bjarte Nore et selvstendig ansvar for å sikre at behandlingen av dine opplysninger har et lovlig grunnlag. Dette prosjektet har rettslig grunnlag i EUs personvernforordning artikkel 6a og artikkel 9 nr. 2 og ditt samtykke.

Du har rett til å klage på behandlingen av dine opplysninger til Datatilsynet.

JEG ER VILLIG TIL Å DELTA I PROSJEKTET

Det benyttes digital signering via Posten signering

3. Follow-up questionnaire for general practitioners 1 year after study completion

UNIVERSITETET I BERGEN

KOLSKALKULATOR OPPFØLGINGSSPØRRESKJEMA

Takk for at du deltok i kolskalkulatorstudien i 2019. Som oppfølging til denne studien ber vi deg besvare 5 spørsmål. Informasjon du oppgir blir behandlet anonymt. Bruk ID nummer oppgitt på e-posten med linken til dette skjema for ID og ikke navn.

ID nummer

Alder

Kjønn

- Mann
- Kvinne

Årstall for autorisasjon som lege

Har du året etter studien i 2020 benyttet kolskalkulator.no ?

- Ja
- Nei

Dersom du svarte ja på forrige spørsmål, på skala fra 1-10 hvor nyttig opplevde du dette verktøyet? (1-unyttig, 10 nyttig) La stå åpent dersom du ikke har benyttet kolskalkulator i 2020

Send

4. Ethical Clearance from REK- Case number 2018/947

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK midt	Linda Tømmerdal Roten	73597506	02.11.2018	2018/947/REK midt
			Deres dato:	Deres referanse:
			13.10.2018	

Vår referanse må oppgis ved alle henvendelser

Bernt Bøgvald Aarli
Haukeland universitetssykehus/ Universitetet i Bergen

2018/947 Beslutningsstøtteverktøy ved kolsbehandling
Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble første gang behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK midt) i møtet 06.06.2018. Vedtak ble da utsatt fordi prosjektet hadde noen uklarheter knyttet til mulige interessekonflikter. Prosjektleder ble bedt om å gi en tilbakemelding. Tilbakemelding ble mottatt 13.10.2018. Tilbakemeldingen ble vurdert av komiteens representant for sykepleie på fullmakt med hjemmel i forskrift om behandling av etikk og redelighet i forskning § 10. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikklovens § 4.

Komiteens opprinnelige prosjektsammendrag
Kronisk obstruktiv lungesykdom (KOLS) har blitt en av de nye store folkesykdommene også i Norge. Imidlertid er retningslinjene for diagnostisering og behandling av KOLS ikke oppdatert siden de ble publisert i 2012, og det er usikkert om de også har blitt fulgt. Denne studiens formål er å undersøke nytten av et digitalt hjelpemiddel for å gi leger best mulig beslutningsstøtte i behandling av KOLS-pasienter. Legene deles i to grupper, hvorav den ene gruppen leger skal bruke et dataverktøy som gir tilbakemeldinger med anbefalt behandlingstiltak skreddersydd til den den enkelte pasient. Den andre gruppen leger skal kun oppgi resultater fra spirometri og oksygenmetning målt med en fingerelektrode og får ingen tilbakemelding. For pasientene innebærer deltakelse at de må fylle ut spørreskjema for kartlegging av symptomer (på nettbrett), gjennomføre spirometriundersøkelse og måling av oksygenmetning. I tillegg registreres pasientens vekt og høyde. Studien er samtykkebasert, og utgår fra Haukeland universitetssykehus.

Oppsummering av prosjektleders tilbakemelding
I tilbakemeldingen har prosjektleder redegjort for Boehringer Ingelheims rolle i prosjektet, og presisert at firmaets interesse for studien er av vitenskapelig art og ikke kommersiell eller salgsfremmende. Videre ber prosjektleder om at kravet om ekstern monitor revurderes fordi det her kun er snakk om en avgrenset pilotstudie og ikke legemiddelutprøving eller utprøving av medisinsk utstyr (dokumentasjon er vedlagt tilbakemeldingen). Prosjektleder skriver også at siden verktøyet er ment å brukes i allmennpraksis vil monitorering undergrave en evaluering av den kliniske nytten av det. Når en større studie er aktuell å gjennomføre vil det være naturlig og behov for å involvere eksterne monitorer. Reviderte informasjonsskriv og forskningsprotokoll var vedlagt tilbakemeldingen. Prosjektleder opplyste om at Universitetet i Bergen vil være forskningsansvarlig institusjon og at kontaktperson er dekan ved det medisinske fakultet.

Forsvarlighet
Komiteen har vurdert tilbakemelding, søknad, forskningsprotokoll, målsetting og plan for gjennomføring. Komiteen mener at prosjektleder har gitt grundig og tilfredsstillende informasjon om Boehringer Ingelheims rolle i prosjektet, og at kravet om å involvere en uavhengig monitor i det avgrensede pilotprosjektet kan frafalles. Informasjonsskrivene er revidert i henhold til komiteens punkter, men det bes om noen ytterligere endringer i skrivene (se eget avsnitt under). Komiteen har ellers ingen forskningsetiske innvendinger til

