An evaluation of screening for COPD against the National Screening Committee criteria

Author:
Sally Cartwright
April 2012
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1. Introduction
This paper reviews the evidence for a UK screening programme for chronic obstructive pulmonary disease (COPD). An NSC policy review has not previously been conducted on COPD, although there has been increasing focus on COPD at a national level.

The Department of Health has recently (July 2011) published *An Outcomes Strategy for Chronic Obstructive Pulmonary Disease and Asthma in England* [1], laying out the government’s approach to tackling the growing burden of these respiratory problems. NICE guidance has also recently (June 2010) been updated on the management of COPD in adults in primary and secondary care [2], providing useful, up-to-date evidence on the diagnosis and management of the disease.

For the US Preventive Services Task Force (USPSTF), a summary of the evidence around screening for COPD using spirometry was produced in April 2008 [3], allowing the USPSTF to issue a statement on the subject. In this statement, the USPTF does not recommend screening for COPD.

As the USPTF review was conducted in 2006 (published in 2008), this current review focused on evidence published since 2006, in order to focus on new evidence since that review. A literature review was conducted, details of which can be found in appendix 1. A further 4531 potential references were elicited. These titles were further reviewed for relevance, giving 605 references for review. The evidence from these papers, along with the NICE guidance and summary for the USPSTF, form the basis of this review.

2. The condition

2.1. Is the condition an important health problem?
COPD is the fifth biggest killer disease in the UK, killing about 25,000 people per year [1]. It is estimated that 3 million people are affected by COPD in the UK – and of that it is estimated that there are about 2 million people with undiagnosed COPD [4]. The BOLD (Burden of Obstructive Lung Disease) study has estimated the global prevalence to be 10.1% overall [5].

There is a growing body of evidence indicating that COPD is under-diagnosed. Studies have found varied prevalence of undiagnosed COPD in the population – prevalences of 7.4% and 8.4% have been found in the general population [6, 7] and ranges from 18.9% to 27.9% in at-risk populations [6, 8-11].
2.2. Is the epidemiology and natural history known?

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) have developed standardised definitions and classifications of COPD that are recognised worldwide [12].

The GOLD standard definition of COPD is

“a preventable and treatable disease with some significant extra-pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles”

GOLD have also established internationally recognised classifications of severity of COPD. This includes 4 stages: stage I, mild; stage II, moderate; stage III, severe; stage IV, very severe. NICE guidance classifications are now, following the 2010 update, in agreement with these classifications [2].

Early symptoms of COPD include cough, production of sputum, and/or dyspnoea (breathlessness) related to physical exercise, or evidence of airflow obstruction without symptoms. In severe stages, exacerbations can occur regularly [13]. Many cases of COPD are not diagnosed until later in the disease. At early stages some patients appear to be asymptomatic. However, it is more likely that these “asymptomatic” individuals are affected in ways that are difficult to perceive or measure, and which can easily be dismissed as being attributable to ageing [14].

Adults who are current and ex-smokers are the group most at risk of developing COPD, as well as those that have been exposed to inhaled dusts and gases in the workplace or have a genetic problem leading to the onset of emphysema or a previous diagnosis of asthma [5]. Deprived populations have the highest prevalence of diagnosed and undiagnosed COPD – estimates suggest that routine and manual occupational groups represent almost half of the people with diagnosed or undiagnosed COPD in England [5].

However, not all smokers develop COPD. In the review for the USPTF [3], it was concluded that “older adults and current or past smokers are at increased risk for severe disease, but age and smoking status do not reliably discriminate between high and average risk populations” – i.e. older age and smoking do not necessarily predict COPD. Previously, the GOLD stages included a “stage 0, at risk”. However this is no longer included as there is “incomplete
evidence that the individuals who meet the definition “at risk” (chronic cough and sputum production, normal spirometry) necessarily progress on to stage I.”[12]. A recent analysis of the Framingham Offspring Cohort [15] found that 33% of continuous smoker males and 24.2% of continuous smoker females developed airflow obstruction, and 7.4% of male and 5.6% of female never smokers. The researchers also found that the presence of respiratory symptoms at baseline affected the rate of decline of FEV1 (a measure of lung function) compared to continuous smokers with no symptoms.

A large population study [16] found symptomatic GOLD stage I patients to have increased respiratory care utilization, lower quality of life, and faster decline of FEV1 than asymptomatic subjects with normal lung function, but found asymptomatic GOLD stage I subjects to have no significant differences in the same measures compared to those with normal lung function. The study concludes that respiratory symptoms are of major importance for predicting long-term clinical outcomes in COPD patients with mild obstruction.

The longitudinal ECLIPSE study [17-19] provides useful new evidence around the natural history of COPD. The study aimed to identify biomarkers to help predict disease progression, and to identify a frequent-exacerbation phenotype of COPD that is independent of disease severity. Substantial heterogeneity was found across the stages of COPD [17]. Severity of airflow limitation was poorly related to the degree of breathlessness, health status, co-morbidity, exercise capacity, and exacerbations, and the distribution of these variables within the stages was wide. A substantial proportion of subjects with severe airflow didn’t report symptoms. Exacerbations appeared to become more frequent and more severe as disease progresses, but the rate at which they occur appears to reflect an independent susceptibility phenotype [18]. The rate of change in FEV1 among patients with COPD was found to be highly variable, with increased rate of decline among current smokers, patients with bronchodilator reversibility, and patients with emphysema [19]. Further longitudinal analysis of the subgroups will add further understanding to the complexities and heterogeneity of the disease.

The full picture of the natural history of COPD is still not known. Particularly, there is limited evidence on treatment outcomes in asymptomatic, mild, or moderate disease (discussed further in section 4.1.2). More recently, large, prospective trials have been completed, evidenced by the TORCH [20-22], UPLIFT [23, 24] and ECLIPSE trials which included moderate COPD cases, but further evidence is needed to fully understand outcomes across the course of the disease.
2.3. Have all cost-effective primary prevention interventions been implemented?

As smoking is the biggest risk factor for COPD, it follows that the primary measure that can be taken to prevent COPD is smoking cessation and tobacco control.

In England, the prevalence of smoking has fallen from 25% in 2004 [25] to 21% in 2011 [26]. While this is a substantial decrease, smoking is still known to be one of the biggest challenges to public health and the primary cause of preventable disease.

