Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
KCE

Longfunctietesten bij volwassenen

KCE reports 60A

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2007

Het Federaal Kenniscentrum voor de Gezondheidszorg

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Contact

Federaal Kenniscentrum voor de Gezondheidszorg (KCE)
Wetstraat 62
B-1040 Brussel
Belgium

Tel: +32 [0]2 287 33 88
Fax: +32 [0]2 287 33 85

Email : info@kce.fgov.be
Web : http://www.kce.fgov.be

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ANN VAN DEN BRUEL, JEANNINE GAILLY, STEPHAN DEVRIESE,
FRANCE VRIJENS, DIRK RAMAEKERS .

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Titel : Longfunctietesten bij volwassenen

Auteurs : Ann Van den Bruel (KCE), Jeannine Gailly (KCE), Stephan Devriese (KCE), France Vrijens (KCE), Dirk Ramaekers (KCE)

Externe experten: Johan Buffels (KULeuven); Dirk Coolen (Middelheim ziekenhuis); Marc Decramer (KULeuven); Luc Delaunois (UCL); Marion Delcroix (KULeuven); Erik Derom (UGent); Paul De Vuyst (ULB); Guy Hollaert (SSMG); Giuseppe Liistro (UCL); Roger Sergysels (St Pierre Hopital); Michiel Thomeer (ZOL); Karel Van de Woestijne (KULeuven)

Externe validatoren: Chris Van Weel (University Medical Centre Nijmegen, Nederland), Wilfried De backer (UA), Raynaud Louis (ULG) .

Conflict of interest : geen gemeld

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Layout: Nadia Bonnouh, Ine Verhulst

Brussel, juli 2007

Studie nr 2006-06
Domein : Good Clinical Practise (GCP)

MeSH : Respiratory Function Tests, Chronic Obstructive Pulmonary Disease, Asthma, Interstitial Lung Diseases, Health Care Quality Assurance

NLM classification : WF 141

Taal : Nederlands, Engels
Format : Adobe® PDF™ (A4)

Wettelijk depot : D2007/10.273/27

Elke gedeeltelijke reproductie van dit document is toegestaan mits bronvermelding.

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Hoe refereren naar dit document?
Ann Van den Bruel, Jeannine Gailly, Stephan Devriese, France Vrijens, Dirk Ramaekers. Pulmonary Function Tests in Adults, Good Clinical Practise (GCP) Brussel: Federaal Kenniscentrum voor de gezondheidszorg (KCE); 2007. KCE reports 60A. (D2007/10.273/27)

VOORWOORD

De eerste longfunctie testen gaan terug tot de 19e eeuw, toen John Hutchinson de eerste metingen van de vitale capaciteit uitvoerde met wat nu is geëvolueerd tot de moderne spirometer. In de huidige aanpak van longziekten zijn longfunctietesten niet meer weg te denken en maken ze een integraal deel uit van zowel diagnose als behandeling van longaandoeningen. Op zich is het zelfs zo dat vaak het resultaat van een longfunctietest zal bepalen of iemand een bepaalde longziekte heeft. In functie van de gekozen afkappunten krijgen we zo meer of minder personen met de diagnose van longziekte.

Met het verouderen van de bevolking neemt het aantal patiënten met longaandoeningen zoals bijvoorbeeld chronisch obstructief longlijden toe. Anderzijds neemt het aantal rokers – roken is nog steeds oorzaak nummer 1 van longziekten – nu wel af. Het voorkomen van andere longaandoeningen zoals astma is de laatste tijd ook gestegen. De vraag naar respiratoire zorg zal dus vermoedeliik in de volgende jaren nog toenemen, tegelijkertijd met een vraag naar zorg van hoge kwaliteit en een zoektocht naar de meest doelmatige besteding van de beschikbare middelen. Longfunctietesten zijn daarbij onontbeerlijk vermits ze , omdat zij bijkomende testen of behandeling zullen sturen. De juiste keuze in en kwaliteit van die testen is dan ook cruciaal.

In het verleden werden al belangrijke inspanningen gedaan wereldwijd om longfunctie testen te standaardiseren. Referentiewaarden waarmee metingen bij patiënten worden vergeleken en kwaliteitsnormen waaraan metingen moeten voldoen werden ontwikkeld in gezamenlijke acties. Klinische praktijkrichtlijnen bieden meer en meer een leidraad aan clinici over het juist gebruik van diagnostische testen.

Al deze inspanningen werden in dit rapport samengebracht, resulterend in klinische aanbevelingen voor Belgische artsen, zowel voor de huisarts als voor de longarts. Deze richtlijn werd ontwikkeld in samenwerking met diverse klinische en wetenschappelijke experten - waarbij we hier onze welgemeende appreciatie willen benadrukken voor hun niet geringe inspanning - en zijn gebaseerd op de beschikbare wetenschappelijke bewijzen waar mogelijk. De systematische review van de literatuur was een bijzondere uitdaging in dit geval, gezien de meeste studies dateren van meerdere decennia geleden en recente studies schaars zijn. In zo'n geval zijn beargumenteerde expertenopinies van onschatbare waarde. Het leert ook dat EBM niet op alle vragen een antwoord kan bieden

Jean-Pierre CLOSON
Adjunct algemeen directeur

Dirk RAMAEKERS
Algemeen directeur

EXECUTIVE SUMMARY

INTRODUCTIE

Longfunctietesten worden gebruikt om de functie van de luchtwegen, long parenchym, vaatstelsel en ademhalingsspieren te meten. De testen die beschouwd werden in dit rapport waren spirometrie, bronchodilatatie test, bronchoprovocatie testen, longvolumes, diffusie capaciteit en luchtwegen resistentie.

Het rapport start met een beschrijving van het huidige gebruik van de longfunctietesten in België. Vervolgens werd een literatuuroverzicht van de doeltreffendheid van longfunctietesten gemaakt, dat dan als basis heeft gediend voor de aanbevelingen voor de klinische praktijk die werden geformuleerd door een groep experten.

HUIDIGE PRAKTIJK

Gegevens over het gebruik en de uitgaven voor de zes geselecteerde testen tussen 1995 en 2004 waren beschikbaar via het RIZIV. Gedetailleerde analyses van het gebruik van deze tests werden gemaakt op basis van gegevens van het Intermutualistisch Agentschap (IMA).

De meerderheid van de geselecteerde longfunctietesten werd ambulant uitgevoerd; behalve voor spirografie met provocatie is het gebruik van deze testen gestegen, terwijl het in het ziekenhuis is gedaald. De totale uitgaven voor de zes longfunctietesten in 2004 was €48 844 757 waarvan €34 072 393 voor ambulante testen en €14 772 364 voor testen uitgevoerd in het ziekenhuis. De meeste testen werden uitgevoerd door specialisten interne geneeskunde, gevolgd door longartsen.

Mannelijke patiënten krijgen gemiddeld meer longfunctietesten dan vrouwen, behalve voor spirografie met provocatie. De meeste testen worden uitgevoerd bij patiënten tussen 66 en 75 jaar.

Meer dan 50% van de patiënten die minstens één longfunctietest kregen, kregen een combinatie van spirografie met of zonder bronchodilatatie, residueel volume, diffusie capaciteit en ventilatie mechaniek (deze laatste code bestaat uit luchtwegen resistentie, respiratoire resistentie en compliance)

KWALITEIT EN STANDARDISATIE

Kwaliteit en standaardisatie zijn essentieel bij longfunctietesten om precieze en reproduceerbare resultaten te verkrijgen. Het toepassen van international geaccepteerde standaarden zou een mogelijk mechanisme kunnen zijn om de uitvoering, technische kwaliteit en interpretatie van longfunctietesten te verbeteren.

In 2005 werd door de American Thoracic Society en de European Respiratory Society Task Force een gezamenlijke consensus gepubliceerd over nieuwe standaarden voor spirometrie, diffusie capaciteit en longvolumes, waarbij belangrijke aspecten zoals kwaliteit, materiaal, test procedures en interpretatie strategieën werden besproken. De Belgische consensus uit 2001 bevat ook hoofdstukken over kwaliteit en standaardisatie.

Aspecten die hierbij aan bod kwamen, hadden betrekking op de patiënt, het longfunctie laboratorium, het materiaal, hygiëne en infectiecontrole, personeelskwalificaties en referentie waarden.

LITERATUURSTUDIE

De literatuurstudie werd op drie verschillende manieren benaderd. Eerst werd naar studies gezocht op basis van klachten en symptomen, meer bepaald chronische hoest en dyspnee. Daarna werd informatie gezocht op basis van de aandoening, namelijk COPD, astma en interstitiële longaandoeningen. Tenslotte werden studies gezocht voor een selectie van testen.

De methodologie doorheen het hele rapport was die van een systematische review. De zoektocht was iteratief, waarbij eerst naar synthesemateriaal gezocht werd (systematische reviews en HTA rapporten) gevolgd door een aanvullende zoektocht naar originele studies. Richtlijnen werden gebruikt als bron van praktijkaanbevelingen. De databanken die hierbij gebruikt werden waren Medline, Embase, CRD, NICE, National Guideline Clearinghouse, Scottish Intercollegiate Guidelines Network, National Library of Health. De zoektermen werden gekozen in functie van het onderwerp.

Vervolgens werden de studies geselecteerd en op hun kwaliteit beoordeeld op basis van vooraf gedefinieerde, expliciete criteria.

SYMPTOOM GEBASEERD

Studies op basis van de klachten en symptomen van de patiënt zijn het meest informatief voor de klinische praktijk. Maar, voor dit rapport werden geen studies van goede kwaliteit gevonden over de waarde van longfunctietesten bij patiënten met dyspnee of chronische hoest.

AANDOENING GEBASEERD

COPD

Luchtwegobstructie zoals gedocumenteerd door spirometrie is essentieel voor de diagnose van COPD. Het bepalen van de graad van obstructie kan nuttig zijn voor prognostische of therapeutische doeleinden. Spirometrie tijdens een exacerbatie is van weinig nut. Daarbij is spirometrie ook geïndiceerd voor het opvolgen van de ziekte. Voor de frequentie waarmee spirometrie moet herhaald worden is geen wetenschappelijke onderbouwing en hangt af van het klinische oordeel van de behandelende arts.

Er zijn goede studies die aantonen dat een abnormale spirometrie de kans op rookstop niet doet toenemen.

Er is geen overeenstemming over het nut van de bronchodilatatie test voor de initiële diagnose en het beoordelen van de respons op behandeling. Richtlijnen verschillen ook over het nut van longvolumes en diffusie capaciteit.

Astma

Het documenteren van variabele luchtwegobstructie is essentieel in de diagnose en opvolging van patiënten met astma. De graad van luchtwegobstructie wordt ook gebruikt om de ernst van de aandoening te bepalen.

Spirometrie of peak flow meting tijdens een acute astma-aanval documenteert en kwantificeert de daling in expiratoire flow, om de behandeling te bepalen en de respons op behandeling te meten.

De bronchodilatatie test kan nuttig zijn om een diagnose van astma te bevestigen, als er een significante omkering van de luchtwegobstructie wordt aangetoond. Niettemin sluit een negatieve bronchodilatatie test astma niet uit.

Bij geselecteerde patiënten kan een bronchoprovocatie test nuttig zijn om astma uit te sluiten.

Restrictief longlijden

Richtlijnen zijn het over het algemeen eens over de waarde van de vitale capaciteit en diffusie capaciteit voor de diagnose en opvolgen van patiënten met interstitieel longlijden.

Longfunctietesten worden ook gebruikt bij patiënten met pulmonaire arteriële hypertensie. Patiënten met scleroderma geassocieerde pulmonaire hypertensie en een verminderde diffusie capaciteit hebben een slechtere prognose.

TEST GEBASEERD

Bronchodilatatie test

Gebaseerd op de beschikbare studies kan een bronchodilatatie test niet gebruikt worden om astma van COPD te onderscheiden. De hypothese dat de bronchodilatatie test gebruikt kan worden om de diagnose van astma te stellen bij een significante reversibiliteit wordt niet bevestigd door deze review.

Longvolumes

Er werden geen kwalitatief goede studies over de klinische waarde van longvolumes geïdentificeerd.

CO diffusie capaciteit (DI_{CO})

Bij patiënten met idiopathische pulmonaire fibrose correleert Dlco met de prognose, maar niet met de respons op behandeling. Een zeer lage Dlco wijst op een slechte prognose bij patiënten met scleroderma-geassocieerde pulmonaire arteriële hypertensie. Bij patiënten met gevorderde pulmonaire arteriële hypertensie correleert Dlco sterk met de ernst van de ziekte.

Bij COPD patiënten voorspelt een lagere Dlco een hogere mortaliteit bij patiënten die zuurstoftherapie krijgen of bij patiënten die een longreductie ondergaan.

Luchtwegen weerstand

Er werden geen kwalitatief goede studies over de klinische waarde van luchtwegen weerstand geïdentificeerd.

Respiratoire weerstand

Er kan geen duidelijk besluit getrokken worden over de diagnostische waarde van de forced oscillation technique of de interrupter technique, op basis van de resultaten van deze review.

KLINISCHE PRAKTIJKAANBEVELINGEN

METHODE

Gebaseerd op de beschikbare studies uit de vorige hoofdstukken heeft een expert panel bestaande uit longartsen en huisartsen klinische praktijkaanbevelingen geformuleerd.

Elke aanbeveling kreeg een graad van aanbeveling (grade of recommendation) volgens GRADE, waarbij het niveau van bewijs gecombineerd wordt met de balans tussen voor- en nadeel voor de patiënt. Het niveau van bewijs (level of evidence) werd ingedeeld in A, B of C verwijzend naar hoog, matig of laag en heel laag niveau van bewijs. De balans tussen voor- en nadeel is ingedeeld in 1 en 2, verwijzend naar respectievelijk een sterke aanbeveling en een zwakke aanbeveling.