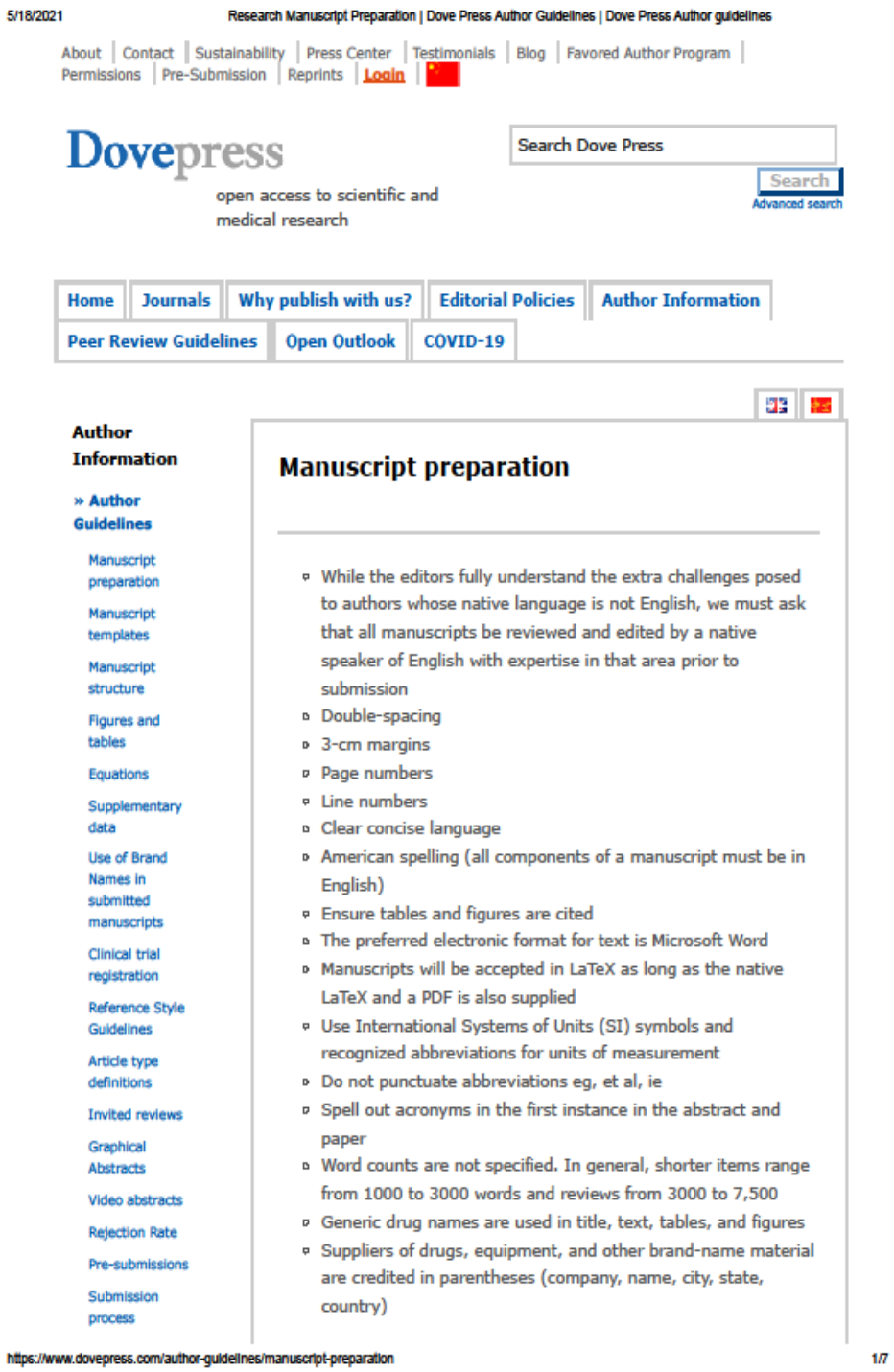
Besøksadresse:
Fakultet for medisin og helsevitenskap Mauritz Hansens gate 2, Øya helsehus

Telefon: 73597511
E-post: rek-midt@ntnu.no
Web: http://helseforskning.etikkom.no/

All post og e-post som inngår i saksbehandlingen, bes adressert til REK midt og ikke til enkelte personer

Kindly address all mail and e-mails to the Regional Ethics Committee, REK midt, not to individual staff

5. International Journal of COPD- Manuscript Guidelines. Available at: [Manuscript Preparation Guidelines]



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Role of a digital clinical decision support system in general practitioners' management of COPD in Norway

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Correspondence

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Abstract:

BACKGROUND: The study investigated if a web-based clinical decision support system (CDSS) tool increased general practitioner's (GPs) adherence to GOLD guidelines in the management of patients with chronic obstructive pulmonary disease (COPD), compared with standard of care.

METHODS: GPs were randomized to either a single use of the CDSS or continuing standard of care. The clinical recommendations of the CDSS were based on the GOLD guidelines and provided suggestions for treatment and management of COPD. Data was collected digitally from GPs and patients in both groups using a tablet computer. A follow-up questionnaire was sent to the GPs one year after conclusion of the study.

RESULTS: 25 GPs (31% women, mean age 41 years) participated, N=12 randomized to using the CDSS tool and N=13 followed standard of care when assessing their next 5-10 COPD patients. 149 patients with presumed COPD were included (N=88 CDSS group, N=61 standard of care group). In the CDSS group, no (0%) COPD misdiagnosis occurred, 98% received vaccine recommendations, and all smokers (N=39) received smoking cessation advice. The standard of care group had 23% misdiagnosis ($p< 0.001$), only 67% received vaccine recommendations ($p<0.001$), and 87% smoking cessation advice ($p= 0.022$. 31% of patients did not receive medication as recommended according to guidelines with no significant differences between the groups. GPs rated the CDSS as very useful. Mean usage time was 3 min, 26 sec. A majority (13/19, 68%) of GPs continued using the CDSS after conclusion of the study. CAT score identified twice as many patients as having more symptoms than the mMRC indicating the added value of multi-item questionnaire.