In England there is an established NHS Stop Smoking Service, offering structured support to help people quit smoking. The service currently follows the Department of Health’s Stop Smoking Service Delivery and Monitoring Guidance [27] at a local level, as well as NICE guidance Smoking Cessation Services Guidance: PH10 [28].

In 2010/11, 383,548 people quit smoking successfully (based on 4 week quit through the Stop Smoking Service). This was 220% higher than in 2001/2 when 119,834 people quit smoking through the service. People could have also been quitting outside of the structure of the Stop Smoking Service, and also starting to smoke again after a recorded “4-week quit”. However, the Stop Smoking Service is considered a cost-effective service contributing to the decrease in smoking rates in the UK [28].

The government has also established a new tobacco control strategy [29], incorporating stop smoking services and wider tobacco control activity at policy level such as point of sale displays, and activity to prevent young people from starting to smoke. The strategy supports the six internationally recognised strands of tobacco control which are:

- stopping the promotion of tobacco
- making tobacco less affordable
- effective regulation of tobacco products
- helping tobacco users to quit
- reducing exposure to second-hand smoke
- effective communications for tobacco control

In July 2011, the Government published An Outcomes Strategy for Chronic Obstructive Pulmonary Disease and Asthma in England [1]. This strategy lays out plans that include management and diagnosis of those with the conditions, as well as prevention of new cases. The five strands of the strategy related to COPD are as follows:

1. To improve the respiratory health and well-being of all communities and minimise inequalities between communities
2. To reduce the number of people who develop COPD by ensuring they are aware of the importance of good lung health and well-being

3. to reduce the number of people with COPD who die prematurely through a proactive approach to early identification, diagnosis and intervention, and proactive care and management of all stages of the disease

4. To enhance quality of life for people with COPD, across all social groups, with a positive, enabling, experience of care and support through to the end of life.

5. To ensure that people with COPD, across all social groups, receive sage and effective care which minimises progression, enhances recovery and promotes independence

Within the objective around prevention, the strategy will focus on:

- developing prevention strategies
- raising awareness of good lung health
- persuading the public to take lung health seriously
- ensuring employers are doing all they can to protect staff and encourage good lung health
- empowering partners to support the process of encouraging prevention

The strategy also highlights the importance of tobacco control, and links to the aims and objectives of the tobacco control strategy.

3. The test

3.1. Is there a simple, safe, precise and validated screening test?

Models for case-finding and screening have been suggested [30-32] involving two options. Both options involve first identifying the at-risk population. This would be through either a risk evaluation questionnaire, a specified population group e.g. smokers over 35, or those with symptoms (this last option would be for case finding rather than screening). Following this step, the first option would involve using case-identification/”screening” spirometry in primary care, followed by referral to diagnostic spirometry for those with a positive result, and in the second option the at-risk population would attend diagnostic spirometry directly.

The aim of the “screening” spirometry (as in option 1) is to exclude patients with symptoms but normal lung function and identify those who require more complete investigation for COPD including “diagnostic standard” spirometry. These “exclusion” first assessments can be less specific but relatively sensitive to move forward by exclusion [30].
NB - A screening programme would offer spirometry to all people in a selected population who meet certain criteria, whereas case finding tests only people who present at their GP for other health problems and are either symptomatic or thought to be at risk of COPD [33]

3.1.1 Risk assessment Questionnaire
A number of studies have looked into the validity of a screening questionnaire for COPD. Different questionnaires have achieved varying sensitivity and specificity. The main questionnaires developed have been the COPD Diagnostic Questionnaire [34-36], the Lung Function Questionnaire [37, 38], the COPD Population Screener Questionnaire [39], and the IPAG questionnaire [40].

Development and validation work has been conducted on the Lung Function Questionnaire (LFQ) [37, 38]. The questionnaire contains questions on 5 areas: age, cough, wheeze, dyspnea, smoking. The two developmental studies found the questionnaire to have a sensitivity of 82.6% and 73.2%, and specificity of 47.8% and 58.2%, respectively. The accuracy was assessed using a binary scale (yes/no) and ordinal scale (1-5). It was concluded that the ordinal scale was more acceptable to patients and also more accurate as a screening tool [38]. The negative predictive value was found to be 92%.

In the development of the COPD Population Screener Questionnaire [39], five items were found to predict airflow obstruction – breathlessness, productive cough, activity limitation, smoking history, and age. A score on the questionnaire of greater than 5 had a positive predictive value of 56.8% and negative predictive value of 86.4%. This would mean a substantial number of false positives.

A study by Price et al found the ability of the Diagnostic Questionnaire to discriminate between patients with and without COPD was poor (area under ROC curve 0.65, specificity 24.4%) although sensitivity was again high (89.2%)[35]. In the development of this same questionnaire, when used with smokers only it was found it could have a sensitivity of 80.4% and specificity of 72% [36].

A study investigating the validity of the International Primary Care Airways Guidelines (IPAG) questionnaire alongside the PiKo-6 flow meter [40] found that with the questionnaire alone, in patients over 40, there was a sensitivity of 91% and specificity of 46%. Along with the PiKo-6 spirometer sensitivity and specificity were 72% and 97% respectively.
A study by Buffels et al which used a symptom-based questionnaire prior to spirometry on all participants with positive answers found the positive predictive value of the questionnaire to be low at 18%, with just 58% sensitivity and 78% specificity. 42% of newly diagnosed cases in the study would not have been found with the questionnaire alone without spirometry [7].

The evidence suggests that questionnaires could have some usefulness in ruling out COPD, perhaps as a first step in a screening programme, but all those above would lead to a substantial number of false positives. This would mean a large number of unnecessary diagnostic tests/further assessment and use of resources, and potential unnecessary stress to the individuals involved.

### 3.1.2 Spirometry

Spirometry measures airflow and can measure either forced expiratory volume (FEV) at 1 or 6 seconds, or forced vital capacity (FVC). The measures used in standard diagnostic spirometry are FEV1/FVC, and FEV1 as a percentage of the value predicted for the population [2, 12]. Spirometry is a well established test for COPD, and is used as the diagnostic gold standard [12].