Er worden enkel aanbevelingen gedaan over de geselecteerde longfunctie testen. Deze richtlijn moet derhalve niet beschouwd worden als een exhaustieve richtlijn over het volledige klinische beleid van de patiënt. Andere testen, zoals uitgeademd NO, arteriële bloedgassen of testen van de respiratoire spierkracht kunnen in bepaalde situaties geïndiceerd zijn maar worden hier niet beschouwd.

In de aanbevelingen wordt de term 'verwezen patiënten' gebruikt om alle patiënten te beschrijven die zich aanbieden aan de tweede, gespecialiseerde lijn na een initiële evaluatie in de eerste lijn. Het is niet de bedoeling van het experten panel om te beschrijven wanneer en hoe patiënten moeten verwezen worden. De term wordt louter gebruikt om een geselecteerde groep van patiënten aan te duiden die op het vlak van klinische presentatie, duur van de ziekte, differentiële diagnosen en dergelijke verschilt van patiënten uit de eerste lijn. Gemiddeld presenteren patiënten in de tweede lijn als groep met een ander spectrum: zeldzamere aandoeningen zijn meer frequent, patiënten presenteren zich in een verder gevorderd stadium van de ziekte, reageren slechter op therapie en hebben vaker co-morbiditeit.

Astma diagnose

Bij patiënten met klachten en symptomen suggestief voor astma moet variabele luchtwegobstructie worden aangetoond, door spirometrie of een andere methode [grade of recommendation 1A]. In een geselecteerde groep, waar er diagnostische onzekerheid blijft kan een bronchodilatatie test, totale long capaciteit, luchtwegen resistentie en provocatie testen geïndiceerd zijn [1C]. DI_{CO} is niet geïndiceerd, tenzij er verdenking is op COPD, waardoor deze patiënten ook in de categorie 'COPD diagnose' vallen [1C].

Astma follow-up

Patiënten moeten een spirometrie krijgen tijdens de follow-up [1A]. Het optimale interval tussen testen hangt af van de klinische presentatie van de patiënt. Een bronchodilatatie test is aanbevolen bij luchtwegobstructie ondanks behandeling [2C]. Als er een vermoeden is van 'small airway disease' is een totale long capaciteit geïndiceerd [1C]. Luchtwegen weerstand kan getest worden bij die patiënten die bij diagnose een abnormaal resultaat hadden [2C]. Algemeen gesteld is een provocatie test niet nodig bij de follow-up, behalve bij patiënten met seizoensgebonden astma met symptomen buiten het pollenseizoen [1B]. DI_{CO} is niet geïndiceerd [1C].

Asthma exacerbatie

Dezelfde testen worden aanbevolen bij een astma opstoot, behalve provocatie testen die hier niet geïndiceerd zijn [1C].

Screening voor COPD

Er werd geen studies gevonden die het nut van COPD screening aantonen. Daarbij werd de veronderstelling dat de aanwezigheid van luchtwegobstructie, zoals vastgelegd door spirometrie, de patiënt zou aanzetten tot rookstop niet bevestigd in meerdere gerandomiseerde studies. Om die redenen wordt screening in gezonde personen niet aanbevolen [1A].

Case finding van COPD

Gerandomiseerde studies die een positief effect op de uitkomst bij de patiënt aantonen zijn niet beschikbaar. Maar studies hebben wel aangetoond dat case finding in staat is om COPD patiënten in een vroeg stadium van de ziekte te diagnosticeren, en dat behandeling mogelijk effectief is bij deze patiënten. Om die redenen wordt case finding van COPD aanbevolen [1B].

COPD diagnose

Patiënten met verdenking op COPD op basis van hun klachten en symptomen moeten een spirometrie krijgen [1A]. Een bronchodilatatie test moet gereserveerd blijven voor patiënten met blijvende diagnostische onzekerheid [1C]. Totale long capaciteit en thoracaal gas volume zijn niet geïndiceerd bij patiënten in de eerste lijn, maar kunnen geïndiceerd zijn bij patiënten verwezen naar de tweede lijn, omwille van het prognostische belang van een abnormaal resultaat [respectievelijk 2B and 2C]. Een DI_{CO} is ook geïndiceerd bij verwezen patiënten, of bij patiënten met klachten en symptomen die niet in verhouding staan tot het spirometrie resultaat [2B]. Luchtwegen weerstand en provocatie testen zijn niet geïndiceerd, omdat zij na spirometrie geen bijkomende informatie geven op basis van de momenteel beschikbare studies [1C].

COPD follow-up

Spirometrie is aangewezen bij de follow-up van COPD patiënten [1A]. Ook hier is het interval afhankelijk van de klinische presentatie. Andere longfunctietesten zijn niet nodig [1C], behalve thoracaal gasvolume als de symptomen niet in verhouding zijn tot het spirometrie resultaat en er een vermoeden is van hyperinflatie [1B].

COPD exacerbatie

Patiënten opgenomen in het ziekenhuis omwille van een COPD opstoot moeten een spirometrie krijgen, hoewel deze niet altijd mogelijk is tijdens de acute fase [2C].

Interstitiële longaandoening, systemische aandoening en primaire pulmonaire hypertensie, diagnose

Bij de initiële presentatie moeten deze patiënten een spirometrie en een totale longcapaciteit krijgen gezien deze mee de ziekte definiëren [1A]. Patiënten gediagnosticeerd met scleroderma moeten een DI_{CO} krijgen [1B]. DI_{CO} geeft prognostische informatie in de overige patiënten [1C].

Interstitiële longaandoening, systemische aandoening en primaire pulmonaire hypertensie, follow-up

Zoals bij de diagnose zijn spirometrie en totale longcapaciteit geïndiceerd [1A]. DI_{CO} is geïndiceerd voor prognostische redenen bij patiënten met ILD, scleroderma en pulmonaire hypertensie [1B].

Thorax wand pathologie, diagnose

Alle patiënten met verdenking op thorax wand pathologie moeten een spirometrie en totale long capaciteit krijgen [respectievelijk 1A and 1B].

Dyspnee

Patiënten met klachten en symptomen suggestief voor astma of COPD vallen in die categorie en worden hier niet beschouwd.

Elke patiënt met dyspnee moet een spirometrie [1A], totale longcapaciteit [1C], en DI_{CO} [1C] krijgen. Een provocatie test is geïndiceerd wanneer er diagnostische onzekerheid blijft na voorgaande testen [1C].

Chronische hoest

Zoals bij de patiënten met dyspnee, horen patiënten met een beeld suggestief voor astma of COPD hier niet thuis.

Elke patiënt met chronische hoest moet een spirometrie [1A] en een totale longcapaciteit [1C] krijgen. Zoals hierboven zijn provocatie testen geïndiceerd in geval van blijvende diagnostische onzekerheid [1C].

	Astma diagnose	Astma follow-up	Astma exacerbatie	COPD diagnose	COPD follow-up	COPD exacerbatie	ILD diagnose	ILD follow-up	Dyspnee	Chronische hoest
Spirometrie	+ [1A]	+ [1A]	+ [1A]	+ [1A]	+ [1A]	+ [2C] opgenomen patiënten	+ [1A]	+ [1A]	+ [1A]	+ [1A]
Bronchodilatatie test	+ [1C] geselecteerde patiënten	+ [1C] onvoldoende respons op therapie	+ [1C] onvoldoende respons op therapie	+ [1C] geselecteerde patiënten	- [1C]	- [1C]	- [1C]	- [1C]	- [1C]	- [1C]
Totale long capaciteit [TLC]	+ [1C] geselecteerde patiënten	+ [1C] small airway disease	+ [1C] small airway disease	+ [2B] verwezen patiënten	+ [1B] hyperinflatie	- [1C]	+ [1A]	+ [1A]	+ [1C]	+ [1C]
Thoracaal gas volume	- [1C]	- [1C]	- [1C]	+ [2C] verwezen patiënten	+ [1B] hyperinflatie	- [1C]	- [1C]	- [1C]	- [1C]	- [1C]
Luchtwegen weerstand	+ [1C] geselecteerde patiënten	+ [2C] abnormaal bij diagnose	+ [2C] abnormaal bij diagnose	- [1C]	- [1C]	- [1C]	- [1C]	- [1C]	- [1C]	- [1C]
Provocatie test	+ [1C] geselecteerde patiënten	+ [1B] seizoensgebonden a met symptomen buiten seizoen	- [1B]	- [1C]	- [1C]	- [1C]	- [1C]	- [1C]	+ [1C] geselecteerde patiënten	+ [1C] geselecteerde patiënten
Diffusie capaciteit	- [1C]	- [1C]	- [1C]	+ [2B] verwezen patiënten	- [1C]	- [1C]	+ [1B] sclerodermapatiënten + [1C]	+ [1B]	+ [1C]	- [1C]

CONCLUSIES EN BELEIDSAANBEVELINGEN

Het gebruik van longfunctietesten is bijna verdubbeld op 10 jaar en dit quasi overwegend in de ambulante zorg. Meer dan de helft van de patiënten die minstens één longfunctietest krijgen, krijgt een combinatie van testen. De Belgische nomenclatuur is verouderd, en correspondeert slecht met de wetenschappelijke literatuur zowel op het vlak van benamingen van testen als op het vlak van klinische indicaties. Vooral de code 'ventilatie mechaniek' is onduidelijk en kan aanleiding geven tot ongepast gebruik.

- De klinische aanbevelingen uit dit rapport zouden de basis moeten vormen van een integraal programma voor kwaliteitsverbetering. Andere interventies die hierin kunnen worden opgenomen zijn feedback rapporten waarin de arts informatie krijgt over zijn/haar longfunctie aanvragen in vergelijking met andere artsen of richtlijnen, discussie groepen waarin de richtlijnen worden aangepast aan de locale context, of financiële incentives die het aantal testen doen verminderen.
- Kwaliteitscontrole en standaardisatie zijn essentieel voor het correcte gebruik van longfunctie testen. Kwaliteitsindicatoren die ontwikkeld en opgevolgd worden kunnen deze kwaliteit en standaardisatie mee garanderen.
- De terugbetaling van elke longfunctie test apart fungeert als een financiële stimulans voor het gecombineerd en repetitief aanwenden van deze testen. Een globale terugbetaling voor longfunctie evaluatie zou deze financiële stimulans verminderen, en tegelijk flexibiliteit bieden voor de introductie van nieuwe technieken, zoals uitgeademd NO. Dit mag echter een onafhankelijke evaluatie van nieuwe technologie vooraleer deze toegepast wordt in de klinische praktijk niet uitsluiten.

Scientific Summary

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1 INTRODUCTION

1.1 GENERAL CONSIDERATIONS

Pulmonary function tests are used to measure the function of the airways, pulmonary parenchyma, pulmonary vasculature and respiratory muscles. They may be helpful to detect and quantify pulmonary dysfunction in a range of clinical situations such as the initial diagnosis of pulmonary diseases, assessment of disease severity, monitoring disease progression and response to therapy, assessment and monitoring of toxic effects, assessment of preoperative risk and assessment of disability and impairment. Pulmonary function tests have also been used to categorise patients in terms of impairment, disability and handicap.

Tests considered in this report are those reimbursed by the Belgian health care, and are by consequence those tests commonly used in daily practice: spirometry, lung volumes, diffusing capacity and resistance. It should be noted that various, more recent pulmonary tests are not considered in this report, such as exercise testing, analysis of exhaled gases, or measurement of muscular strength.

Spirometry is the cornerstone of pulmonary function testing, particularly in obstructive disease. Conditions causing an obstructive defect include asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, bronchiectasis and less frequent disorders such as bronchiolitis. In COPD, the airflow obstruction is mainly localised in the small airways, whereas in asthma obstruction is localised in both the large and small airways. In spirometry, the patient inhales to total lung capacity (TLC) and then exhales with maximal effort to residual volume (RV). The forced expiratory volume exhaled in 1 second (FEV1) can be recorded and expressed as a percentage of the expiratory forced vital capacity FVC (FEV1/FVC ratio). However, the European Respiratory Society advises the use of the vital capacity (VC) instead of the FVC, as they state that FEV1/FVC underestimates the degree of obstruction. Results for an individual can be compared with reference values matched for age, gender, standing height and ethnicity. The range of normal values for the FEV1 and FVC is between ±1.64 SD of that predicted from reference values. Spirometry results are dependent on lung elastic recoil, expiratory muscle strength and airway obstruction, as well as patient cooperation in performing the test. Other influencing factors are thickening of the airway mucosa, loss of airway parenchyma dependence and competition for space. As spirometry is effort-dependent, trained personnel are required in order to obtain reproducible results. In interpreting the results of the spirometry, the quality of the manoeuvre, the flow-volume loops and volume-time tracings should be taken into account.

Flow volume loops are a graphic display of in- and expired lung volume on one axis and simultaneously measured airflow on the other axis. By visual inspection of its shape, flow volume loops allow a rapid screening for certain disorders such as upper airway obstruction, peripheral airway obstruction or muscle weakness.

Reversibility of airflow limitation is assessed by performing spirometry before and after bronchodilator administration. By definition, a patient in whom the airflow obstruction is completely reversible is diagnosed with asthma.

Bronchial hyperresponsiveness may be demonstrated by an exaggerated response to a bronchoconstrictor stimulus, which can be pharmacological (e.g. histamine, metacholine) or physical (e.g. cold, dry air and nonisotonic aerosols).

Office spirometers are used outside the pulmonary function laboratory, for example in general practice. Precision of these spirometers has been found to be sufficient, although some showed limits of agreement with conventional spirometers for FEV1/FVC of -16.2 to 20.3%[1].

Peak expiratory flow (PEF) monitoring using a portable PEF meter can be valuable in assessing the diurnal variability of airflow obstruction, as well as the response to therapy

in patients with asthma. PEF is also used in patients suspected of occupational asthma, or as a screening test at the emergency department. PEF measurements are also effort dependent and some instruments have been found to have fairly low agreement with spirometry[2].