CONCLUSION: Use of the CDSS was associated with preventing misdiagnosis of COPD and improved adherence to recommended non-pharmacological measures, but a one-time use did not improve pharmacological treatment considerations.

Chronic Obstructive Pulmonary Disease (COPD) is a preventable and modifiable disease, characterized by irreversible, or poorly reversible, airflow obstruction, in addition to persistent respiratory symptoms due to airway and/or alveolar abnormalities. The disease is caused by prolonged exposure to noxious particles or gases, primarily from cigarette smoking [1]. COPD contributes heavily to the morbidity and mortality rate worldwide. In 2019, it was the third-highest cause of all deaths globally, with over 3 million fatalities [2], accounting for 6% of all the deaths. In a population based study in Norway in people aged >40 years performed in 2015-2016, 6% had COPD using the Lower Limit of Normal (LLN) criteria of the FEV_1/FVC ratio and the Global Lung Index (GLI 2012) [3], which correspond to 150,000 people. However, only half are currently receiving treatment for COPD according to the national prescription database, reflecting that a significant proportion are being undiagnosed, as is also seen in many other countries [4, 5]. This discrepancy could be related to several factors. One reason may be that the general physicians (GPs) who are the primary care givers for patients with COPD, are overwhelmed by a rising number of different national, regional and international guidelines across many different disease-areas, for diagnostics, treatment and follow-up, which increases the risk of information overload for physicians and risk for clinical inertia [6].

As early diagnosis of COPD is recommended [7], and establishing early management-strategies and initiating treatment has been seen to reduce both morbidity and mortality [8], tools to support the GPs identifying and managing people with COPD are needed, and a Clinical Decision Support System (CDSS) could be one.

CDSS have various definitions. An early paper in clinical decision making defined CDSS as a software that analyses clinical information and presents conclusions (guidelines) for clinicians as output information [9]. The input may be patient symptoms, the results of lab or imaging investigations. Generated output may be diagnostic or therapeutic recommendations. Previous interventions with CDSS have shown that if performed successfully, such tools may increase adherence to evidence-based guidelines, reduce healthcare costs, lead to a reduction in unnecessary diagnostic procedures being performed, and reduce inappropriate pharmacological treatment [10-12]. CDSS have been used in the diagnosis and management of chronic conditions including hypertension [13], deep vein thrombosis [14], asthma [15], and type 2 diabetes [16, 17]. A meta-analysis of a range of studies investigating the use of CDSS on patients with asthma showed a positive impact of the intervention on the management of the disease [18]. At least two studies using a CDSS in managing acute exacerbation of COPD in the emergency department [19, 20] has been published, whereas there is a lack of studies investigating the impact of CDSS at the primary care level for managing stable COPD.

The present study explores the feasibility of an existing web based CDSS tool for COPD in general practice. Our main goal was to investigate if such a tool would improve the accuracy of diagnosis, and whether non-pharmacological, and pharmacological treatment was aligned with COPD guidelines.

Methods

Participants

We recruited GPs by personal invitation from the greater area of the West-Norwegian City Bergen, during the month of March 2019. Bergen has a population of approximately 275000, and 238 GP practices. The invited GPs were randomized into two groups, one using an online digital CDSS for decision support, the other continued providing standard of care without the CDSS. Both groups were asked to include their next 5-10 patients with newly diagnosed or established COPD to participate in the study. A follow-up questionnaire was sent to the GPs one year after the conclusion of the study. Written, informed consent was obtained from all patients and also from the GPs who completed the follow-up questionnaire. The study was approved by the Regional Committees for Medical and Health Research ethics, REK midt (REK 2018/947) in Norway and performed in accordance with the Declaration of Helsinki. A flow chart illustrating inclusion of patients and GPs for the study is shown in figure 1.

About the digital CDSS

The digital CDSS was based on the 2019 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines and the Norwegian COPD guidelines from 2012. The CDSS was developed by our group in cooperation with the Norwegian Heart and Lung Association. While the CDSS has been freely available for use since 2014, its use has not been widespread. For the purpose of the study, the existing web-based CDSS was customized to a "study-version" for data collection purposes. In addition, data was collected digitally, in both groups using a 9.7-inch tablet computer (iPad 6th generation, Apple Inc, Cupertino, California, USA), transferring data anonymized to a secure study database.

Data collection and system-feedback for the GPs using the CDSS

GPs entered the patient's sex, age, ethnicity, height, weight, smoking status, number of exacerbations requiring oral steroids and/or antibiotics or hospitalization the past year, the modified Medical Research Council dyspnea scale score (mMRC) [21], and the COPD Assessment Test score (CAT) [22]. During the clinic visit all patients performed spirometry recording the forced expiratory volume in 1 second (FEV_1) and the forced vital capacity (FVC).

The system-generated feedback to the GP included a summary of the results entered in a tabulated manner. If spirometry was consistent with airflow obstruction, defined as having a FEV_1/FVC ratio <0.7 or below the lower limit of normal (LLN) using the GLI 2012 [3], the diagnosis of COPD was reported as "Probable" under the condition that the airflow obstruction was persistent. The severity of airflow limitation and the ABCD patient group, according to the GOLD guidelines was also provided [1]. If no obstruction was found on spirometry, the diagnosis of COPD was labelled "Unlikely" with spirometry-feedback either as "Normal" or "Restrictive pattern".