However, spirometry is not used for asymptomatic COPD - the American College of Physicians has clearly stated in a recommendation that spirometry should not be used to screen for airflow obstruction in asymptomatic individuals [41].

In screening for COPD, some alternative measurements from the recognised standards of FEV1/FVC and FEV1 as percentage of normal have been suggested.

One alternative option suggested as an initial screening tool is measuring the FEV1/FEV6 ratio (i.e. forced expiratory volume at 1 second compared to at 6 seconds), such as with the PiKo-6 spirometer. A study looking at the accuracy of this as a screening tool was shown to have a case-finding sensitivity of 81% and case-finding specificity of 71%, and a negative predictive value of 91%, but a positive predictive value of only 52% [42]. This would again lead to a substantial number of false positives.

A further measurement option is using peak expiratory flow (PEF) as a step in screening, using PEF < 70% predicted as the cut-off. Using this in conjunction with a risk-factor questionnaire as a second step of a step-wise approach was reported in one study to be a cost-effective approach to screening (although abstract only was available so full appraisal of this evidence was not possible) [43].
In some case-finding studies, challenges have been found in the accuracy of spirometry in primary care, which could lead to false positives and/or false negatives. False positives and false negatives can be reduced if good technical standards are met [44].

One study [9] assessing the quality of spirometry carried out by general practitioners in primary care found that in 95% of cases fewer than 5 trials were required to achieve the highest quality grade, concluding that spirometries undertaken in general practice are of acceptable quality and reproducible in only 60% of measurements. The results of this study suggest a need for high quality initial training and refresher training for spirometry.

Another study [10] investigated the feasibility of practice nurses undertaking case-finding spirometry in general practice. While the study only involved small numbers of diagnoses, it was concluded that the practice nurses required more training than they were originally given - again highlighting the importance of high quality training if spirometry were to be used successfully in primary care.

A further study [45] investigating the quality of spirometry in primary care, through spirometry results and interpretations being sent from primary care to specialists to analyse, found over 15% of the tests were sent for reporting without complete data, and almost 40% of those that were complete were reported by specialists to be unacceptable. Clinically significant differences were found in the interpretation of the acceptability of the test in 32% of tests, of the diagnoses in 29% of the tests, and of the severity of the condition in 32% of the tests. The results showed unacceptable quality in the provision of spirometry within primary care for patients with COPD within this study. The study was limited to a small sample of general practices, so it cannot be assumed that similar results would be found on a bigger scale, but does again suggest that there is a need to ensure adequate training is given if spirometry is to be performed appropriately in primary care.

However, another study, conducted with community pharmacists, found that 73% of spirometries carried out by pharmacists were found to be of acceptable quality by lung function experts in the acute setting [11].

It can be concluded from the above evidence that challenges could exist in both selection of a suitable spirometric screening test as well as in maintaining the quality of spirometric tests in primary care.
3.2. Is the distribution of the test values in the target population well known and a suitable cut-off agreed?

There are GOLD established parameters for diagnosis of COPD using FEV1/FVC and FEV1 and for the stages of COPD. These are as follows [12]:

<table>
<thead>
<tr>
<th>Stage of COPD</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I: Mild</td>
<td>FEV1/FVC &lt; 0.70</td>
</tr>
<tr>
<td></td>
<td>FEV1 ≥ 80% predicted</td>
</tr>
<tr>
<td>Stage II: Moderate</td>
<td>FEV1/FVC &lt; 0.70</td>
</tr>
<tr>
<td></td>
<td>50% ≤ FEV1 &lt; 80% predicted</td>
</tr>
<tr>
<td>Stage III: Severe</td>
<td>FEV1/FVC &lt; 0.70</td>
</tr>
<tr>
<td></td>
<td>30% ≤ FEV1 &lt; 50% predicted</td>
</tr>
<tr>
<td>Stage IV: Very severe</td>
<td>FEV1/FVC &lt; 0.70</td>
</tr>
<tr>
<td></td>
<td>FEV1 &lt; 30% predicted or</td>
</tr>
<tr>
<td></td>
<td>FEV1 &lt; 50% predicted plus chronic</td>
</tr>
<tr>
<td></td>
<td>respiratory failure</td>
</tr>
</tbody>
</table>

However, in “screening” or case-finding spirometry, the International Primary Care Respiratory Group (IPCRG) recommends that the cut-points should be different to those used in diagnosis, as the purpose is to exclude those with normal lung function and identify those who require more complete assessment for COPD – i.e. more sensitive but less specific. For these purposes, the IPCRG recommends cut-offs of FEV1 ≤ 80%, or FEV1/FVC ≤ 80%, or FEV1/FEV6 ≤ 80% [30]. No information was found in the literature regarding the sensitivity and specificity of using this alternative limit.

However, office spirometry has been used in a number of studies for case-finding in a primary care setting using the GOLD classification of lung function limitation of FEV1/FVC ratio < 0.7 [6, 8, 10, 11, 46], rather than 0.8 as suggested by the IPCRG.

Various other classification systems have also been established – the American Thoracic Society & European Respiratory Society (ATS/ERS), NICE, and the Institute for Clinical Symptoms Improvement. Across these classifications, all are in agreement of the definition for mild and moderate COPD – mild being FEV1/FVC<0.7 or FEV1≥80%, and moderate being FEV1 between 50% and 80% predicted [32]. The ATS/ERS definition also has classification for “at risk”, which none of the other classification systems now have [32].

There have been some issues raised regarding the cut-off points used in the GOLD classifications. The review for the USPTF found there to be evidence of false positives in healthy asymptomatic individuals, particularly in older people using these classifications. There have been similar findings in studies since the USPTF review [47, 48]. To reduce this
misclassification, the use of the lower limit of normal (LLN) for FEV1/FVC has been suggested to define away obstruction (classifying the bottom 5% of the healthy population as abnormal). However, using the LNN would require reference equations for the LNN using post-bronchodilator FEV1 and longitudinal studies to validate the use of the LNN. These are not available and are urgently needed [12]. One study found that using the GOLD guidelines misidentified nearly one half of abnormal younger adults as normal – underdiagnosing younger adults [49]. This study suggests the use of FEV1/FVC ratio below the fifth percentile as more appropriate.