A restrictive ventilatory defect may be suspected on spirometry but should be confirmed by measurements of static lung volumes *(Table 1)*. Spirometry is able to rule in obstruction, but not to rule in restriction. Conditions causing a restrictive ventilatory defect include interstitial lung disease, respiratory muscle weakness and restrictive chest wall disease such as kyphoscoliosis. In addition, patients showing a restrictive pattern may have mixed pathologies, or cardiac failure.

Lung volumes are thus required for the diagnosis of restrictive lung disease, but are also used for the definition of hyperinflation in COPD. In cases of severe airflow obstruction, measurement of lung volumes is required for a reliable estimation of alveolar volume and diffusion capacity. They include subdivisions of vital capacity (which can be measured by simple spirometry) and residual volume (which can not be measured by spirometry but should be measured by either gas dilution, gas wash-out or body plethysmography).

Table 1: simplified classification of ventilatory abnormalities found by spirometry

	Obstructive pattern	**Possible restrictive pattern**
FEV_1	decreased	decreased
FVC	normal (or decreased if very severe)	decreased
FEV_1/FVC	decreased	normal or increased

Table from: Therapeutic Guidelines: Respiratory. Version 3, 2005.

Total lung capacity (TLC) and residual volume (RV) measurements, either measured with a wash-out or gas-dilution technique or a plethysmographic technique require a (slow) spirometry, that is performed either before or after the test, since the primary variable measured is functional residual capacity (FRC), and the RV and TLC values are derived from the FRC value. It is advisable to compare the spirometric maneuvers performed before or after determination of FRC with those obtained previously, during a more relaxed maneuver as some patients experience difficulties to take a full expiration in the plethysmograph or during a lengthy wash-out or dilution technique.

The transfer factor of the lung refers to the gas transfer from alveolar spaces into pulmonary capillary blood, consisting of molecular diffusion and binding to the haemoglobin. Measurement of the transfer factor is done using carbon monoxide because of its high avidity for haemoglobin which allows back pressure to diffusion to be considered negligible. The test is performed for suspected or proven interstitial lung disease, pulmonary vascular disease, pulmonary toxicity caused by drugs or radiation, haemorrhagic lung disease, cardiac failure, systemic disease, COPD, neuromuscular disease, thoracic wall deformity or extrinsic allergic alveolitis. Standardisation efforts have led to increased reproducibility[3]. The choice of reference values for each laboratory needs to take the type of equipment used into account[4]. A determination of the DL_{CO} should be preceded by spirometry, in order to assess whether the patient inhaled enough volume. Indeed, the inspiratory volume should exceed 90% of the vital capacity. The alveolar volume (VA) also has to be measured to assess the diffusion and be compared to the TLC.

2 SCOPE AND METHODS

Data from the Belgian health care insurance indicate increasing volumes of some pulmonary function tests in clinical pulmonary practice: spirometry, bronchodilator reversibility testing, determination of residual volume, diffusing capacity (Dlco) and the investigation of ventilatory mechanics. It is not within the aim of this report to investigate the reasons for this increase. Various explanations have been proposed, for example increasing prevalence of pulmonary diseases in an aging population, correction of underuse from the past or inappropriate use.

The report will focus on those pulmonary function tests that are currently included in the Belgian nomenclature. As the highest volumes and/or increases in volumes are noted in adult patients in ambulatory practice, the scope of this project will be restricted to this setting.

First, a more detailed description on the use of clinical pulmonary function tests in Belgium is provided, i.e. the Belgian health care nomenclature, medical specialties that have access to pulmonary function nomenclature-codes and the actual use of pulmonary function tests.

Secondly, a literature review on quality standards and clinical efficacy of pulmonary function tests are presented. In this review, systematic methods were used to search and assess studies. It should be noted that many studies on pulmonary function tests date from several decades ago, when quality standards for diagnostic or prognostic studies were less well developed. As will become apparent from the results of the review, many studies were excluded due to either insufficient detail for quality assessment or to study design prone to bias. Due to the relative small evidence base, an additional approach starting from disease-based guidelines was chosen as well.

Finally, based on the best available evidence, recommendations on the most appropriate use of the pulmonary function tests were made. In case no evidence was available, expert opinion was used to formulate clinical practice recommendations. Assessment of preoperative risk and of disability and impairment is beyond the scope of this project. A preceeding KCE report authored guidance on the preoperative evaluation of adults eligible for elective surgery (excluding patients having thoracic or cardiac surgery)[5].

3 PULMONARY FUNCTION TESTING IN BELGIUM

3.1 INTRODUCTION

The present chapter discusses the use of and expenditure for pulmonary function tests in Belgium. It is intended as background to the main topic rather than comprising an exhaustive overview.

The health care insurance in Belgium reimburses pulmonary function tests using a dedicated nomenclature. In this nomenclature, each item is identified by a unique number and is attributed a fixed reimbursement amount. The pulmonary function tests described in the previous chapters do not map one to one with the nomenclature used for pulmonary function tests. For certain pulmonary function tests, different nomenclature numbers can be charged depending on the addition of e.g. bronchodilation or provocation. Moreover, nomenclature numbers can represent more than one type of pulmonary function test. In the present study, six nomenclature items were retained for further study of pulmonary function tests in Belgium (see table 2):

Table 2. Nomenclature with nomenclature cost (2004) for tests performed ambulatory[1].

		Preferential[2]		Non-preferential	
Nomenclature	Description	RIZIV[3]	Patient	RIZIV	Patient
471251/471262	Complete spirography	10.19 €	0.00 €	8.67 €	1.52 €
471273/471284	Spirography + bronchodilation	20.38 €	0.00 €	17.33 €	3.05 €
471295/471306	Spirography + provocation	35.67 €	0.00 €	30.32 €	5.35 €
471310/471321	Residual volume	40.77 €	0.00 €	34.66 €	6.11 €
471354/471365	Diffusion capacity	40.77 €	0.00 €	34.66 €	6.11 €
471376/471380	Ventilatory mechanics	40.77 €	0.00 €	34.66 €	6.11 €

[1] The nomenclature cost for the in hospital tests considered here is equal to the ambulatory performed tests except for the non-preferential, where the reimbursement is equal to the preferential.
[2] for patients having the benefit of a larger reimbursement in the Belgian Health Insurance
[3] Rijksinstituut voor Ziekte- en Invaliditeitsverzekering / Institut national d'assurance maladie invalidité (INAMI)'

The full description of these nomenclature numbers and their specific rules of application can be found in the appendix to this chapter.

From the rules of application 3 and 7 (see appendix) it is inferred that ventilatory mechanics is confined to measurement of airway resistance, measurement of dynamic resistance (respiratory resistance) and measurement of lung compliance with an intraesophageal catheter. Airway resistance (Raw) is measured by Body Plethysmography. Respiratory resistance (Rrs) is measured by the Forced Oscillation Technique or Interrupter Technique.

Our first objective concerns the use and health care expenditure for the government of pulmonary function tests: to what extent have the nomenclature numbers been used in Belgium and what is the corresponding expenditure for the governmental health care insurance?

We explored the use and health care expenditure in more detail for 2004 on data retrieved from the Belgian health insurers. The following questions were studied:

1. What was the number of tests in function of the patient characteristics given the pulmonary function tests concerned?
2. Which combinations of the pulmonary function tests were usually performed together (i.e. on the same day), and were these tests repeated frequently within one year?
3. Who were the main performers of these tests?

3.2 METHODOLOGY

Data on use of and nomenclature expenditure for the six selected pulmonary function tests between 1995 and 2004 were obtained from the national institute for health care insurance 'Rijksinstituut voor Ziekte- en Invaliditeitsverzekering (RIZIV) / Institut National d'Assurance Maladie Invalidité (INAMI)'. A distinction was made between tests performed ambulatory and tests performed in hospital. Moreover, for 2003, we retrieved the number of physicians by specialist category and the number of tests they had performed from RIZIV/INAMI. The appendix to this chapter contains a table specifying how we defined the specialist categories. In short, physicians were categorised according to their RIZIV/INAMI code.

Data from the RIZIV/INAMI do not allow a detailed analysis in terms of test combinations or repetition in the same patient. Therefore, the detailed analyses of use of the six tests in 2004 were conducted on data retrieved from the Belgian health insurers (Intermutalistisch Agentschap; IMA). IMA has drawn a sample from the total health insurers' database: 1 out of 40 (2.5%) of the Belgian population up until the age of 64 and 1 out of 20 (5%) of the Belgian population over 65 (for a detailed description of the sampling procedure see[6]). Of this sample of the Belgian population, all patients with at least one of the pulmonary function tests in table 1 were selected. This dataset was used for the analyses in the present chapter. Data were available on number of tests, patient characteristics and combinations of tests. Tests were considered to be administered in combination when the multiple tests occurred on the same day for the same patient.

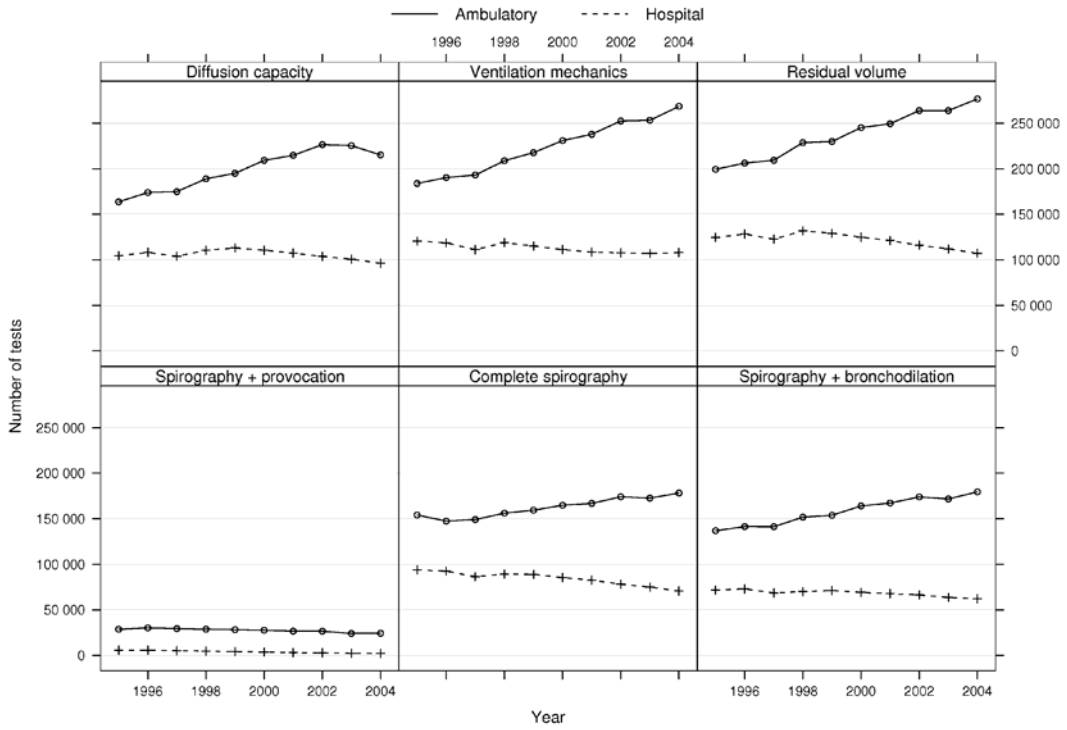
Data analyses and graphs were produced using SAS 9.1.3[7] and R 2.4.0[8].

3.3 RESULTS

3.3.1 RIZIV/INAMI data on nomenclature

The majority of the selected pulmonary function tests were performed ambulatory (see figure 1). Except for Spirography with provocation, all tests performed ambulatory showed an increase of use, while those performed in hospital tended to decline over the years (see figure 1).

Figure 1. Number of tests between 1995 and 2004 performed ambulatory or in hospital of six pulmonary function tests (RIZIV)

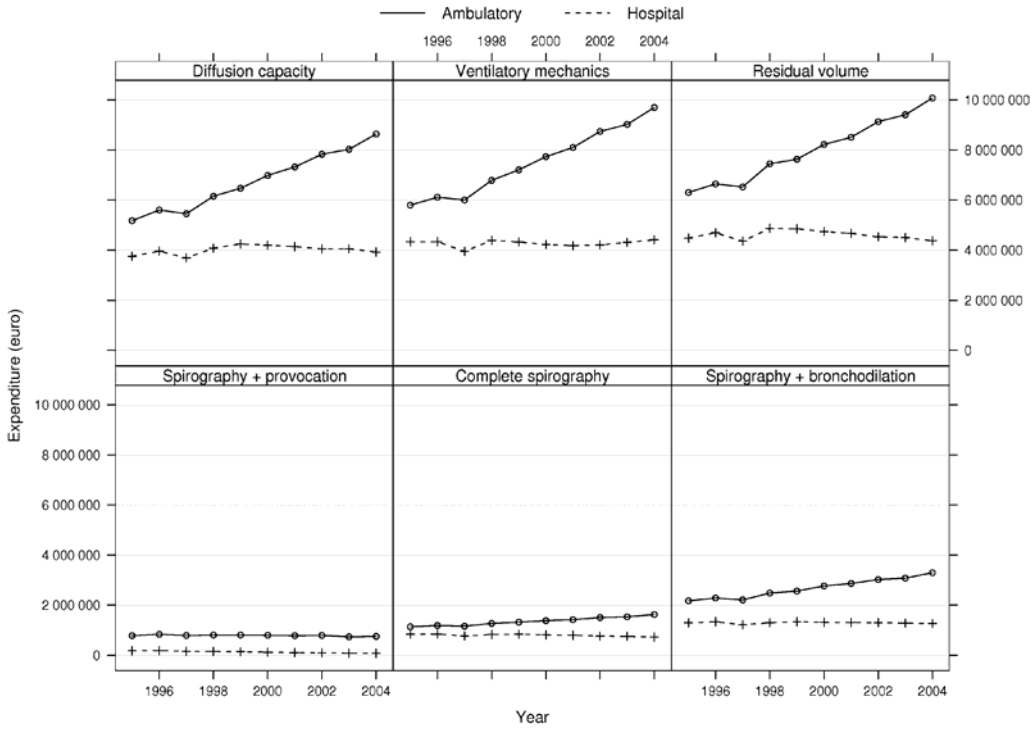


The most common tests used were diffusion capacity, residual volume, and ventilatory mechanics, followed by complete spirography and spirography with bronchodilation. Combining the various codes pertaining to spirometry, spirometry with or without bronchodilation or provocation is the most commonly performed test. The results in figure 1 suggest that diffusion capacity, residual volume, and ventilatory mechanics were often performed in one session. However, the nature of the RIZIV/INAMI data does not allow the linking of the tests. The more detailed analysis provided in the section on IMA data further on considers the linkage of pulmonary function tests.