Treatment advice based on GOLD ABCD group for the individual patient was provided (i.e., first line medication and additional medication suggestions in case of symptoms of dyspnea or exacerbations). Finally, a summary of other COPD management topics (smoking cessation recommendations in smokers; physical exercise, pulmonary rehabilitation, and flu vaccination) was listed. At the end of the consultation, the GP handed over the iPad to the patients to complete the study questionnaires.

Data collection procedures for the GPs not using the CDSS

At the end of a COPD consultation the GP filled out spirometry results, current medication used for COPD on a tablet and then handed it over to the patient to complete the study questionnaires.

Patient reported data

The modified Medical Research Council dyspnea scale score (mMRC), the COPD assessment test (CAT), questions on exacerbation history, physical activity habits, and smoking status. All patients were asked if they had received information on physical activity, pulmonary rehabilitation, and/or flu vaccination during the consultation. Current smokers were asked if smoking cessation had been discussed.

Follow-up data from GPs

A follow-up questionnaire was sent to the GPs 1 year after conclusion of the study where we asked for the GPs age, sex, year of obtaining medical license, if they had used the CDSS following the completion of the study, and if that was the case, how useful they found it on a scale from 1-10.

Definition of adherence to GOLD guidelines

Categorization in GOLD treatment groups was based on the degree of symptoms evaluated by both CAT and mMRC score in addition to exacerbation history [1]. We defined appropriate medication as receiving medication as described by the GOLD ABCD medication group with/without add-ons for dyspnea and/or exacerbations and “undertreated” if receiving less treatment. Patients were considered to be treated outside of the GOLD guidelines if they were prescribed either of the following: i) oral corticosteroids (OCS) in stable COPD, ii) inhaled

corticosteroids (ICS) in a mono inhaler, iii) PDE4 inhibitor when FEV1 >50%, iv) 2 or more drugs belonging to the same medication class, v) if using both a short and a long-acting muscarinic antagonist, vi) if using montelukast for COPD.

Definition of misdiagnosis of COPD

If no obstruction was found on spirometry, the diagnosis of COPD was considered misdiagnosed.

Statistical analysis

Statistical analysis was performed in IBM SPSS Statistics, version 26 (SPSS, Inc., Chicago, IL USA). Data is presented as mean (standard deviation), median (quartiles), or percentage. Independent samples T-test was used comparing data with a normal distribution, while non-parametric data were compared with independent samples Mann-Whitney U test and Chi-square test.

Results

Figure 1 shows the study design. Of 36 GPs invited, 25 participated. 13 GPs were randomized to use the CDSS tool (31% women, mean age 41 years) and 12 to continue standard of care without the CDSS (33% women, mean age 50 years). 149 patients were included, N=88 in the CDSS group 37 women, (mean age 72 years) and N=61 in the control group without the digital CDSS (30 women, mean age 68 years). 19 GPs (76% completed a follow-up questionnaire one year after the study).