The lack of normal ranges for certain ethnic groups can also create diagnostic difficulties. No specific recommendation was made on this matter in the NICE guidelines while data from international research is awaited [2]. Therefore the current reference values are not applicable in black and Asian populations.

3.3. Is the test acceptable?

3.3.1 Questionnaire
In the development of the Lung Function Questionnaire [37] the face validity was tested with a focus group of patients. Initial concerns raised over the questionnaire feeling like a “smoking questionnaire”, and simplification of the instructions, were addressed and amended. None of the other studies investigating the use of questionnaires directly looked at the acceptability of the questionnaire with the population, but neither did any issues with the acceptability arise.

Another study found that of those identified as being at-risk (over 40 and current or ex-smokers) invited by letter to attend an appointment for spirometry, only 19.75% responded to the invitation [10]. This low response rate raises questions about the acceptability of this method.

3.3.2 Spirometry
Spirometry is a reliable, simple, non-invasive, safe, and non-expensive procedure [31].

However there are some challenges with its acceptability. A false positive could lead to unnecessary diagnostic testing and stress. A false negative can lead to a false sense of being healthy – a smoker may not give up smoking for example leading to further problems later in life either through more severe lung obstruction or other smoking related diseases [44]. However, there is some evidence that having a spirometry test increases motivation to quit irrespective of the result [50].
In one study [51] of smokers who had their lung function measured and received a subsequent diagnosis of COPD, 86% agreed that it was justified to measure lung function in heavy smokers. However this study included only smokers who were motivated to quit smoking and who had been newly diagnosed with airflow obstruction and so could have been more likely to give a positive response regarding its implications. It did not include smokers not motivated to quit smoking, or smokers who had received a normal spirometry result, or any false negatives or false positives.

A further study [52] suggests that a normal spirometry result in smokers does not deter smoking cessation. On follow up, the quit rate in the group of smokers with normal spirometry was comparable and not significantly different from 3 comparison groups (9.1%, compared with 8.9%, 8.2% and 10.3%).

3.4. Is there an agreed policy on further diagnostic investigation of positive test results and the choices available to them?

NICE provide clear guidance on diagnosis of COPD [2]. As previously discussed, as part of a screening programme diagnostic spirometry could be conducted directly on the at-risk population following a risk-based questionnaire, or it could follow “screening” spirometry. Diagnostic-standard spirometry could be conducted in primary care provided spirometers are available and training has been carried out, or in an acute setting with further additional investigation. The NICE guidance states that

- All health professionals involved in the care of people with COPD should have access to spirometry and be competent in the interpretation of results
- Spirometry can be performed by any healthcare worker who has undergone appropriate training and who keeps his or her skills up to date

The GP Quality Outcomes Framework [53] requires diagnosis in primary care to be confirmed by post bronchodilator. The 2010 updated NICE guidance also now recommends spirometry to be conducted post-bronchodilator.

Due to the issues around mis-diagnosis in older and younger groups (see section 3.2), NICE guidance also states that alternative diagnosis or further investigation should be considered in:

- older people without typical symptoms of COPD where the FEV1/FVC ratio is <0.7
- Younger people with symptoms of COPD where the FEV1/FVC ratio is ≥ 0.7

One of the challenges of diagnosis is differential diagnosis between COPD and other disorders which may present with similar symptoms, particularly asthma. Traditionally, measurement of
the degree of reversibility using bronchodilators has been used to confirm the diagnosis and separate those with asthma from COPD. However, NICE guidance states that post-bronchodilator FEV1/FVC and FEV1 are used for diagnosis and assessment of severity; the degree of reversibility of airflow limitation is not recommended for diagnosis or for predicting response to long term treatment with bronchodilators.

COPD and asthma can be differentiated on the basis of history and examination, and these features should be used to differentiate whenever possible. Longitudinal observation can also be used. If diagnostic uncertainty still remains then referral for more detailed investigations should be considered.

In assessing severity it is important to consider that COPD is heterogeneous, so no single measure can give an accurate picture for a patient. Spirometry can be used to assess the severity of airflow obstruction and to guide therapy and predict prognosis. A more complete assessment of severity includes the degree of airflow obstruction and disability and the frequency of exacerbations and additional prognostic factors, such as BMI, exercise capacity. The BODE – BMI, airflow obstruction, dyspnoea and exercise capacity – should be used to assess prognosis where information is available [2].

4. Treatment

4.1. Is there an effective treatment or intervention for patients identified, with evidence of early treatment leading to better outcomes?

GOLD guidelines on management and diagnosis of COPD state that early diagnosis can markedly slow decline in lung function, although not halt it altogether, and lengthen the period of time that a person can lead an active life [12]. Within GOLD guidelines, the following system for managing stages of COPD applies:

- stage I – The focus should be on management of risk factors and influenza vaccination, with short acting bronchodilator when needed;
- stage II - As stage I with addition of treatment with one or more long-acting bronchodilator and rehabilitation;
- Stage III as stage II with addition of inhaled glucocorticosteroids;
- Stage IV as stage III with addition of long-term oxygen if chronic respiratory failure and consider surgical treatment.
4.1.1 Smoking cessation

It has been well established since the 1970s that stopping smoking following diagnosis of COPD will slow the rate of deterioration of lung capacity for someone with COPD. Fletcher and Peto produced a well-known model to demonstrate this, showing the clear slowing of decline on smoking cessation [54].

The Framingham study [15] further updated this knowledge. In this study the FEV1 of smokers who quit at different ages was compared with healthy never smokers and continuous smokers. Those that quit before 30 years old were shown to have a decline in lung function comparable to never smokers. Those that quit after 40 years old showed a much steeper rate of decline that was not statistically different from continuous smokers.

Recommendations from the NICE guidance around smoking cessation are that:
- all COPD patients still smoking, regardless of age, should be encouraged to stop, and offered help to do so at every opportunity
- Unless contra-indicated, NRT, varenicline or bupropion should be offered to people who are planning to stop smoking combined with an appropriate support programme to optimise smoking quit rates for people with COPD.

The benefits of stopping smoking are clear, and further evidence around this is covered in the NICE guidance, however the evidence as to whether a diagnosis of COPD or a spirometric result motivates individuals to give up smoking is inconsistent. In the USPTF report it was concluded that the evidence on spirometry as a motivational tool is inconclusive. A number of studies since have found that a diagnosis of airway obstruction motivates people to quit smoking, but these findings have not been consistent across all studies.