The total expenditure for the six pulmonary functions tests for 2004 was €48 844 757 of which €34 072 393 for ambulatory tests and €14 772 364 for in hospital tests. In comparison, the total nomenclature expenditure for article 20 §1b of the nomenclature (specialism pneumology) was €48 844 757, while €425 885 751 for article 20 (specialism internal medicine including pneumology). As a further comparison, the expenditure of ambulatory attested medication in ATC class level R03 (drugs for obstructive airway diseases) in 2005 was €155 698 696.

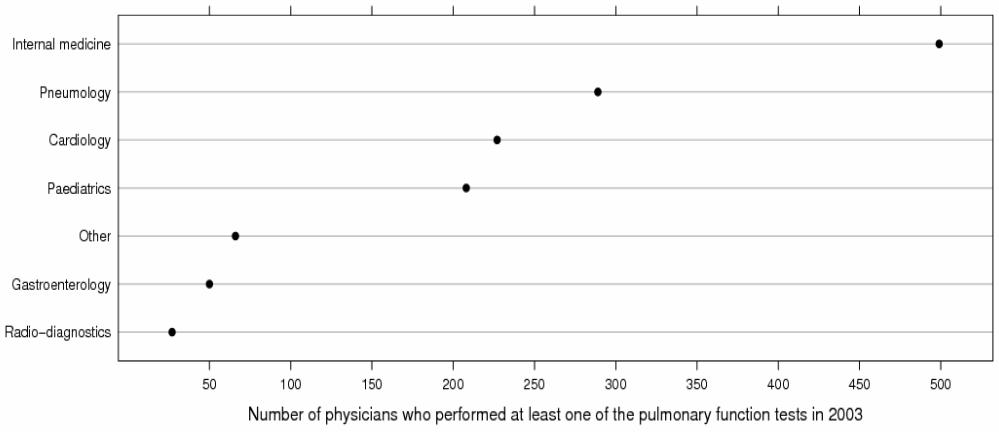
Because the nomenclature numbers corresponded to a fixed reimbursement amount, all effects on number of tests equally apply to the expenditure for these tests. Therefore, the results concerning the number of tests by test and year were similar for the expenditure (see figure 2).

Figure 2. Expenditure in euro between 1995 and 2004 performed ambulatory or in hospital of six pulmonary function tests (RIZIV)



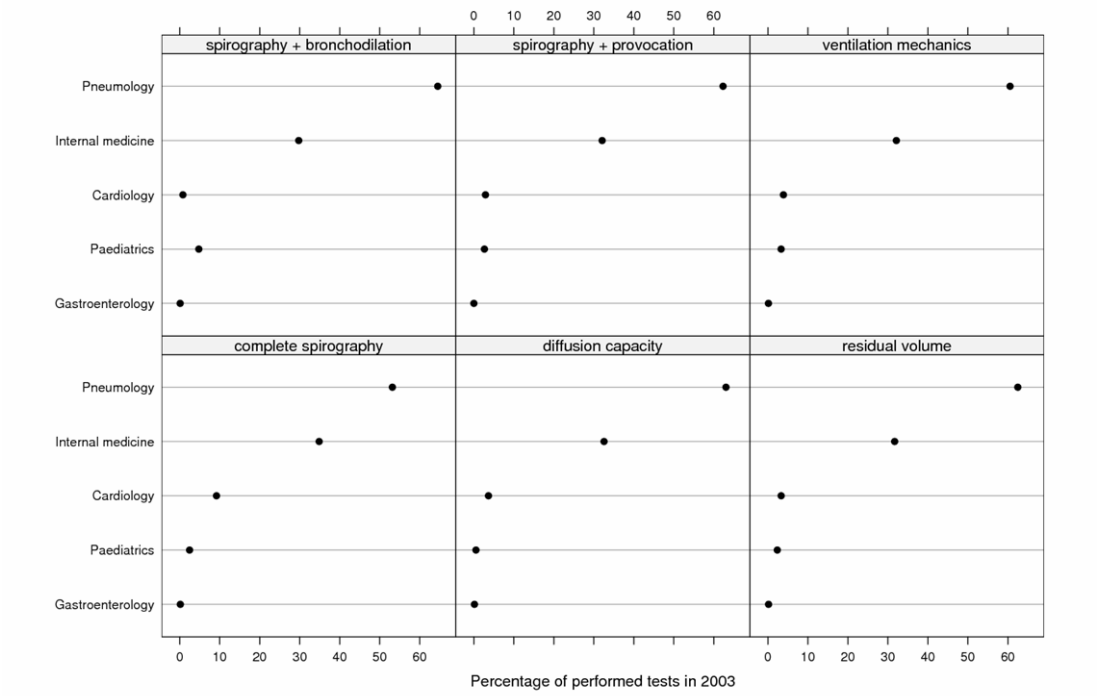
The largest group of performers of pulmonary function tests were internal medicine physicians, followed by pulmonologists, cardiologists and paediatricians (see figure 3).

Figure 3. Number of physicians by specialism in 2003 who performed at least one of the selected respiratoy function tests



The vast majority of the tests in 2003 were performed by pulmonologists (over 55%) and internal medicine physicians (over 30%) (figure 4). A similar distribution of the proportion of tests per specialism is found for all selected pulmonary function tests.

Figure 4. Percentage of performed tests per specialism for each of the selected pulmonary function tests in 2003 (only the five largest proportions are shown).

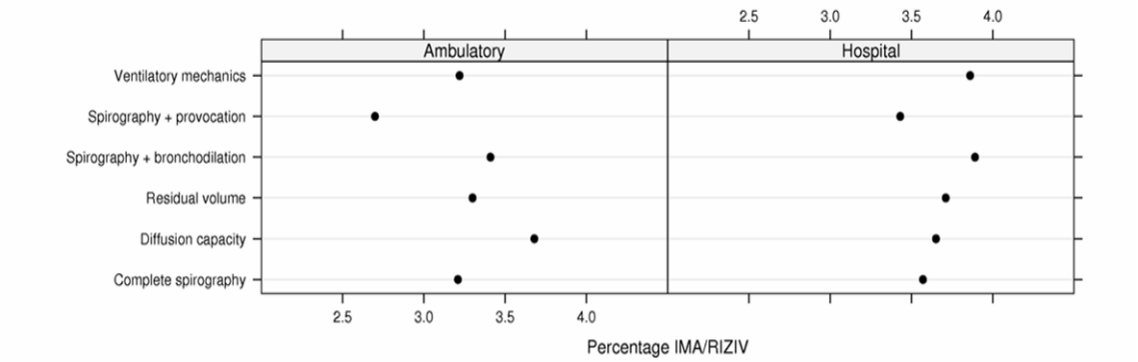


3.3.2 IMA data for 2004

As an approximation for the representativeness of our sample, we compared the number of tests in the IMA sample for 2004 with the total number of tests according to RIZIV/INAMI data for 2004. The results showed that the sample was slightly larger than was to be expected from the sampling procedure[a]: all ambulatory tests but one over 3% and all hospital tests but one over 3.5% (see figure 5).

[a] 1 in 40 (2.5%) under 65 and 1 in 20 (5%) over 65 .

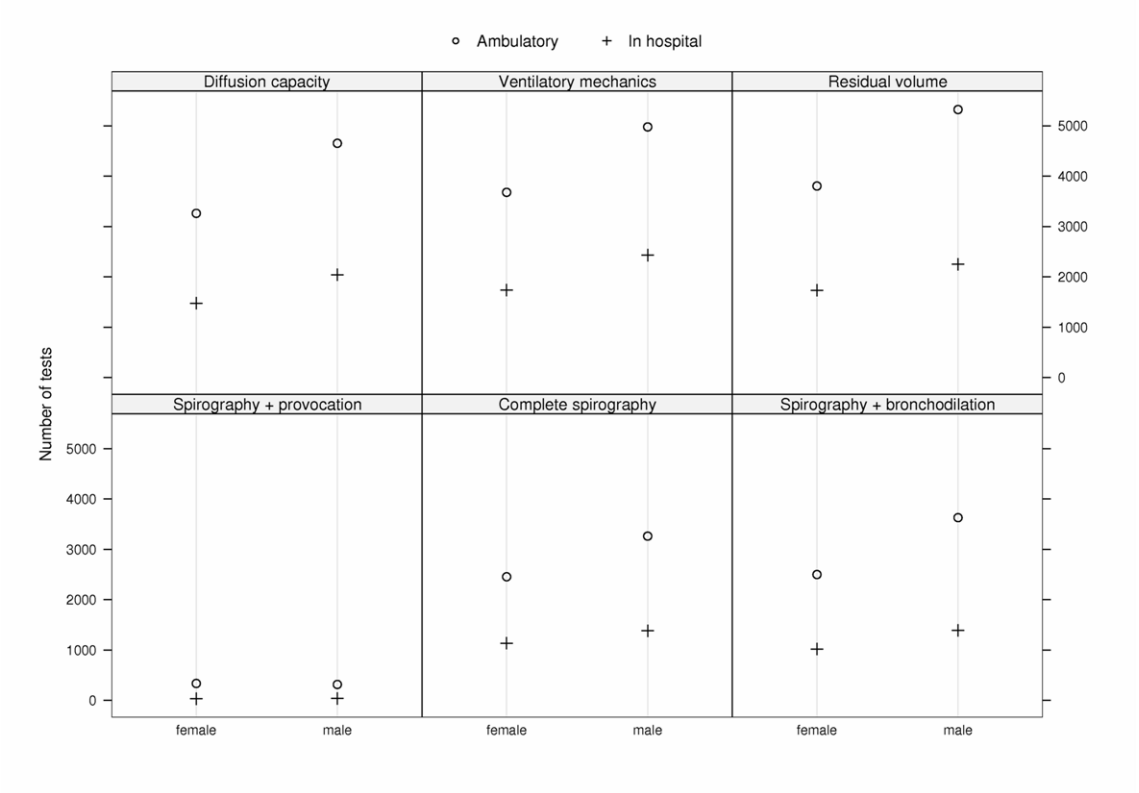
Figure 5. Percentage of number of tests in IMA sample versus number of tests in RIZIV data in 2004 by pulmonary function test and type of performance



3.3.2.1 *Number of tests and patient characteristics in the IMA sample of 2004.*

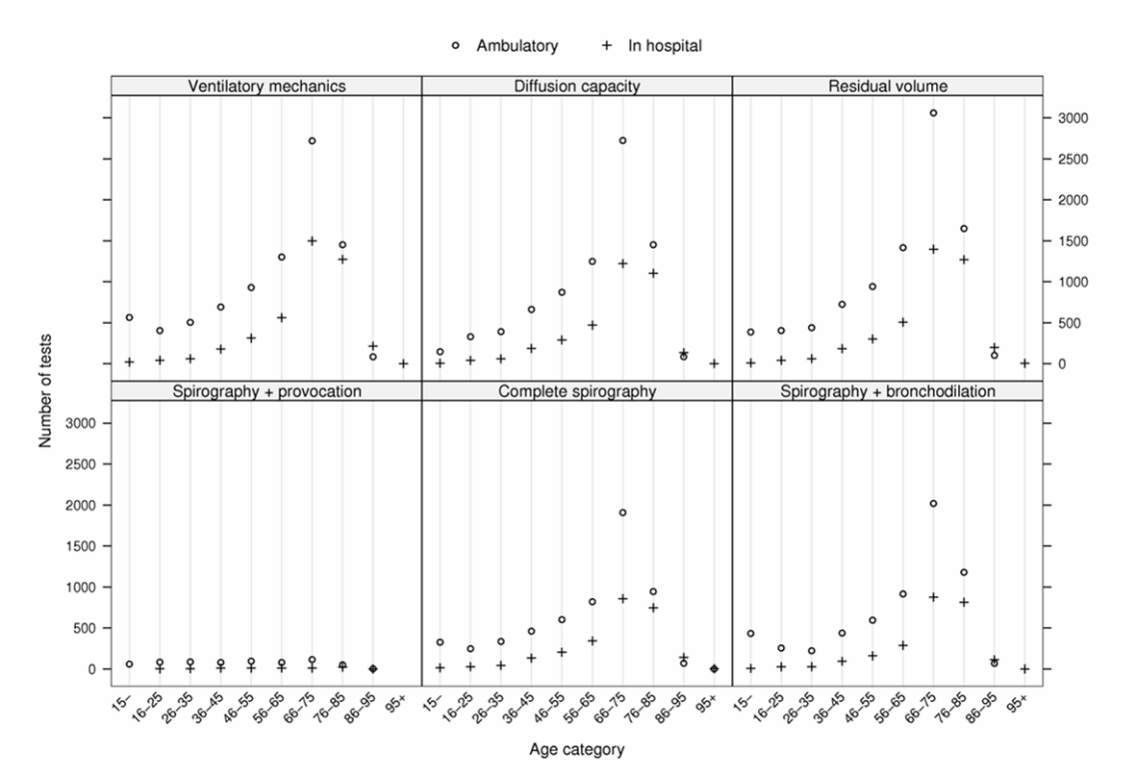
Male patients in the sample had a larger number of tests compared to female patients for all selected pulmonary function tests except for Spirography with provocation (see figure 6). This was found independent whether the test was performed ambulatory or in hospital.