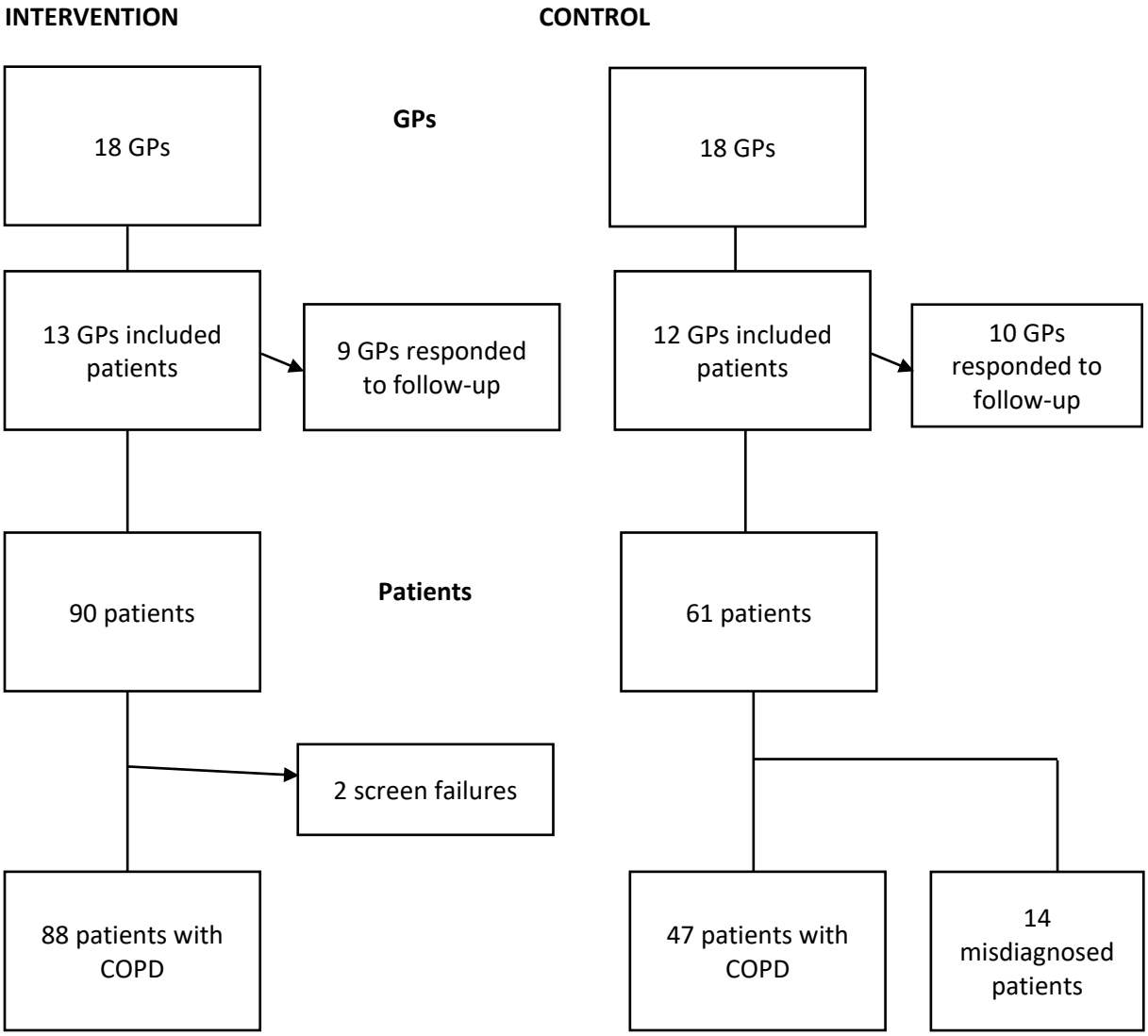

Figure 1: Flow chart describing inclusion of both general practitioners (GPs) and patients with chronic obstructive pulmonary disease (COPD) in the study. Feedback from the digital clinical decision support system (CDSS) prevented inclusion of screen failures among GPs using the CDSS if spirometry did not show airway obstruction.

Table 1 shows the characteristics of the GPs and patients in the intervention and control groups. Characteristics of the patients were mostly comparable. There were no misdiagnoses in the intervention group, while in the control group almost one-fourth (n=14) of the patients were diagnosed as having COPD despite spirometry being normal (n=11) or restrictive (n=3). The COPD patients had a mean FEV1 1.5L (0.7) and FVC 2.8L (1.0). Median CAT score 13 (9). Characteristics of misdiagnosed patients were comparable for most characteristics as the COPD

patients, differing only in spirometric results with a mean FEV1 2.8L (1.3) and FVC 3.1L (1.3), table 1.

Table 1. Characteristics of patients and GPs in the intervention and the control group

Patient Characteristics	**Intervention**	**Control**	**p-Value**
N	88	61	
Age (years)	72 (9)	68 (9)	.014
Height (cm)	168 (9)	171 (9)	ns
Women	59 %	49 %	ns
Current smokers	44 %	38 %	ns
FEV1 (L)	1.5 (0.6)	1.9 (1.0)	ns
FVC	2.6 (0.9)	3.0 (1.2)	ns
FEV1/FVC	0.57 (0.11)	0.61 (0.19)	ns
mMRC[a]	1 (1)	1 (1)	ns
CAT[a]	12 (8)	15 (10)	.019
Exacerbations[a]	0 (1)	0 (1)	ns
Obstructive spirometry	100 %	77 %	<.001
Drug Class			
SABA	46 (52%)	40 (66%)	ns
SAMA	4 (5%)	9 (15%)	.030
LABA	60 (67%)	44 (72%)	ns
LAMA	65 (73%)	38 (62%)	ns
ICS	46 (52%)	27 (44%)	ns
GP characteristics			
N[b]	9	10	
Age[b]	49 (12)	39 (9)	ns
Women[b]	33 %	40 %	ns
Clinical Experience[b]	17 (12)	11 (8)	.023
Number of patients[b]	8 (4)	5 (1)	ns

Intervention group defined as general practitioners (GP) using a digital clinical decision support system (CDSS). The control group continue standard care without the CDSS. Data presented as mean (standard deviation) unless otherwise stated. FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; mMRC, modified Medical Research Council dyspnea scale score; CAT, COPD Assessment Test. [a] Median (interquartile range). †Only GPs who answered follow-up questionnaire and signed consent form. [b] Only GPs who answered follow-up questionnaire and signed consent form.

19 GPs (76%) completed a follow up questionnaire one year after the study. 6 of the GPs in the non-CDSS group had misdiagnosed one or more patients. The GPs who had included misdiagnosed patients were younger, mean age 35 (7) years and had their license to practice

medicine for a shorter period 5.3 (2.9) years compared with GPs with no misdiagnosis, mean age 45 (11) years, and having had their medical license for 17 (10) years (p=0.05).

Table 2. Comparison of characteristics between COPD and misdiagnosed patients

Patient Characteristics	**COPD patients**	**Misdiagnosed patients**	**p-Value**
Subjects(n)	135	14	
Age(years)	71 (9)	67 (11)	.014
Height(cm)	169 (9)	169 (10)	ns
Women	55 %	57 %	ns
Current smokers	42 %	36 %	ns
FEV1(L)	1.5 (0.7)	2.8 (1.3)	<.001
FEV1 (% predicted)	58 (21)	99 (26)	<.001
FVC(L)	2.8 (1.0)	3.1 (1.3)	ns
FEV1/FVC	0.56 (0.11)	0.87 (0.10)	<.001
mMRC[a]	1 (1)	1 (1)	ns
CAT[a]	13 (9)	16 (11)	ns
Exacerbations[a]	0 (1)	0 (2)	ns
GP characteristics			
N	13	6	
Age[b]	45 (11)	35 (7)	.004
Women[b]	37 %	50 %	ns
Clinical experience†	17 (10)	5.3 (2.9)	<.001

Data presented as mean (standard deviation) unless otherwise stated. FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; mMRC, modified Medical Research Council dyspnea scale score; CAT, COPD Assessment Test; GP, general practitioner. [a]Median (interquartile range). [b]Only GPs who answered follow-up questionnaire and signed consent form.