In a study [55] offering spirometry to all patients who met the criteria of being over 35, smokers or ex-smokers and with one or more respiratory problem, approximately 50% of the current smokers stated that they were not interested in quitting smoking, and there was no difference between smokers with and without airway obstruction.

In a study investigating whether performing spirometry changes attitudes towards smoking, it was found that after spirometry the percentage of individuals had no intention of quitting smoking decreased significantly (from 57% to 9% in COPD group, and from 53% to 38% in non-COPD group). Three months later there was still a marked decrease but this had increased to 28% in the COPD group and 48% in the group with normal spirometry [50]. This suggests that spirometry motivates people to quit smoking – in both those diagnosed with COPD and with
normal lung function - but this is more significant directly after spirometry. In this study the COPD group was much smaller than the normal spirometry group (77 vs 410) which may effect the power of the results in that group. Although it cannot be assumed that motivation to quit smoking necessarily translates into actual quits, the results of this study also showed that 30% of the COPD and 14% of the normal spirometry group had already quit smoking at 3 months.

A study [56] found that in 4494 current smokers that had been tested for lung obstruction, smoking cessation rate after one year in those with airway obstruction was 16.3% compared with 12% (p=0.0003) in those with normal spirometric parameters. Independent predictors of successful smoking cessation included older age, older age when started smoking, fewer cigarettes per day, lower cumulative tobacco exposure, lower nicotine dependence, and lower spirometric values.

In the Step2quit trial [57], all participants were offered spirometry and their results were given either in terms of “lung age” (intervention) or their FEV1 figure (control). Both groups were advised to quit and offered referral to NHS stop smoking services. Quit rates in intervention and control were 13.6% and 6.4% respectively, showing a statistically significant increase in quit rates if spirometry results are fed back in terms of lung age. However, there was no difference in quitting success relating to spirometric result.

A further study conducted in Belgium on smokers who were willing to quit smoking did not find a statistical difference in a quit smoking success rate between control and intervention group – where control was smokers supported by their GP to quit smoking, and the intervention group in addition to this undertook spirometry and had results fed back to them. At 6 months, 1year, 17 months, and 2 years the quit rate in the spirometry group was higher each time but not statistically significant. Therefore the authors found no arguments in favour of the use of spirometry to enhance smoking cessation in primary care [58]

4.1.2 Pharmacotherapies

NICE guidance gives substantial evidence around the inhaled therapies available to COPD patients and their efficacy. The following gives a summary of the treatments recommended and evidence given in the NICE guidance.

- **Bronchodilators** - Beta2-agonists and anticholinergics both improve breathlessness and hyperinflation – leading to clinical benefits without improving FEV1.
Short-acting beta2-agonists (SABA) to be effective when used on an as-needed basis and when used regularly. Short-acting bronchodilators should be the initial treatment for the relief of breathlessness and exercise limitation.

Long-acting beta2 agonists (LABA) show significant differences in terms of exacerbations.

Long-acting anticholinergics (long acting muscarinic antagonists or LAMA) - Tiotropium is the only one available. Its duration of action means that it can only be given once daily. Has shown a significant increase in FEV1 and FVC in favour of LAMA vs placebo, and a lower proportion of patients experiencing exacerbation.

Both LABA and LAMA found to be clinically effective in preventing exacerbations – the guidance concludes that there is no evidence to support one over the other.

- **Inhaled corticosteroids** - Little evidence that inhaled steroids have any effect on the inflammatory cells present in COPD, although benefits have been shown in some studies using a variety of doses of varying steroid molecules.

- **Theophylline** (oral treatment) - Should only be used after a trial of bronchodilators or in patients who are unable to use inhaled therapy, as plasma levels and interactions need to be monitored.

- **Oral mucolytics** - Have been found to reduce exacerbations, increase the number of people who remain exacerbation free, and increase FEV1% predicted. Recommendation is that they should be considered in patients with a chronic cough productive of sputum but not used to prevent exacerbations in people with stable COPD.

- **Combination therapy** - If patients on one therapy remain symptomatic then treatment should be intensified by combining therapies in effective combinations such as: beta2 agonist and theophylline; anticholinergic and theophylline; combination of bronchodilators (further evidence of effectiveness of different combinations given in NICE guidance)

Although there is a strong evidence base regarding pharmacological treatment for COPD, there is limited evidence on treatment outcomes in asymptomatic, mild, or moderate disease – as would be detected in a screening programme. The USPTF report concluded that
pharmacological treatments modestly reduce exacerbations in patients with symptomatic severe 
COPD, but that there was an absence in the literature of evidence from patients with mild or 
moderate COPD in most therapeutic trials, or of asymptomatic patients. At the time of the 
USPTF review there was very limited evidence on treatment effects on these stages of COPD. 
However, more recently, large, prospective trials have been completed, evidenced by the 
TORCH, UPLIFT and ECLIPSE trials, which included moderate (GOLD stage II) COPD.

Subset analyses of the TORCH [21] and UPLIFT [24] trials have shown pharmacological 
treatment to be effective in moderate COPD. In the TORCH trial, the same proportionate 
reduction in exacerbations, and treatment effect on FEV1 was seen across all stages of COPD. 
In UPLIFT, GOLD stage II COPD patients showed an improved rate of decline of FEV1, 
improved health status measurement, and improved time to first exacerbation when compared 
to the control group. Both trials were large; TORCH had 6112 participants with a third of these 
GOLD stage II, and UPLIFT had 8020 participants with again approximately a third of 
participants GOLD stage II.

A further study by Johansson et al [59], reported topropium-treated patients with mild to 
moderate COPD had significantly improved lung function versus baseline and placebo. 
However the size of this study was relatively small, with only 224 patients included. A further 
trial [60] on COPD of different severities found tiotropium to lead to increases in FEV1 in all 
severities, and the improvements were most pronounced in mild COPD.

Although these studies give new information on treatment in mild and moderate COPD, there is 
still limited information on mild (GOLD stage I) COPD and asymptomatic COPD. The majority 
of effectiveness studies have still not included patients with mild to moderate COPD [61], and 
trials evaluating therapies in patients with airflow limitation who do not recognise or report 
symptoms are lacking [3]. A reported limitation of the UPLIFT trial in terms of analysis of 
moderate COPD is that those with less severe and asymptomatic stage II COPD are likely to 
have been excluded.