Figure 6. Number of tests in 2004 for male and female patients by type of pulmonary function test and by type of performance



Up until the age category of 66 to 75, the older the patient, the more tests were performed for all selected pulmonary function tests. From the age category of 76 to 84 onward a decline was noted (see figure 7). Patients in the 66 to 75 age category received the largest number of tests. No difference in age distribution was found between tests performed ambulatory and tests performed in hospital.

Figure 7. Number of tests in 2004 for different age categories by type of pulmonary function test and by type of performance

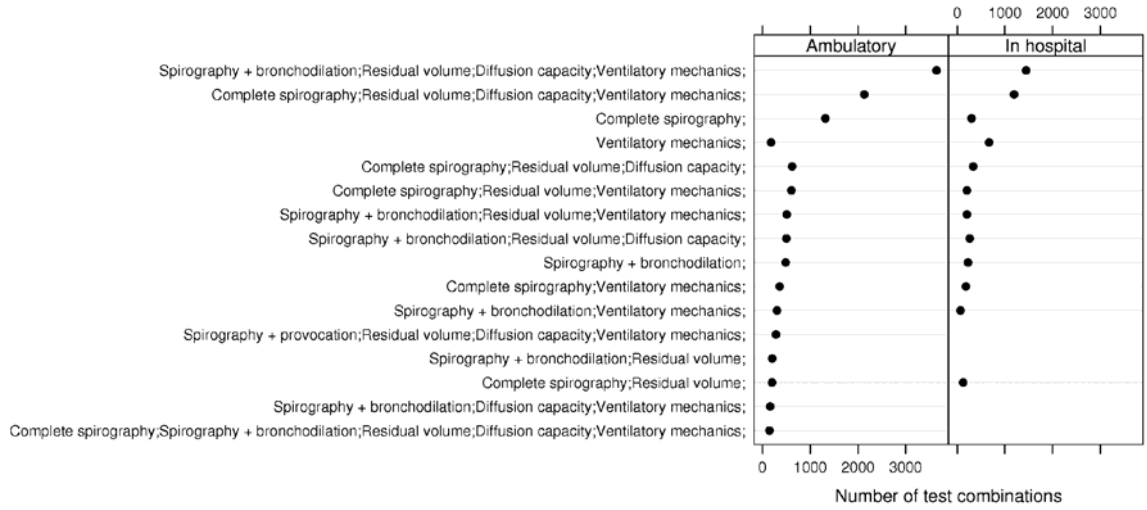


3.3.2.2 Combinations of tests

In this section, it was analysed whether or not patients received more than one test on one day. Every possible test combination was analysed, including single tests.

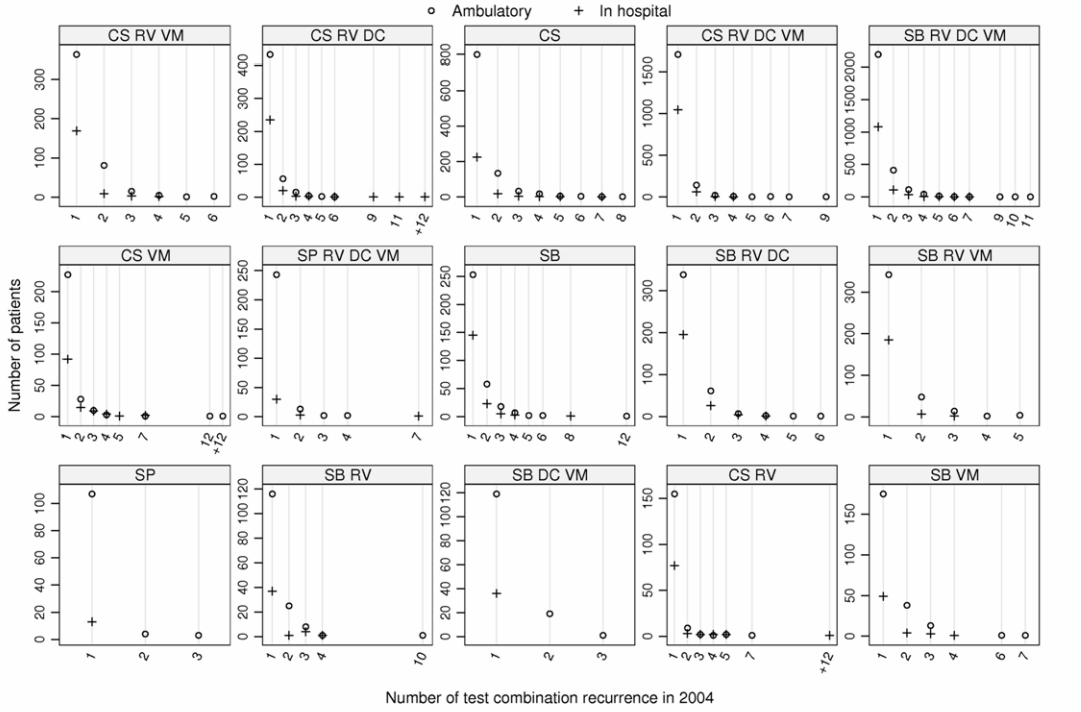
By far the most commonly performed, was spirography with bronchodilation combined with residual volume, diffusion capacity, and ventilatory mechanics (see figure 8). This combination represented respectively 29.4% and 25.8% of all ambulatory and in hospital performed tests in the IMA sample. The second most common comprised complete spirography and the same sequence of tests of the first combination except for spirography with bronchodilation. This combination represented respectively 17.2% and 21.8% of all ambulatory and in hospital performed tests in the IMA sample. These two combinations account for over 50% of all tests performed in both ambulatory and hospital care. For ambulatory performed tests, complete spirography was the third most common test, representing 10.6% of all tests. For tests performed in hospital, ventilatory mechanics claimed third place (11.9%). The appendix to this chapter provides the list with all 49 test combinations found in the IMA sample.

Figure 8. Number of test combinations in the IMA sample 2004 per combination of tests by type of performance (only combinations representing at least 1% of the total number of tests are shown; for all combinations, see appendix to this chapter)



Most of these test combinations were performed only once or twice per patient in 2004 in the IMA sample (see figure 9). Only a small minority of the patients in the sample received the same test combination more than three times within the same year. This pattern did not differ for test combinations performed ambulatory or in hospital. However, not all test combinations were performed both ambulatory and in hospital (see table in the appendix to this chapter and figure 9). Particularly the high recurrences of test combinations were found either in ambulatory tests or in tests performed in hospital. Recurrence of combinations of tests more than 12 times within the same patient within the same year was rare.

Figure 9. Number of patients in function of test combination recurrence in 2004 by test combination. Only test combinations having at least 100 patients who had the test combination once in 2004 are shown. The scales of the y-axis of the panels differ in range. Test combinations are abbreviated:

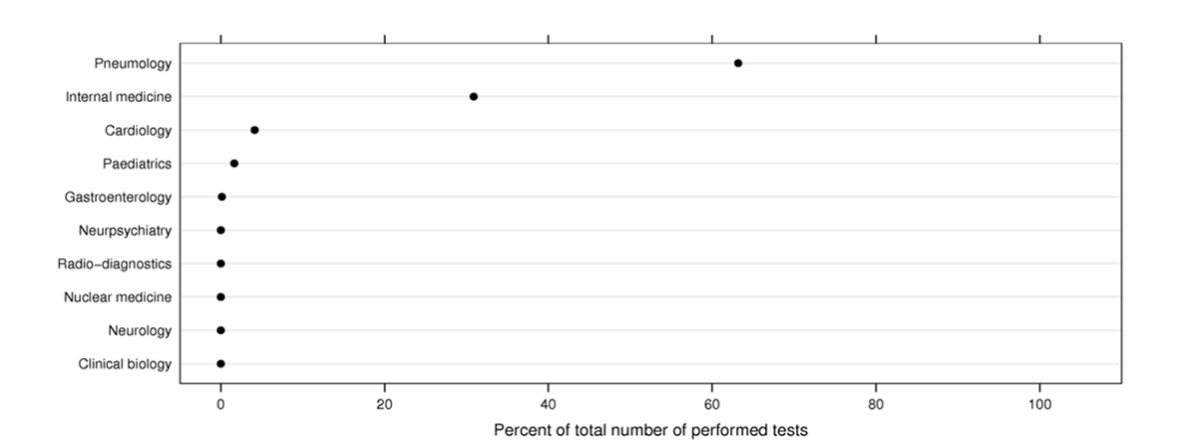


CS	Complete spirography;
CS RV	Complete spirography;Residual volume;
CS RV DC	Complete spirography;Residual volume;Diffusion capacity;
CS RV DC VM	Complete spirography;Residual volume;Diffusion capacity;Ventilatory mechanics;
CS RV VM	Complete spirography;Residual volume;Ventilatory mechanics;
CS VM	Complete spirography;Ventilatory mechanics;
SB	Spirography + bronchodilation;
SB DC VM	Spirography + bronchodilation;Diffusion capacity;Ventilatory mechanics;
SB RV	Spirography + bronchodilation;Residual volume;
SB RV DC	Spirography + bronchodilation;Residual volume;Diffusion capacity;
SB RV DC VM	Spirography + bronchodilation;Residual volume;Diffusion capacity;Ventilatory mechanics;
SB RV VM	Spirography + bronchodilation;Residual volume;Ventilatory mechanics;
SB VM	Spirography + bronchodilation;Ventilatory mechanics;
SP	Spirography + provocation;
SP RV DC VM	Spirography + provocation;Residual volume;Diffusion capacity;Ventilatory mechanics;

3.3.2.3 Type of performer

Almost all the tests in the IMA sample were performed by either pneumologists (63.17%) or by internists (30.88%) (see figure 10).

Figure 10. Percent of total number of performed tests in function of performing specialism



3.4 DISCUSSION

The RIZIV data on number of tests showed a clear increase in the ambulatory use of pulmonary function tests since 1995. In contrast, the use in hospital showed a slight decline. Overall, the number of pulmonary function tests, and consequently the RIZIV/INAMI expenditure, has increased since 1995. To what extent these results are attributable to an increase in number of patients or to other causes can not be concluded from the data available in the present study. Most of these tests were performed either by pulmonologists or physicians internal medicine. A similar result on performer was found in the IMA 2004 sample. Given the nature of these specialisms, this finding was not particularly surprising.

The RIZIV/INAMI data seemed to suggest that diffusion capacity, residual volume, and ventilatory mechanics were often administered in combination. The IMA 2004 sample confirmed this hypothesis. These three pulmonary function tests were often performed in combination with either complete spirography or spirography with bronchodilation and were the most common test combinations in the IMA 2004 sample.

Most pulmonary function tests in 2004 were performed as part of a limited number of test combinations. The four most common test combinations, the two mentioned previously plus ambulatory complete spirography and in hospital ventilatory mechanics, accounted for over 50% of all performed test combinations. Of the 49 different test combinations in the IMA 2004 sample, the 14 most common test combinations accounted for over 90% of all performed tests both ambulatory and in hospital. In other words, patients in the IMA 2004 sample usually were administered three or four pulmonary function tests in combination rather than a single pulmonary function test.

These test combinations were not repeated frequently per patient within the year 2004. Most patients in the IMA 2004 sample received their test combination only once. A much smaller number received the test combination twice. Three times or more the same test combination within a single year was rare. This suggests that most test combinations were used as a diagnostic tool rather than as follow-up. However, the present dataset did not allow either to confirm or to reject this hypothesis.

Considering the patients characteristics in the IMA 2004 sample, male patients received more pulmonary function tests than female patients. As regards age, most tests were performed in patients aged 56 to 85. Most likely, this corresponded to the higher prevalence of COPD and symptoms of dyspnoea in general within this age group.

Key points

- **In conclusion, the pulmonary function tests studied in this chapter represented a significant expenditure in 2004 to the RIZIV/INAMI.**
- **Their use and expenditure has augmented in the period considered in this study. Whether this increase can be explained by an increase in the number of patients has not been analysed.**
- **Most of these tests in the IMA 2004 sample were performed in combination rather than separately and usually only once or twice per patient in 2004.**

4 QUALITY AND STANDARDIZATION

4.1 BACKGROUND

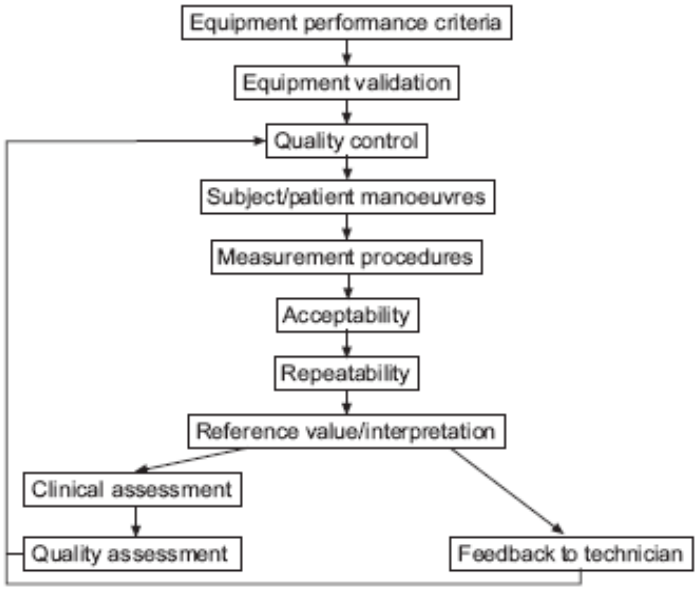
Technical and clinical practice guidelines may have the capability of improving quality, appropriateness and cost-effectiveness of care. A potential mechanism for improving performance, technical quality and interpretation of pulmonary function testing would be to ensure that patients submitted to these tests are investigated according to internationally approved standards and are receiving evidence-based care. In the past, considerable efforts have been made to improve and standardize pulmonary function tests, for example the Belgian consensus report of 2001 i.e. the chapters on quality and standardization[9], which extensively quotes preceding efforts made by the American Thoracic Society (ATS), European Respiratory Society (ERS) and other organisations or experts.