Symptom questionnaires assessment

A moderately strong positive correlation was found between the mMRC and the CAT symptom scores, *r*=0.47, figure 2. However, self-reported dyspnea using the mMRC questionnaire identified only 51 patients (34%) as symptomatic (mMRC ≥2), while the composite CAT score (CAT ≥10), identified 110 patients (73%) as symptomatic. Different proportions of patients in each ABCD treatment group were found when using CAT and mMRC, figure 3. Using the mMRC 59% were defined in group A. Using the CAT score this group was reduced to 27%, leaving group B as the largest, 55%. Using CAT score, group C was almost eliminated.

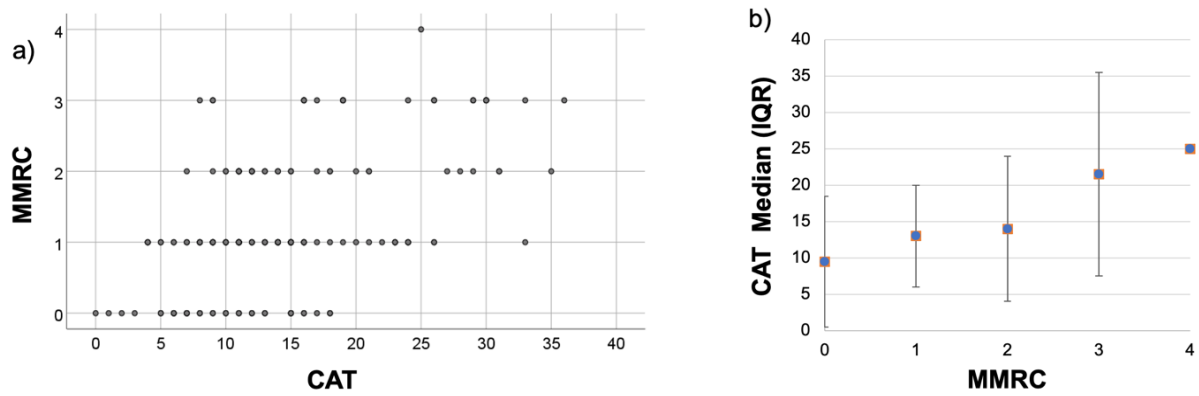

Figure 2: a) Correlation between the COPD assessment test (CAT) and the modified Medical Research Council (mMRC) dyspnea scale scores (N=149), *r* = 0.47, P <0.001. b) Distribution of CAT scores (median) according to the mMRC score. Error bars represent the interquartile range (IQR).

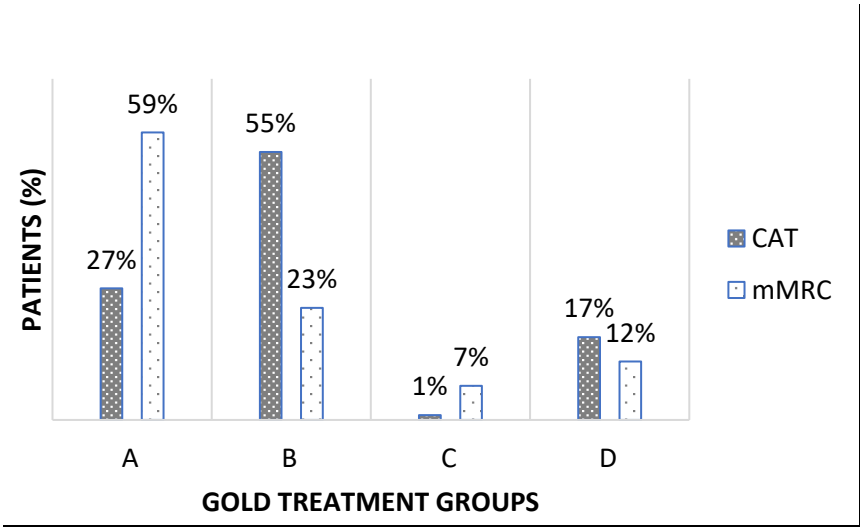

Figure 3: Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) ABCD treatment groups in COPD patients defined a) by the COPD assessment test (CAT) score and b) by the modified Medical Research Council (mMRC) dyspnea scale score, misdiagnosed patients excluded (N=135).

Pharmacological treatment

Pharmacological treatment with the various COPD medications is presented in table 1. There were no notable differences in the prescription pattern between the two groups, although patients in the control group were prescribed SAMA more often (15% versus 5%). Almost a third (31%) of the patients did not receive medication according to GOLD guidelines, with no significant differences between the groups. Most commonly, they were undertreated (17%),

receiving ICS in a mono-inhaler (8%), or receiving two different medications belonging to the same group of medication (7%), figure 4. Two patients were on oral corticosteroids and an ICS mono-inhaler.