In addition, the clear heterogeneity of the disease, as shown for example in the ECLIPSE trial 
[17] – with some patients still asymptomatic at stage IV - indicates varying outcomes for 
different individuals.

The USPTF review concluded that if 10,000 current smokers over 40 years old and without a 
current diagnosis of COPD received spirometry screening, 207 (2%) would qualify for inhaled 
therapies, which would result in 12 fewer initial exacerbations in the following year – meaning
the number needed to screen to prevent one initial exacerbation would be 833 – concluding that this would not be a cost-effective use of resources.

4.1.3 Vaccination and anti-viral therapy
The USPTF review concluded that influenza vaccination reduces exacerbations in patients with COPD but that evidence regarding pneumococcal vaccination was insufficient. Another conclusion was that evidence regarding whether benefits vary according to severity of COPD was insufficient.

Pneumococcal vaccination and annual influenza vaccination are recommended for all patients with chronic respiratory disease by the Chief Medical Officer. Influenza vaccination has been shown to be associated with a reduction in risk of death in COPD patients, and influenza and pneumococcal vaccination combined have shown a reduction in hospitalisation for pneumonia, and a reduction in risk of death.

4.1.4 Other forms of treatment/management
- **Nutritional factors** - NICE recommends BMI is monitored and if low patients should be given nutritional supplements and take exercise.
- **Education** - NICE guidance states specific educational packages should be developed for COPD taking into account the different needs of patients at different stages of the disease.
- **Self management** - The main aim is to prevent exacerbations and to acquire the skills to treat exacerbations at an early stage. NICE guidelines cover what self-management should cover and who should receive it.

4.1.5 Management of more severe COPD
As COPD picked up in a screening programme would be mild or moderate, the evidence around management of more severe COPD is not directly relevant to this review, however the main treatments recommended by NICE are as follows (NOTE - this is not a complete review of treatment and should not be seen as such):
- **Oral corticosteroid therapy** - Maintenance of oral corticosteroid therapy in COPD is not normally recommended – although some patients with advanced COPD may require maintenance oral corticosteroids when they cannot be inhaled following an exacerbation.
- **Pulmonary rehabilitation** - Should be made available to people with COPD when symptoms and disability are present – and should be offered to all who consider
themselves functionally disabled by COPD. By definition, this is an interventions for moderate and severe COPD.

- **Oxygen** - As COPD progress patients often become hypoxaemic. Oxygen can be administered for long periods during day and night, as ambulatory oxygen, or as short burst therapy to relieve symptoms. The general need for oxygen therapy should be assessed in all patients with very severe airflow obstruction (FEV1 < 30% predicted)

- **Nebuliser therapy** - Patients with distressing or disabling breathlessness despite maximal therapy using inhalers should be considered for nebuliser therapy.

- **Lung surgery** - Bullectomy, lung volume reduction surgery, and lung transplantation have all been used to treat patients with COPD.

- **Managing anxiety and depression** - NICE guidance highlights that the presence of anxiety and depression should be considered particularly in those patients who are hypoxic, have severe dyspnoea, who have been admitted to hospital with an exacerbation.

4.1.6 Managing exacerbations

An exacerbation is a sustained worsening of the patient's symptoms from his or her usual stable state that is beyond normal variations and is acute. This can result in hospital admission and often necessitates change in medication. NICE guidance covers in more detail the management of exacerbations, for management in primary care and in patients referred to hospital. The guidance covers use of pharmacological management, oxygen therapy, and respiratory physiotherapy.

4.2. Is there agreed evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered?

Treatment options are discussed in section 4.1 above, as recommended in NICE. As COPD is heterogeneous in nature, the treatment that individuals receive depends very much on clinical diagnosis and individualised treatment plans, following NICE guidance.

4.3. Are clinical management of the condition and patient outcomes currently optimised by health care providers?

NICE clearly lays out guidance on the appropriate treatment and management of COPD. Once diagnosis has occurred, then treatment and care pathways should be appropriate. The heterogeneous nature of the disease requires individualised care plans and management through multi-disciplinary teams.
However, the issue appears to be the significant proportion of those with COPD estimated to be undiagnosed in the community. The COPD strategy highlights a proactive approach to early identification, diagnosis, and management of the disease, and NICE guidance recommends opportunistic case finding on patients who are over 35, current or ex-smokers, and have a chronic cough.

NICE, as part of the guidance on COPD, carried out analysis to assess the cost effectiveness of opportunistic case finding with those that are diagnosed then targeted with an intensive smoking cessation programme. The aim was to compare the costs and benefits of opportunistically testing patients who present at the GP with the following characteristics: over 35; smoker/ex-smoker; chronic cough, with current practice. Cost per life year gained and the cost per QALY were calculated. The model was built from the perspective of the NHS. The probability of airflow obstruction was taken as 27% (the prevalence found in a previous case-finding study). Costs were calculated of diagnosis and intervention (smoking cessation), and the cost of care for each year alive. The results were that even with very conservative estimates of successful smoking cessation rates, opportunistic case finding was found to be a relatively cost-effective strategy. However the model assumed 100% specificity and sensitivity – which we know not to be the case.

5. The programme

5.1. Is there evidence from high quality randomised controlled trials?
There have not been any randomised controlled trials on screening for COPD.

There is currently a study underway in Copenhagen [33] in which subjects aged 65 and older registered with a general practitioner will receive a written invitation and a simple questionnaire around risk factors for COPD. Subjects who meet certain criteria will then be encouraged to undergo spirometric testing. The results of this study have not yet been published.

5.2. Is there evidence that the complete screening programme is clinically socially and ethically acceptable to health professionals and the public?
There are a number of issues regarding a screening programme for COPD:

- Screening will pick up mostly mild disease (In a case-finding project, tinkleman et al [8] found the yield of mild COPD to be 57%, moderate 36.8%, and severe 5.8%). However,
there is a lack of evidence around the outcomes of pharmacological treatment options in mild and asymptomatic disease.