4.2 ATS/ERS CONSENSUS ON CLINICAL LUNG FUNCTION TESTING

Global initiatives undertaken for the diagnosis and treatment of pulmonary diseases have increased the pressure for more uniform pulmonary function testing across the world. This has prompted the ATS and ERS in 2001 to appoint a joint Task Force to provide standards for clinical pulmonary function tests, consisting of 19 experts in pulmonary function testing. In 2005, this joint ATS/ERS Task Force has authored a consensus on new standards on spirometry, single-breath carbon monoxide uptake in the lung ($D_{L,CO}$), and determination of lung volumes, addressing essential issues of standardization including quality, equipment, test procedures and interpretative strategies[10-15].

Elements included in the standardization are patient considerations, laboratory and equipment considerations, hygiene and infection control, personnel qualifications, reference values. In figure 1, the spirometry standardization steps are provided as an example.

Figure 1: Spirometry standardization steps, from Miller et al. Eur Resp J 2005; 26:319-38.



As these recommended standards reflect the current knowledge in the field, it should be used as a guide for good clinical practice until changes based on new scientific evidence are made.

Key points

- **Quality and standardisation are essential in pulmonary function testing to obtain precise and reproducible test results.**
- **A recent ATS/ERS consensus on pulmonary function testing (2005) aimed to summarize the knowledge in the field on quality and standardisation, which ought to be fulfilled while performing pulmonary function tests.**
- **Equipment, personnel and other measures should comply with quality standards.**

5 PULMONARY FUNCTION TESTING: SYMPTOM BASED APPROACH

A proportion of patients presenting to the physician are known to have a certain disease, and are subsequently monitored during the course of their illness. But, a proportion of patients presents with signs and symptoms suggestive of a pulmonary illness, in which diagnoses are not yet made. In addition, patients already diagnosed with a pulmonary illness may present with new signs and symptoms, warranting new investigations for possible co-morbidity.

In this chapter, a symptom based approach was followed, to summarize the evidence on the clinical effectiveness for pulmonary function tests in patients presenting with certain signs and symptoms. The signs and symptoms considered most relevant for pulmonary practice are dyspnoea and chronic cough.

5.1 DYSPNOEA

A literature search for diagnostic studies on pulmonary function tests in patients suffering from dyspnoea was conducted, starting with guidelines, subsequently followed by systematic reviews and original studies. Search date was February 2007. Inclusion criteria: pulmonary function tests, patients presenting with dyspnoea; exclusion criteria: children, hospitalized patients.

5.1.1 Guidelines:

National Guideline Clearinghouse: none

NICE: none

SIGN: none

European Respiratory Society: none

American Thoracic Society: Dyspnea - official statement

The ATS statement does not contain any details on methodology. The quality of the evidence underlying the statement therefore can not be assessed.

5.1.2 Systematic reviews:

The search terms used were ("Dyspnea"[MeSH] AND "Respiratory Function Tests"[MeSH]) AND systematic[sb]. Literature was searched in Medline and DARE.

The search identified 14 articles, of which none was relevant to the research question according to in and exclusion criteria.

5.1.3 Original studies

The search terms used were ("Dyspnea"[MeSH] AND "Respiratory Function Tests"[MeSH]) AND (specificity[Title/Abstract]). Literature was searched in Medline.

The search identified 26 articles of which 2 fulfilled in and exclusion criteria. These 2 articles were subsequently evaluated in full text, for a quality appraisal using QUADAS. The article by Malas et al.[16] failed on 8 QUADAS items, and was scored with unclear on 4 items. The article was therefore excluded from the review. The other article by Hsiue et al. failed on 7 items and was scored unclear on 4 items[17]. Equally, the article was excluded.

In conclusion, no good quality evidence on the diagnostic value of pulmonary function tests in patients presenting with dyspnoea was identified in this literature review.

5.2 CHRONIC COUGH

A similar search strategy was performed for studies on chronic cough.

5.2.1 Guidelines

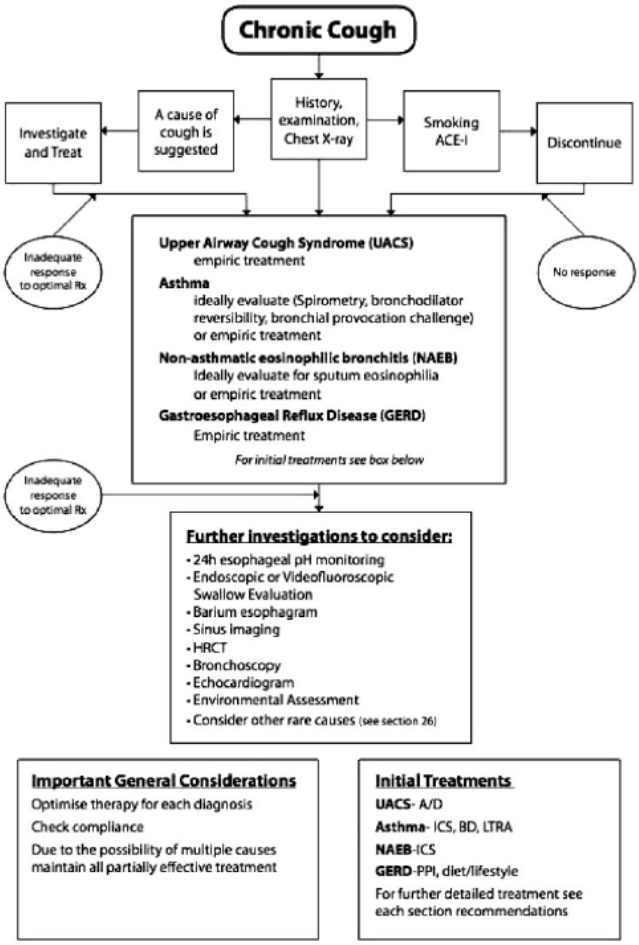
1. ERS: guideline on chronic cough management, Morice et al.[18]
2. ATS: none
3. National Guideline Clearinghouse:
   - 1 British Thoracic Society Guideline (BTS)[19];
   - 1 American College of Chest Physicians (ACCP) guideline[20].
4. NICE: none
5. SIGN: none

No details are given on the methodology of the ERS guideline. An appraisal of the quality of the guideline was therefore not possible.

The BTS guideline by Morice et al. provides details on methodology, although the authors stress the lack of evidence that was identified in the systematic literature search preceding the guideline. In general, the quality of the guideline is fair. According to the guideline, all patients suffering from chronic cough should be offered a chest radiograph and a spirometry. Patients with normal spirometry and bronchodilator response in whom the diagnoses of cough predominant asthma or eosinophilic bronchitis are being considered should be offered a therapeutic trial of corticosteroids.

The methodology for the ACCP guideline was found at the developers' website, in a separate report[21]. Systematic reviews of the evidence were made for therapeutic issues, but not for diagnostic issues. An explicit grading system was used. The guideline states that in patients with chronic cough and a normal chest roentgenogram finding who are nonsmokers and are not receiving therapy with an ACE inhibitor, the diagnostic approach should focus on the detection and treatment of upper airway cough syndrome (formerly called post nasal drip syndrome), asthma, non asthmatic eosinophilic bronchitis, or gastro oesophageal reflux disease, alone or in combination. (Level of evidence, low; benefit, substantial; grade of recommendation, B)

The following algorithm is provided on the diagnosis and management of chronic cough.



5.2.2 Systematic reviews

The search terms used were ("Cough"[MeSH] AND "Respiratory Function Tests"[MeSH]) AND systematic[sb]. Literature was searched in Medline and DARE.

The search identified 8 articles, of which none were relevant to the research question.

5.2.3 Original studies

The search terms used were ("Cough"[MeSH] AND "Respiratory Function Tests"[MeSH]) AND (specificity[Title/Abstract]). Literature was searched in Medline.

The search identified 15 articles, of which 1 was relevant to the research question (Hsiue 1993). Referring to the previous section on dyspnoea, this articles was excluded based on low quality.

Some additional articles were provided by the external experts. McGarvey et al.[22] evaluated the value of various diagnostic tests, with the resolution of symptoms after treatment as the reference standard. The study recruited a very selected patient population, as only lifetime non-smokers with a non-productive cough of more than 3 weeks, with a normal chest radiograph and spirometry were eligible. Resolution of symptoms after treatment might be a valid reference standard, provided that a randomized controlled design were used. As this was not the case, the results of this study were biased.

Two other articles, one by Pratter et al[23]. and the other by DePaso et al.[24], reported on the etiology of chronic cough and were not diagnostic accuracy studies; the articles were therefore not included in the report.

Key points

- **A symptom based approach is most informative for clinical practice.**
- **Good quality evidence on the value of pulmonary function tests in patients presenting with dyspnoea or chronic cough was not found in this review.**

6 PULMONARY FUNCTION TESTING: A DISEASE-BASED APPROACH

Chronic obstructive pulmonary disease (COPD) and asthma are the most prevalent lung diseases in developed countries, both characterized by airflow obstruction. In COPD, airflow obstruction is not fully reversible and usually progressive. Asthma is characterized by variable airflow obstruction and airway hyper-responsiveness. A restrictive ventilatory defect encompasses a large variety of pulmonary diseases. Although restrictive lung disease is much less prevalent than COPD and asthma, its diagnosis is important. In the following sections, we will assess the clinical efficacy of pulmonary function tests in these disorders by identifying and summarizing evidence synthesis from HTA-reports, systematic reviews and clinical practice guidelines.

A clinical practice guideline has been defined as a collection of "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances"[25]. With recent increases in published guidelines, concern has grown on the variations in guideline recommendations and quality, underscoring the need for an appraisal tool to evaluate the methodological quality of clinical practice guidelines. The Appraisal of Guidelines for Research and Education (AGREE) instrument[26] is an internationally rigorously developed and validated instrument that compares favourably with other guideline appraisal tools[27]. It is one of the few guideline assessment instruments to demonstrate validity and reliability. When issues included in the AGREE instrument are addressed in a guideline, this guideline is more likely to reflect a rigorous development process. The AGREE instrument has been used throughout this report to assess guidelines on quality.

6.1 PULMONARY FUNCTION TESTING IN COPD

6.1.1 Background

COPD is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases[28].

COPD affects a substantial proportion of the population, mainly middle-aged and elderly people. In the UK, physician diagnosed prevalence was 2% in men and 1% in women between 1990 and 1997. In 1998, the World Health Organisation (WHO) estimated that COPD was the fifth common cause of death worldwide, responsible for 4.2% of all mortality (estimated 2.249.000 deaths in 1998) and morbidity is increasing. Estimated prevalence in the USA rose by 41% between 1982 and 1994 and age adjusted death rates rose by 71% between 1982 and 1995. All cause age adjusted mortality declined over the same period by 22% and mortality from cardiovascular diseases by 45%.

The main cause of COPD is exposure to tobacco smoke, making it a largely preventable disease. Other risk factors include air pollution, allergy, and bronchial hyperresponsiveness. Airway obstruction is usually progressive in those who continue to smoke, resulting in early disability and shortened survival. Smoking cessation reverses the rate of decline in pulmonary function to that of non-smokers. Many people will need medication for the rest of their lives, with increasing doses and additional medications during exacerbations. The aims of intervention are to alleviate symptoms; to prevent exacerbations; to preserve optimal pulmonary function; and to improve activities of daily living, quality of life and survival.

According to the guideline authored by the Global Initiative for Chronic Obstructive Lung Disease[28], reflecting the position statement of the ATS/ERS on COPD[29], a diagnosis of COPD should be considered in any patient who has symptoms of cough, sputum production, dyspnea, and/or a history of exposure to risk factors for the disease. There is general agreement that a COPD diagnosis and severity staging system should be based on a spirometric assessment of airflow limitation i.e. a reduced FEV1

value. However, from the next section on "evidence from clinical practice guidelines", it appears that actual defining values and categories of disease severity assessment may vary. In order to define normal and abnormal results of a patient's spirometric values, these values are compared with reference values. These reference values are established from population studies of healthy subjects and are corrected for age, gender, standing height and ethnicity. In general, the results of the fifth percentile of airflow values from these populations are arbitrarily considered abnormal and define the cut-off level of normal airflow versus airflow limitation. Thus, the specificity of the test is arbitrarily set at 95%, accepting a 5% rate of false positive results. The sensitivity varies according to the population studied. By consequence, if a diagnosis would be exclusively based on spirometric values, airflow limitation is falsely diagnosed in those at the left end of the the curve.

6.1.2 Evidence from Clinical Practice Guidelines

As no clinical practice guidelines were found that specifically addressed pulmonary function testing in COPD, evidence was searched by identifying, analysing and comparing content on pulmonary function testing from the four most recent guidelines on diagnosis and management of COPD.

In an additional search, we identified a technical and clinical guideline on pulmonary function testing on the website of the Belgian Thoracic Society[9].

6.1.2.1 Guideline selection and appraisal

The technical and clinical guideline on pulmonary function testing, authored by the Belgian Thoracic Society, is a consensus-based guideline adressing quality, clinical indications and standardization[9]. Indications for pulmonary function testing in COPD i.e. in the diagnosis, acute exacerbation and follow up are given in a table and provided with an abbreviation referring to the recommendation (S, U or I). It is specified that "systematically indicated" (S) means that the investigation provides important or essential information for the clinician on diagnosis or therapy. "Useful" (U) is specified as recommended in that indication. "On indication" (I) means that the test is justified in a specific clinical context (for instance, an additional unexpected complaint, starting a new therapy, an unexpected evolution, exclusion or confirmation of a second pathology). Other tests without a symbol in the table should be considered as only required exceptionally. The chapter on clinical indications of pulmonary function tests in COPD provides no methodology section on the processes used to gather and synthetize the evidence and to formulate and update the recommendations. Therefore, a guideline appraisal is either not applicable or would inevitably yield a too low score in the domain of "rigor of development" (score of 1 for "strongly disagree"" on each of the 7 topics in this domain; domain score of 7/28). Because of a lack of details on clinical indications of PFT in COPD, this guideline is not suitable for a formal comparison of guideline recommendations *(Table in Appendix)*.