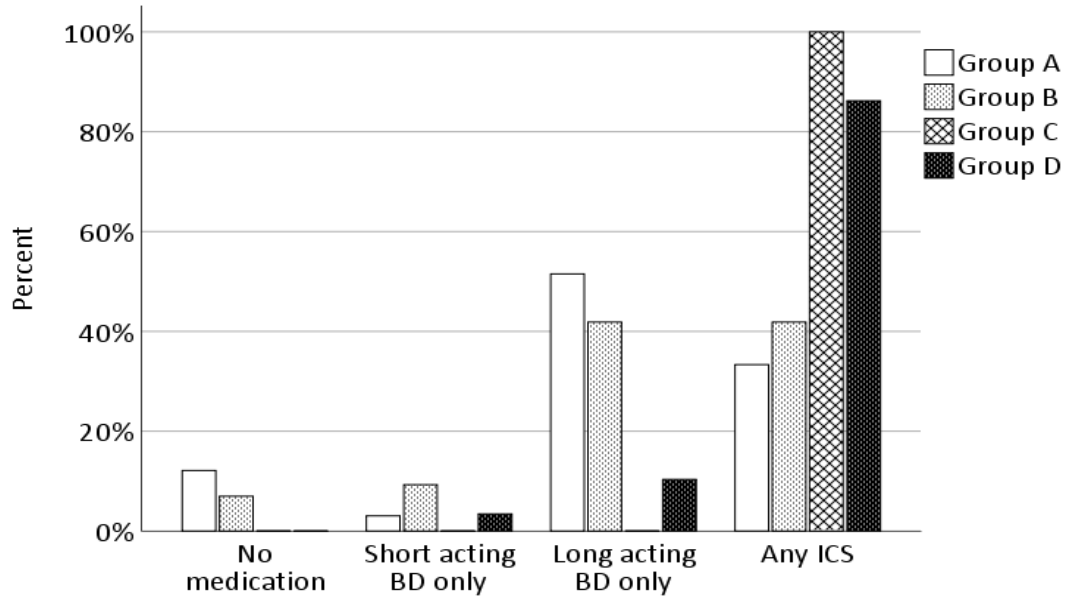

Figure 4: Medication use in the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) ABCD treatment groups generated using the COPD Assessment Test for symptom evaluation. BD, bronchodilator; ICS, inhaled corticosteroid.

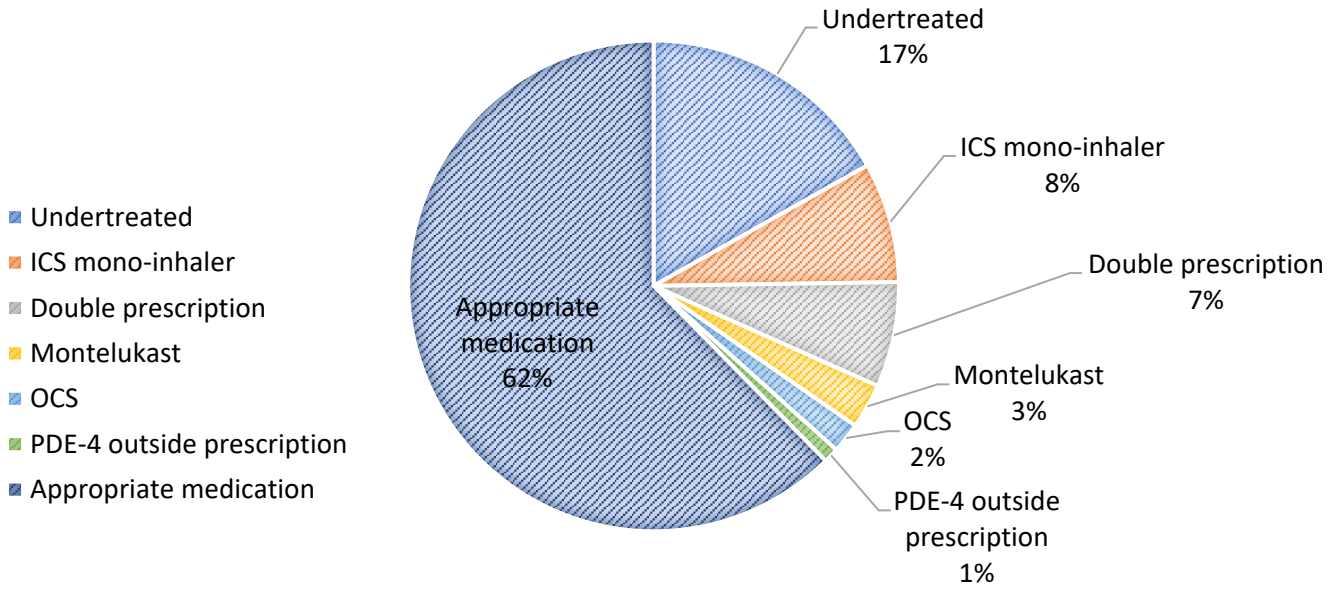

Figure 5: Pie chart showing medication among the patients. Appropriate medication defined as receiving medication as described by the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) ABCD medication group with/without add-ons for dyspnea and/or exacerbations. ICS, Inhaled Corticosteroid; PDE4: Phosphodiestase-4 inhibitor; OCS, Oral Corticosteroid.

Non-pharmacological interventions

A comparison of non-pharmacological interventions between the two groups is shown in table 3. Significant differences between the groups were observed for flu vaccination and smoking-cessation recommendations. All current smokers in the intervention group were offered smoking cessation advice and 98% flu vaccination advice, compared with 87% for smoking cessation and 67% for vaccine recommendations in the control group.

Table 3. Non-pharmacological treatment

Non-pharmacological treatment	**Intervention**	**Control**	**p-Value**
Smoking Cessation[a]	39 (100%)	20 (87%)	.022
Physical activity	73 (82%)	54 (89%)	ns
Pulmonary rehabilitation	13 (15%)	12 (20%)	ns
Flu vaccination	87 (98%)	41 (67%)	<.001

Intervention group defined as general practitioners using a digital clinical decision support system (CDSS). The control group continue standard care without the digital CDSS. Data reported in absolute numbers (percentage). [a]Among current smokers, N=39 in the intervention group and N=23 patients evaluated in the control group.