- GOLD recommends reduction of risk factors as the primary intervention for those with mild COPD. Therefore smoking would be the primary intervention for individuals diagnosed in a screening programme. However, there is not a clear conclusion from the evidence regarding whether spirometry increases motivation and success in quitting smoking. In addition, the impact to the individual of providing a smoker with a “healthy” reading is not clear.

- There is a risk of false positives and false negatives, and the potential impact of these on the individual is not clear from the evidence

- It is not clear from the evidence the best model for a screening programme – a screening questionnaire, “screening” spirometry, or a combination of both before referring positive screens for diagnostic standard spirometry. Both questionnaires and spirometry in primary care have shown to have challenges:

  o Questionnaires –
    • The evidence reviewed in this paper indicates that these would produce high rates of false positives. This would lead to unnecessary resources and stress from diagnostic investigation, or further “screening” spirometry
    • If a risk questionnaire is the first stage in a step-wise approach, there are queries regarding how this would be administered. Being sent may yield a low response rate, yet inviting to an appointment would have significant resource implications if a large proportion are not at risk and do not require further investigation.

  o Screening spirometry –
    • The evidence has shown there could be challenges with quality of spirometry if conducted on a large scale in primary care – again leading to inaccuracies and mis-diagnoses.
    • In addition, spirometry has been shown to produce mis-diagnosis in older population groups, meaning these individuals would need to be referred for further diagnostic testing in a specialist setting.
Alternatives to the diagnostic-standard FEV/FVC<0.7 spirometry have been suggested as a screening test, but no conclusion reached as to the most cost-effective or accurate spirometry measure to be used in a screening programme.

- There is no evidence around the capacity in both primary care and secondary care to manage a population screening programme

5.3. Do the benefits of the screening programme outweigh the physical and psychological harm?
The evidence detailed in this report does not give clear conclusions regarding the benefits of a screening programme for COPD – and therefore the evidence does not indicate that the benefits would out-weigh the harm.

This is particularly given the limited evidence around the treatment outcomes that would be achieved in identifying mild COPD.

5.4. Are the opportunity costs of the screen programme economically balanced in relation to expenditure on medical care as a whole – i.e. would a screening programme represent value for money?
The costs of a screening programme for COPD were not reviewed as part of this report.

5.5. Have all other options for managing the condition been considered?
There are a number of recent national strategies and guidelines which will work together to address COPD, which need time to be fully implemented and established:

- NICE guidance *Chronic Obstructive Pulmonary Disease: Management of chronic obstructive pulmonary disease in adults in primary and secondary care* [2], which recommends active case-finding for COPD after showing evidence of its cost-effectiveness
- The Department of Health *An outcome strategy for COPD and asthma* [1] - the national approach for addressing the growing burden of COPD
- The Department of Health tobacco strategy, *Healthy lives health people: A tobacco control plan for England* [29]
5.6. Are there adequate staffing facilities for the programme?
The evidence around this has not been considered as part of this review. However, a screening programme for COPD would require substantial staffing infrastructure in primary and secondary care.

5.7. Is there evidence-based information, explaining the consequences of testing, investigation and treatment, available to potential participants?
This has not been considered as part of this review.

5.8. Has public pressure for widening the eligibility criteria or reducing the screening interval, and for increasing the sensitivity of the testing process been anticipated?
This has not been considered as part of this review.

6. Conclusion
This analysis of the evidence for a screening programme for COPD against the National Screening Centre Criteria indicates that a screening programme for COPD is not recommended at this time. The key reasons for this are as follows:
- No RCTs have been conducted on screening for COPD
- The evidence on outcomes of treatments and interventions for early stage COPD are still limited
- The evidence regarding whether spirometry prompts people to quit smoking is inconclusive
- Challenges still exist with the test options for a population-wide screening programme
- Current prevention activity including the national COPD and tobacco strategies are yet to be fully implemented
- Cost-effective evidence does exist for case-finding symptomatic individuals with more developed COPD and this should continue.
References

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20. Calverley, P.M.A.A., JA; Celli, B; Ferson GT; Jenkins, C; Jones, PW; Crim, C; Willits LR; Yates JC; Vestbo, J, Cardiovascular events in patients with COPD: TORCH Study results. Thorax, 2010. 65: p. 719-725.
21. Jenkins, C.J., PW; Calverley, PMA; Celli, B; Anderson JA; Ferguson, GT; Yates, JC, Willits, LR; Vestbo, J, Efficacy of salmeterol/fluticasone propionate by GOLD stage of chronic obstructive pulmonary disease: analysis from the randomised, placebo-controlled TORCH study. Respiratory research, 2009. 10:59.


Appendix 1 – Literature review search strategy

Knowledge update on screening for chronic obstructive pulmonary disease (COPD)
Paula Coles, Information Scientist
February 2012

BACKGROUND:

Department of Health. 2011. *An outcomes strategy for chronic obstructive pulmonary disease (COPD) and asthma in England.*


The searches for the U. S. Preventive Services Task Force searched for studies up to December 2006 and the NICE guidelines were updated in 2010 the databases were searched from January 2006 until February 2012.

SOURCES SEARCHED: Medline (OvidSP), Embase, PsycINFO and the Cochrane Library.

DATES OF SEARCH: January 2006 – February 2012

SEARCH STRATEGY:

1. Pulmonary Disease, Chronic Obstructive/(16609)
2. COPD.tw. (19410)
3. chronic obstructive pulmonary disease.tw. (21045)
4. (airflow or airway) adj (obstruction or limitation)).tw. (14935)
5. 1 or 2 or 3 or 4 (435999)
6. exp Spirometry/ (16562)
7. spirometry.tw. (8874)
8. bronchspirometry.tw. (156)
9. Respiratory Function Tests/ (39614)
10. respiratory function test$.tw. (849)
11. 6 or 7 or 8 or 9 or 10 (53473)
12. Mass screening/ (72270)
13. screen$.tw. (370430)
14. (test or tests or testing).tw. (1274565)
15. detect$.tw. (1281994)
16. Pulmonary Disease, Chronic Obstructive/di [Diagnosis] (2679)
17. 12 or 13 or 14 or 15 or 16 (2618227)
18. 5 and 11 and 17 (3556)
19. Smoking/ (104732)
20. Smoking Cessation/ (16416)
21. smoking cessation.tw. (12615)
22. Primary Prevention/ (12262)
23. 19 or 20 or 21 or 22 (125762)
24. 11 and 23 (3891)
25. (long or short) adj acting beta$ agonist$.tw. (1185)
26. Selective beta$ agonist$.tw. (85)
27. Adrenergic beta-Agonist$.tw/ (13670)
28. Albuterol/ or salbutamol.tw. or Terbutaline/ or terbutaline.tw. (12956)
29. (formoterol or salmeterol or indaceterol).tw. (2835)
30. (long or short) adj acting muscarinic antagonist$.tw. (42)
31. (antimuscarinic adj (bronchodilator$ or antagonist$)).tw. (11)
32. cholinergic antagonists/. (3074)
33. muscarinic antagonists/. (5951)
34. Ipratropium/. (1651)
35. Ipratropium/ or ipratropium.tw. or tiotropium.tw. (2649)
36. inhaled corticosteroid$.tw. (5701)
37. Glucocorticoids/. (42856)
38. Beclomethasone/ or Beclomethasone.tw. or Budesonide/ or Budesonide.tw. or fluticasone.tw. (8511)
39. Oxygen Inhalation Therapy/. (10649)
40. oxygen therapy.tw. (6369)
41. Exercise Therapy/. (21711)
42. exercise tolerance/. (6592)
43. Dyspnea/rh [Rehabilitation]. (155)
44. pulmonary rehabilitation.tw. (1522)
45. Respiration, Artificial/. (34624)
46. Positive-pressure respiration/. (13945)
47. (nippv or nivm).tw. (379)
48. non invasive mechanical ventilation.tw. (155)
49. Self Care/. (19868)
50. Patient Education as Topic/. (63079)
51. Primary Health Care/. (46085)
52. Pneumococcal Vaccines/. (3822)
53. Influenza Vaccines/. (13233)
54. 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 (307054)
55. randomized controlled trial/. (318550)
56. Random Allocation/. (72884)
57. (random* adj5 (alloca* or assign* or control*) ).tw. (189618)
58. double-blind method/ or single-blind method/(127320)
59. exp clinical trial/. (600665)
60. (clinical adj5 trial*).tw. (179205)
61. ([singl* or doubl* or trebl* or tripl*] adj5 (blind* or mask*)).tw. (114739)
62. Placebos/. (30377)
63. (placebo* or random*).tw. (633562)
64. Research Design/. (64423)
65. “review/” or evaluation studies/. (1809590)
66. exp Longitudinal Studies/. (748716)
67. (compare* adj5 (report* or stud* or trial*)).tw. (349855)
68. meta-analysis/. (31166)
69. “Review Literature as Topic”/. (4052)
70. “review/”/. (1053833)
71. systematic review.tw. (27859)
72. meta-analysis?.tw. (38421)
73. 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 (3654369)
74. 54 and 73 (104800)
75. 18 and 74 (589)
76. Epidemiology/ or epidemiology.tw. (90936)
77. Prevalence/ or prevalence.tw. (356917)
78. Incidence/ or incidence.tw. (506874)
79. 76 or 77 or 78 (878785)
80. 18 and 79 (538)
81. 18 or 24 or 75 or 80 (6757)
82. 81 (6757)
83. limit 82 to yr="2006 -Current" (2134)

Similar searches were also carried out in Embase, PsychINFO and the Cochrane Library.
All searches carried out on 3 February 2012

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<td>Cochrane Library</td>
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<tr>
<td>PsycINFO</td>
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<td><strong>Total</strong></td>
<td><strong>6191</strong></td>
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**Inclusions and exclusions**

The above search strategies retrieved 6191 references in total. After duplicate references were removed a total of 4531 potentially relevant references were left. The title and abstracts of the remaining citations were scanned for relevance to screening for COPD in adults, focussing on the following:

**The condition**
- The clinical context of the condition is discussed in the full NICE guidance and therefore not specifically focused on in this search. However, incidental studies recovered through the searches on prevalence, morbidity and mortality have been included.

**Prevention**
- Smoking cessation
- Does giving people their spirometry/lung function etc. results and subsequent risk of COPD affect potential lifestyle changes?

**The test**
- Is there a decent, easily administered test?
- Is there a period when the test is positive but people are asymptomatic?

**The treatment**
- Due to the volume of references, and because of the existence of the NICE guidance on management of diagnosed or stable COPD, only systematic reviews were included for interventions in this population. Studies on interventions of screen-detected COPD would be included.
- Does early intervention improve outcomes?

**The screening programme**
- Targeted and opportunistic case finding were included as well as general population screening programmes in primary care.

**Also**
- Protocols for Cochrane reviews were excluded as were withdrawn reviews.

605 references were considered to be relevant and given to the reviewer to appraise for possible inclusion in the final review.

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<th>Systematic reviews and meta-analyses</th>
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<td>The test (5)</td>
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<td>Interventions (63)</td>
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<td>Pharmacotherapy (24)</td>
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<td>Oxygen/non-invasive positive pressure ventilation (6)</td>
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<td>Patient education (2)</td>
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Guidelines and recommendations 19

General, non-systematic reviews 27

**The condition** 182

- Epidemiology (103)
  - UK (9)
  - Europe (36)
  - USA and Canada (11)
  - Asia-Pacific region (19)
  - Middle East (5)
  - Latin America (4)
  - South Asia (3)
  - Africa (1)
  - Global (3)

- Effect of different definitions (12)
- Natural history/characteristics (23)
- Survival/mortality (11)
- Quality of life (42)
- Costs (3)

Prevention and improvement 106

- Prevention programmes (6)
- Spirometry/lung function/lung age as motivation to stop smoking (40)
- Smoking cessation in COPD (29)
- QOF/national improvement (6)
- Quality of diagnosis in primary care (25)

**The test** 129

- Spirometry reviews (8)
- Accuracy of spirometry in primary care (35)
- Algorithms/reference values etc. (43)
- Algorithms/reference values etc. in older people (7)
- Algorithms/reference values etc. in ethnic groups (3)
- Questionnaires (13)
- Comparison of methods (20)

**The screening programme** 72

- Screening (24)
- Targeted case finding (39)
- Opportunistic case finding (9)

**Total** 605