The four most recent evidence-based guidelines (date released: between 2004 and 2006) on diagnosis and management of stable COPD and acute COPD exacerbations were selected from the National Guideline Clearinghouse (NGC) database (http://www.guideline.gov/).

- Institute for Clinical Systems Improvement (ICSI). Chronic obstructive pulmonary disease. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2005 Dec. The original guideline was released on 2001 Dec (revised 2005 Dec). Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2004 Dec. Electronic copies: Available from the Institute for Clinical Systems Improvement (ICSI) Web site. Web site: www.icsi.org (Accessed 21 April 2006) (ICSI 2005).
- Global Initiative for Chronic Obstructive Lung Disease (GOLD), World Health Organization (WHO), National Heart, Lung and Blood Institute (NHLBI). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda (MD):

Global Initiative for Chronic Obstructive Lung Disease, World Health Organization, National Heart, Lung and Blood Institute; 2006. The original guideline was released in 2001 (revised 2006). Electronic copies: Available from the GOLD (Global Initiative for Chronic Obstructive Lung Disease) Web site (Accessed 28 January 2007) (GOLD 2006).

- Chronic obstructive pulmonary disease. National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. Thorax 2004 Feb;59 Suppl 1:1-232. Electronic copies: Available in Portable Document Format (PDF) format from the National Institute for Clinical Excellence (NICE) Web site (Accessed 21 April 2006) (NICE 2004).
- Finnish Medical Society Duodecim. Chronic obstructive pulmonary disease (COPD). In: EBM Guidelines. Evidence-Based Medicine [CD-ROM]. Helsinki, Finland: Duodecim Medical Publications Ltd.; 2005. The original guideline was released in 2002 (revised 2005). This guideline updates a previous version: Finnish Medical Society Duodecim. Chronic obstructive pulmonary disease (COPD). In: EBM Guidelines. Evidence-Based Medicine [CD-ROM]. Helsinki, Finland: Duodecim Medical Publications Ltd.; 2004; PO Box 713, 00101 Helsinki, Finland; e-mail: info@ebm-guidelines.com; Web site: www.ebm-guidelines.com (Accessed 21 April 2006) (FMS 2005).

The scientific value of the four selected evidence-based clinical practice guidelines on COPD is appraised with the AGREE appraisal tool. Results of this appraisal are summarized in *Appendix.* The guidelines were developed by experienced non-profit organisations, identified and critically appraised the evidence for the recommendations made. The external experts commenting on the current report recommended the use of another guideline, by the European Respiratory Society, issued in 1995. However, the methodology of this guideline as described in the document was not sufficient: no details were provided on the methods for evidence search, appraisal and synthesis, nor for the procedure used to derive recommendations; therefore, the guideline could not be included in the report.

All four guidelines address both diagnosis and management of stable COPD and acute exacerbations of COPD. The GOLD guideline differs from the other three guidelines in its global perspective and in its emphasis on prevention strategies. The ICSI and NICE guideline, like the GOLD guideline, are broad in scope, extensively covering the diagnosis and management of both chronic stable COPD and acute exacerbations of COPD. The ICSI, GOLD and NICE guidelines also differ from the Finnish guideline by including recommendations for pulmonary rehabilitation and surgical treatment of COPD.

These four guidelines do not provide evidence on sensitivity, specificity, positive and negative predictive values or likelihood ratios of spirometry and bronchodilator reversibility testing in the diagnosis and management of chronic stable COPD and of acute exacerbations of COPD. Most recommendations on diagnosis, severity assessment and follow-up of COPD are based on expert opinion and consensus.

In the following sections, recommendations from the four selected guidelines on the role of pulmonary function testing in chronic stable COPD and acute exacerbations of COPD will be compared in terms of areas of agreement and differences.

6.1.2.2 *Spirometry for the diagnosis of COPD*

The four guidelines agree on the importance of early spirometry to assess airflow limitation and diagnose COPD. In addition, ICSI states that full pulmonary function testing with lung volumes and diffusion capacity are neither recommended nor necessary to establish diagnosis or severity of COPD. The NICE guideline states that all patients should receive, in addition to spirometry, a chest radiograph, a full blood count and a body mass index calculation. Additional investigations such as DI_{CO} or alpha-1 antitrypsin should be performed only in some circumstances. Likewise, the GOLD guideline recommends spirometry in every patient suspected of COPD, reserving reversibility testing for some cases in which diagnostic doubt remains.

6.1.2.3 *Spirometry for Assessing Severity of Disease*

All four guidelines classify the severity of COPD based on airflow limitation as measured by spirometry. However, the actual values and categories vary. For instance, the FMS guideline distinguishes two different stages of disease (mild disease and continuous symptoms). NICE describes a three-stage system (mild, moderate, and severe). GOLD describes a four-stage system (mild, moderate, severe, and very severe). GOLD points out that their staging system should only be regarded as an educational tool, and a very general indication of the approach to management. ICSI describes a four-stage system based on the GOLD-classification. An overview of the classifications on assessing COPD severity from the four selected guidelines is provided in *Table 3*.[29].

All guidelines generally agree that the purpose of assessing severity is prognostic and/or therapeutic. Three guidelines (ICSI, GOLD, NICE) emphasize the importance of considering other factors (i.e., signs, symptoms, complications) in addition to FEV_1 values in assessing severity of disease. GOLD points out that the FEV_1 cutpoints are used for the purpose of simplicity, as they are not clinically validated and may overestimate the prevalence of COPD in some groups, such as the elderly. Similarly, NICE warns against the use of spirometry alone to classify severity of disease because the results may underestimate the impact of the disease in some patients and overestimate it in others. Instead of classifying severity of disease, NICE classifies severity of airflow obstruction, which they point out can be used to guide therapy and predict prognosis. Unlike ICSI, FMS or GOLD, NICE recommends evaluation of BMI and exercise capacity in assessing severity, stating that these results reflect the impact of the disease in an individual and predict prognosis.

6.1.2.4 *Bronchodilator Reversibility Testing*

There is disagreement among guidelines on the indications for reversibility testing. Reversibility testing or bronchodilator response is characterized by two measurements of airflow obstruction, one before and the other after the administration of a bronchodilator. The purpose of the test is to assess whether the airways respond to bronchodilating agents.

The GOLD guideline points out that reversibility testing is not able to predict a patient's response to treatment. Likewise, NICE does not consider reversibility testing necessary or helpful in the diagnostic process to plan initial therapy with

Table 3: Assessing Severity of COPD Disease

ICSI (2005)	GOLD (2006)	NICE (2004)	FMS (2005)
Mild: • FEV_1 ≥80% predicted • No abnormal signs; cough ± sputum; little or no dyspnea	Stage I [Mild COPD]: • FEV_1/FVC <70% • FEV_1 ≥80% predicted With or without chronic symptoms (cough, sputum production)		Mild: Patients with occasional symptoms (generally FEV_1 >50% predicted)
Moderate • 50%≤FEV_1 <80% predicted • Breathlessness (± wheeze on moderate exertion); cough (± sputum); variable abnormal signs (reduction in breath sounds, wheezes); hypoxemia may be present	Stage II [Moderate COPD]: • FEV_1/FVC <70% • 50%≤FEV_1<80% predicted With or without chronic symptoms (cough, sputum production)	Mild: • 50-80% predicted FEV_1	
Severe • 30%≤FEV_1<50% predicted • Dyspnea with any exertion; wheeze and cough often prominent; lung hyperinflation usual: cyanosis, peripheral edema and polycythemia in advanced disease; hypoxemia and hypercapnia	Stage III [Severe COPD]: • FEV_1/FVC <70% • 30%≤FEV_1,<50% predicted With or without chronic symptoms (cough, sputum production)	Moderate: • 30-49% predicted FEV_1	Severe • Continuous symptoms • generally FEV_1 <50% predicted
Very severe • FEV_1 <30% predicted • Symptoms and signs similar to severe COPD	Stage IV [Very Severe COPD] • FEV_1/FVC <70% • FEV_1 <30% predicted or FEV_1 <50% predicted plus chronic respiratory failure	Severe: • <30% predicted FEV_1	

bronchodilators or corticosteroids. They argue that results of testing may be unhelpful or misleading; their recommendation is based on hierarchy I or II evidence. Repeated FEV_1 measurements can show small spontaneous fluctuations; over-reliance on a single reversibility test may be misleading unless the change in FEV_1 is greater than 400 mL; the definition of the magnitude of a significant change is purely arbitrary (grades of recommendation B, based on hierarchy II evidence or extrapolated from hierarchy I evidence). Response to long-term therapy is not predicted by acute reversibility testing (grade of recommendation A, based on hierarchy I evidence). Asthma should be differentiated from COPD by features of the history and examination and by longitudinal observations. Reversibility testing should be reserved to resolve diagnostic doubt *(NICE)*.

In contrast, FMS recommends testing with a bronchodilating drug at diagnosis and subsequent assessment of response. ICSI recommends bronchodilator testing at initial diagnosis to identify those patients with partial reversibility of airflow obstruction and to distinguish COPD from asthma, as treatment and prognosis differ. In addition, ICSI also recommends bronchodilator testing in defining a positive or negative response to a trial of oral and/or inhaled corticosteroids.

6.1.2.5 Follow-up of stable COPD

Guidelines agree that spirometry is useful in the follow-up of COPD in monitoring disease progression and development of complications. The exact frequency of follow-up visits is a matter of clinical judgement and should be tailored to the individual patient. ICSI suggests, as a general guide for patients with stable COPD, a yearly follow-up in mild COPD, 3 to 6 month follow-up in moderate severe COPD and 2 to 4 month follow-up or more frequently in severe COPD.

6.1.2.6 Additional recommendations

NICE considers measuring diffusing capacity for carbon monoxide (DIco) to investigate symptoms that seem disproportionate to the spirometric impairment. They also note that COPD is heterogeneous, so no single measure can give an adequate assessment of the true severity of the disease in an individual patient. Severity assessment is, nevertheless, important because it has implications for therapy and relates to prognosis. Mild airflow obstruction can be associated with significant disability in patients with COPD. A true assessment of severity should include assessment of the degree of airflow obstruction and disability, the frequency of exacerbations and the following known prognostic factors (recommendation grade D): FEV_1, DI_{CO}, breathlessness - MRC scale, health status, exercise capacity, BMI, partial pressure of oxygen in arterial blood (PaO_2). FMS considers CO diffusing capacity an additional investigation that may help in differentiating COPD (DI_{CO} decreased) from asthma (DI_{CO} normal).

GOLD states that other pulmonary function tests, such as flow-volume loops, diffusing capacity (DI_{CO}), inspiratory capacity, and measurement of lung volumes are not needed in a routine assessment but can provide information about the overall impact of the disease and can be valuable in resolving diagnostic uncertainties and assessing patients for surgery.

6.1.2.7 Spirometric measurement of airflow limitation in acute exacerbations of COPD

Three guidelines agree in their recommendations on the use of spirometry in diagnosing acute exacerbation of COPD. ICSI states that spirometry is of little value in patients with an acute COPD exacerbation and, for that reason, oximetry and/or arterial bood gas should be monitored. GOLD acknowledges that even simple pulmonary function tests can be difficult for sick patients and are not accurate in these patients; therefore their routine use is not recommended. NICE states that changes in pulmonary function at the time of an exacerbation are usually small and are not helpful in routine practice. However, in certain situations, investigations may assist in ensuring whether appropriate treatment is given,

particularly when the patient presents for the first time during an exacerbation. FMS does not offer specific recommendations for spirometry in acute exacerbations.

Observational studies have shown that spirometry performed at presentation or during treatment was not useful in judging severity or guiding management of patients during acute exacerbation. Additionally, FEV_1 showed no significant correlation with PO_2 and only a weak correlation with PCO_2[30].

Key points

- **Airflow limitation by spirometry is essential in the diagnosis of COPD.**
- **Severity assessment may be useful for prognostic and/or therapeutic purposes. Defining severity varies among guidelines.**
- **Guidelines disagree on lung volumes and diffusion capacity.**
- **Two guidelines (NICE, GOLD) do not consider bronchodilator reversibility testing useful in the initial diagnosis and assessment of treatment response.**
- **Spirometry is indicated, for monitoring disease progression. The exact frequency of follow-up visits is a matter of clinical judgement.**
- **GOLD, ICSI and NICE state that spirometry at the time of an exacerbation is of little value.**

6.1.3 Evidence from HTA reports, systematic reviews or original studies

6.1.3.1 Methods

HTA reports and systematic reviews on pulmonary function tests in COPD were searched in the following databases: INATHA, CRD database (DARE, NHS-EED, HTA), Cochrane Library and Medline (Pubmed: Clinical Queries). Search terms included copd*, lung-diseases-obstructive*, emphysem*, bronchit*, respiratory function tests, spirometry, lung volume measurements, pulmonary diffusing capacity and airway resistance (search date: February 2006).

To update or complement the findings of any HTA report or systematic review, a search for additional evidence synthesis was performed. The following databases were searched: INAHTA, CRD database, the Cochrane Library and Medline. Search terms included copd*, lung-diseases-obstructive*, emphysem*, bronchit*.

Search terms for Medline were

(("Spirometry"[MeSH] OR ("Vital Capacity"[MeSH] OR "Forced Expiratory Volume"[MeSH]) OR ("Bronchodilator Agents"[MeSH] OR "Bronchodilator Agents/diagnostic use"[MeSH])) AND "Lung Diseases, Obstructive"[MeSH]) AND (sensitiv*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic *[MeSH:noexp] OR diagnosis,differential[MeSH:noexp] OR diagnosis[Subheading:noexp]).