User-satisfaction with the CDSS

Mean time from first input until the GP reached the result page in the CDSS group was 3 minutes and 26 seconds. 13 out of 19 (68%) GPs used the CDSS after conclusion of the study including several GPs in the control group. On the scale from 1-10 of usefulness, the CDSS received a mean rating of 8.6 (1.3). Table 4 shows the characteristics of GPs who continued to use the digital CDSS after study conclusion. GPs not using the CDSS after the conclusion of the study were significantly older and had had their medical license longer (p=0.05), table 4.

Table 4. Characteristics of GPs who continued using the digital CDSS after study conclusion

	Continued use	No use	p-Value
Intervention[a]	5	4	-
Control[a]	8	2	-
Women[a]	54 %	0 %	.024
Age[a]	39 (5)	51 (14)	.026
Clinical experience[a]	9 (4)	21 (4)	.034

Intervention group; general practitioners (GPs) using the digital clinical decision support system (CDSS). Control group, GPs giving standard care without the digital CDSS. Data reported in mean (standard deviation). [a]Only GPs who answered follow-up questionnaire and signed consent form.

Discussion

We investigated if a digital CDSS could increase GPs adherence to guidelines treating patients with COPD. The intervention prevented misdiagnosis, improved adherence to the non-pharmacological measures of smoking cessation and flu vaccination but failed to make an impact on pharmacological considerations. Using the CDSS at a single visit made no significant changes to medication with the exception of a lower short-acting muscarinic antagonists (SAMA) use in the intervention group. As a secondary objective we investigated questionnaires used for symptom assessment. Very different proportions of patients were assigned in each ABCD treatment group when mMRC was used compared with the CAT questionnaire, and only half as many were defined as symptomatic by mMRC.

Multiple studies have investigated adherence of general practitioners to COPD guidelines. There is no uniformity in the adherence of GPs to the guidelines or recommendations [23]. GP practices frequently fail to document lung function in COPD patients [24-26], spirometry is often not performed adequately and may be interpreted incorrectly [27, 28], and inappropriate medication is frequently prescribed [26, 27]. Factors such as lack of adequate knowledge and training, and time constraints are posited to be the major barriers [27]. Educational programs aimed towards improving GPs practice in treating COPD patients do not seem to have a significant impact on diagnostic accuracy or pharmacological therapy [26].

Our study shows that the digital CDSS helped GPs interpreting spirometry results and prevented misdiagnosis in the intervention group. We do not know the exact number of screen failures in the CDSS group, as very few GPs provided this information, but feedback from the CDSS prevented these patients from being included as COPD patients. Most patients who were misdiagnosed in the control group had completely normal spirometry while they shared a similar burden of respiratory symptoms as the COPD patients. This may have contributed to misdiagnosis. GPs with the shortest medical professional career had more COPD misdiagnosis, which may reflect better diagnostic skills with longer experience, although more seasoned GPs also simply may know their patients better.

Even though a third of the patients in the study were either undertreated or received medication not recommended by the GOLD guidelines, the study failed to show differences in the pharmacological management, with one exception; the intervention group prescribed less SAMA. It is possible that the visual presentation on screen was not perceived as important enough by the GPs to justify a change in medication or that the low number of participants made the study underpowered to find a difference. However, for cost and simplicity, the study was performed cross-sectionally, examining the patients at a single point in time only in a series of patient follow-ups, and this might not have been a visit where the GP found it necessary to change medication. A longitudinal design would have been better suited to capture changes in medication, optimally with a duration of 12 months which is the maximum duration of a reimbursed prescription in Norway. It is plausible that the lower prescription of SAMA in the intervention group was due to treatment advice provided by the digital CDSS. If a patient already received a long-acting muscarinic antagonist (LAMA), a "stop" sign would appear on all

SAMA, indicating that no additional effect of a SAMA could be expected from this drug on top of a LAMA.

The intervention did improve adherence to the non-pharmacological recommendations of smoking cessation and flu vaccination. Smoking cessation, vaccinations, physical activity, and pulmonary rehabilitation play important roles in the long-term management of the illness and treatment outcomes. In a busy everyday practice, these recommendations may be forgotten. Showing this information on the summary screen of the CDSS proved to be an effective reminder of non-pharmacological recommendations.

MMRC and CAT are considered equal in classifying COPD patient into the ABCD treatment groups. The eight item CAT score, however, identified twice as many patients in our study as having more symptoms than the mMRC. For this reason, we suggest adding a multi-item questionnaire when evaluating symptoms in patients who otherwise are defined as having a low grade of symptoms by the mMRC score alone (mMRC <2).

As all GPs in Norway use a computer and have an internet connection a digital CDSS can easily be implemented for all clinicians. The digital CDSS was quite fast and received a high mark on usefulness. A majority of the GPs also continued using it after conclusion of the study. It is vital that the software is updated regularly to keep track of the latest changes in evidence-based guidelines and national recommendations. We also warn of a safety concern when using a secondary computer program in addition to a patient file system. When using two systems, there is always a risk that the information in one system does not match with the same person in the other. If integrated into the patient file system, safety concerns regarding identity could

be avoided and data could be retrieved from the patient file system, reducing input time. We also would point out that the low number of GPs and patients participating in the study could have introduced a selection bias and limits the generalizability of the study.

Conclusion

A digital CDSS tool prevented misdiagnosis of COPD in general practice and improved adherence to non-pharmacological interventions of flu vaccination and smoking cessation. The intervention did not influence pharmacological treatment choices. The CAT questionnaire identified twice as many symptomatic patients than the mMRC dyspnea scale score, indicating that a multi-item questionnaire should be added when evaluating symptoms in patients who otherwise are defined as having a low degree of symptoms by the mMRC score alone.

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