Inclusion criteria for the selection of articles based on title and abstract were COPD and spirometry. All other studies, including studies on children were excluded. Articles retrieved in full text were appraised for quality with the QUADAS tool[31]. Low quality studies were excluded. In addition, a search for ongoing trials was performed in ClinicalTrials.gov and ISRCTN.

6.1.3.2 Results

One HTA report was identified from the Agency for Healthcare Research and Quality (AHRQ - US) on the use of spirometry for case finding, diagnosis and management of COPD[32]. The literature for this report was searched in Medline from 1966 to May 2005 and the Cochrane Library. Children or individuals with asthma, of alpha-1 antitrypsin disease were excluded. Studies were eligible if they were in English, and reported the results of spirometry testing of community-based adult populations or primary care settings. The quality of this report was good.

Considering the good quality literature search in the previously mentioned HTA report, we limited our literature search for original studies to studies published from January 2005 onwards (search date: February 2006) and yielded 237 articles. From these 237 articles, 21 were selected for assessment in full text[33-52]. After assessing these articles on relevance and quality, 9 articles were included in the review and 12 articles were excluded. In addition, we identified one Cochrane systematic review on interventions for smoking cessation for patients suffering from COPD[53]. No ongoing trials on the value of spirometry in patients with COPD were identified.

6.1.3.3 Diagnostic value of spirometry

As the definition of COPD is based on the determination of airflow limitation with spirometry, the value of spirometry for the diagnosis of COPD is beyond question. This is confirmed in the HTA-AHRQ report which states that there are no data that directly describe the sensitivity and specificity of spirometry, but, compared to clinical examination, spirometry plus clinical examination improves diagnostic accuracy of clinically significant disease in adults who report respiratory symptoms. We have identified one additional study on the diagnostic accuracy of spirometry, published after the literature search of the HTA report. Some patients experience difficulties in reaching the FVC, by which the first 6 seconds of the forced expiratory volume has been suggested as an alternative. In a retrospective analysis the diagnostic value of the FEV1/FEV6 ratio as a replacement of the FEV1/FVC ratio was evaluated [51]. The authors found in this population of patients with a relatively high prevalence of airflow obstruction the FEV1/FEV6 ratio to have a sensitivity of 94.0%, specificity of 93.1%, positive predictive value of 89.8% and negative predictive value of 96.0%, using the FEV1/FVC ratio as a reference standard.

One article was identified on the value of bronchodilator testing[38]. In this study, patients with established diagnoses of COPD and asthma were included. The diagnostic ability of acute bronchodilator responsiveness in separating asthma from COPD was found limited: response in patients with asthma overlaps substantially with the response in patients with COPD. A more detailed review of the evidence on this parameter will be presented in chapter 6.

6.1.3.4 Influence on diagnostic reasoning and patient management

Dales et al. assessed the influence of spirometry on the clinical diagnosis and management of the primary care practitioner, in patients of at least 35 years old and who had smoked at least 20 packages of cigarettes in their lifetime[40]. Airflow obstruction was diagnosed in 9% of patients as a result of spirometry, whereas the diagnosis was removed in 11% of patients. Diagnosis thus remained unchanged in 80%. In 15% of patients, physicians planned to change management after knowing the spirometry result, in 53% of those with FEV1/FVC<70% and in 7% of those with an FEV1/FVC ratio ≥70%. A chart review 6 months after the study documented the addition of respiratory medications in 8% of patients. The study of Buffels et al. found that case-finding was able to diagnose airflow obstruction in 18% of patients with respiratory complaints in primary care, as documented by spirometry. In contrast, patients without complaints were diagnosed with airflow obstruction in 4% of cases[54].

Periodic spirometry measurements are recommended by the GOLD guideline to track the decline in pulmonary function. In theory, periodic assessment would be useful if it would allow treatment to be initiated or modified based on acute spirometric change to therapy, change in spirometry over time or crossing a given spirometric threshold. Other pulmonary function tests, such as diffusion capacity or lung volumes, are not needed in routine assessment, but can be used in resolving diagnostic uncertainties (for example symptoms disproportionate with the spirometry result) or assessing patients for surgery[28]. In the HTA-AHRQ report, studies on treatment effects were included if they were randomized trials that were blinded, used an intention-to-treat analysis and reported attrition. Of the 53 trials that were eligible, 20 studies were not included in a previous systematic review of Sin[55]. Most trials were of short duration, enrolled subjects with a previous clinical diagnosis of COPD, had subjects with severe to very severe COPD and enrolled subjects with stable COPD but relatively frequent exacerbations. Inhaled glucocorticosteroids decrease the proportion of patients experiencing exacerbations, with an absolute risk reduction of 5% (95% CI 3-8), based on a pooled estimate of 10 randomized controlled trials. As was shown in a meta-analysis[55] and a subgroup analysis of the study of van der Valk[56], the effect of inhaled glucocorticosteroids on excerbations is mainly driven by patients with severe COPD with FEV1 of ≤1.7 liter. This suggests a threshold for the initiation of inhaled glucocorticosteroids. Comparative studies suggest that long-acting β agonists and long-acting anticholinergics are of similar efficacy in preventing exacerbations, but inhaled glucocorticosteroids were slightly more effective than long-acting β agonists[32]. Recently, the first results of the TORCH study were published, in which COPD patients with an FEV1 of less than 60% of the predicted value were treated with salmeterol, fluticasone, the combination of both or placebo. No significant effect on mortality was shown, but patients experienced less exacerbations treated with the combination therapy compared to those using placebo (annual exacerbation rate of 0.85 versus 1.13)[57]. The results of the TORCH study strengthen the recommendation to use a combination of beta-agonists and inhaled corticosteroids in patients with severe COPD and frequent exacerbations but not for patients with milder disease or without frequent exacerbations[58].

Based on the average decline of approximately 50 ml/year, Wilt et al. recommended spirometry every 5 to 10 years in patients with moderate airflow obstruction who are not yet receiving treatment. However, there is large variability in these measurements, as was shown in the Lung Health Study I[59] and other cohort studies, by which general guidelines on optimal monitoring intervals is problematic. In any case, no trials are available directly investigating the influence of monitoring intervals on patient outcome.

Acute bronchodilator response does not appear to be useful for initiating or modifying treatment in subjects with COPD or predicting spirometric decline, as was shown in the ISOLDE study and a study by Guyatt et al[32].

6.1.3.5 Influence on patient outcome

Studies have shown that smoking cessation has a positive effect on pulmonary function decline[49] and mortality, even after 14 years of follow-up[60]. In a study by Rose et al.[61] the overall change in pulmonary function was 14% less in the intervention group than in the control group. In the Cochrane review on the effectiveness of smoking cessation in COPD patients, the authors found evidence that a combination of psychosocial interventions and pharmacological interventions is superior to no treatment or to psychosocial interventions alone. Furthermore they conclude that there is no clear or convincing evidence for the effectiveness of any psychosocial intervention for patients with COPD due to lack of a sufficient number of high-quality studies[53]. On the other hand, interventions such as nicotine replacement and pharmacological treatment with bupropion of nortryptiline have been found to be effective in smokers in general[62].

It has been assumed that the diagnosis of airflow limitation could have a motivational effect on the smoker to quit. Several studies have evaluated whether knowing ones spirometric status influences the probability of smoking cessation. However, the HTA report of the

AHRQ found that the evidence on the effectiveness of spirometry on smoking cessation was limited and flawed[32]. Seven (7) randomized trials were assessed in this report, only one study was designed to evaluate the independent effect of spirometry in conjunction with clinical counselling and found a 1% greater quit rate at 12 months in the group assigned to receive spirometry plus repeat smoking cessation counselling[63]. Thus, spirometry is unlikely to have a more than small benefit. This is confirmed in a recent trial of Buffels et al. who found no arguments of confronting smokers with their pulmonary function as a tool for enhancing smoking cessation[64]. Observational studies on spirometry show conflicting results, RCTs on other biomarkers are generally negative. No ongoing trials were identified in either of the trial registries. Therefore, offering smoking cessation is an important element in smokers, whether or not they have evidence of pulmonary function decline. Performing spirometry does not increase smoking cessation rates.

6.1.3.6 Prognostic value

Several studies have shown that FEV_1 correlates poorly with a patient's quality of life, symptoms, exacerbation frequency and exercise intolerance. But, the initial FEV_1 value has been shown to be a good predictor of mortality, in association with the patient's age[65]. The GOLD classification has also been shown to correlate with subsequent risk of mortality. Based on the results of NHANES I, severe or moderate COPD was associated with a higher risk of death: hazard ratios 2.7 (95% CI 2.1 to 3.5) and 1.6 (95% CI 1.4 to 2.0) respectively[66]. A recent study showed that among smoking men the hazard ratio increased stepwise from GOLD stage 1 to stage 4 (p for trend <0.0001)[67]. Smoking men with GOLD stage 1 do not have a significantly different mortality from the reference group (HR 1.13; 95% CI 0.98-1.29), except for those patients experiencing symptoms (HR 2.04; 95% CI 1.34-3.11).

A recent multi-centre study in the United States and Spain analysed the prognostic value of the inspiratory-to-total lung capacity ratio (IC/TLC ratio) in patients already diagnosed with COPD[37]. The IC/TLC ratio is a measure of static hyperinflation, which has been associated with limitations in the functional capacity of patients. The BODE index, which is based on body mass index, airflow obstruction, dyspnoea and exercise performance showed a high predictive value in a multivariable analysis, of which FEV1 contributes most to its predictive value. But, it was found that the IC/TLC ratio was an independent predictor of all-cause and respiratory mortality in patients with COPD, controlled for the BODE index and the Charlson index of comorbidity. No other parameter of lung volumes was found to have any predictive value on mortality.

Further details on this HTA-AHRQ report and the original studies retrieved from the additional search are provided in the evidence tables in the Appendix.

Key points

- **Patients suspected of COPD should have a spirometry.**
- **Spirometry allows identifying individuals who might benefit from pharmacologic treatment in order to reduce exacerbations.**
- **Periodic monitoring of individuals with airflow obstruction is useful to determine whether the patient has crossed a threshold above which treatment with corticosteroids is likely to be beneficial. Optimal monitoring intervals are unknown.**
- **There is good evidence demonstrating a lack of effect of spirometry on smoking cessation rates. Offering smoking cessation interventions is important in every smoker, regardless of the pulmonary function status.**

6.2 PULMONARY FUNCTION TESTING IN ASTHMA

6.2.1 Background

Asthma is characterized by chronic airway inflammation, variable airway obstruction and airway hyperresponsiveness. Symptoms include dyspnoea, cough, chest tightness, and wheezing. The diurnal variation of peak expiratory flow rate (PEFR) is increased in people with asthma.

Reported prevalence of asthma is increasing worldwide. About 10% of people have suffered an attack of asthma. Epidemiological studies have also found marked variations in prevalence in different countries.

Most people with asthma are atopic. Exposure to certain stimuli initiates inflammation and structural changes in airways causing airway hyperresponsiveness and variable airflow obstruction, which in turn cause most asthma symptoms. There are a large number of such stimuli; the more important include environmental allergens, occupational sensitising agents, respiratory viral infections and aspecific triggers such as cigarette smoke and exercise.

In people with mild chronic asthma, prognosis is good and progression to severe disease is rare. However, as a group, people with asthma lose pulmonary function faster than those without asthma, although less quickly than people who smoke. People with chronic asthma can improve with treatment. However, some people (possibly up to 5%) have severe disease that responds poorly to treatment. These people are most at risk of morbidity and death from asthma.

The aim of therapy is to minimise or eliminate symptoms; to maximise pulmonary function; to prevent exacerbations; to minimise the need for medication; to minimise adverse effects of treatment; and to provide enough information and support to facilitate self management of asthma. Relevant outcomes in the management of the asthma patient are symptoms (daytime and nocturnal); pulmonary function, in terms of PEFR and forced expiratory volume in 1 second (FEV_1); need for rescue medication such as inhaled beta2-agonists; variability of flow rates; activities of daily living; adverse effects of treatment[68].

6.2.2 Evidence from HTA reports and systematic reviews

Evidence synthesis from HTA reports and systematic reviews on pulmonary function tests in adult asthma were searched in the following databases: INATHA, CRD database (All Databases DARE - NHS, EED, HTA), Cochrane Library and Medline (Pubmed: Clinical Queries). Search terms included asthma*, lung-diseases-obstructive, respiratory function tests, spirometry, lung volume measurements, pulmonary diffusing capacity and airway resistance (search date: February 2006). No relevant HTA reports or systematic reviews were found.

6.2.3 Evidence from Clinical Practice Guidelines

No guidelines were identified focusing primarily on pulmonary function testing in asthma. Therefore evidence was searched by identifying, analysing and comparing content on pulmonary function tests from four recent guidelines on diagnosis and management of asthma. We searched for guidelines developed by the same or related organisations that also released the guidelines on COPD that were selected in Chapter 5. In an additional search, we identified a technical and clinical guideline on pulmonary function testing on the website of the Belgian Thoracic Society[9].

6.2.3.1 Guideline selection and appraisal

The technical and clinical guideline on pulmonary function testing, authored by the Belgian Thoracic Society (BTS), is a consensus-based guideline adressing quality, clinical indications and standardization[9]. As already described in the previous chapter on COPD, the guideline is not suitable for a formal comparison due to lack of details on the methodology used.

Four recent (date released: between 2004 and 2006) evidence based clinical practice guidelines on asthma were developed by the same or related organisations that also released the selected guidelines on COPD in Chapter 5.

- Institute for Clinical Systems Improvement (ICSI). Diagnosis and outpatient management of asthma. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2005. The original guideline was released in 1998 (revised 2005). Electronic copies: Available from the Institute for Clinical Systems Improvement (ICSI) Web site. Web site: www.icsi.org (Accessed 21 April 2006).
- Global Initiative for Asthma (GINA), National Heart, Lung and Blood Institute (NHLBI). Global strategy for asthma management and prevention. Bethesda (MD): Global Initiative for Asthma (GINA), National Heart, Lung and Blood Institute (NHLBI); 2006. The original guideline was released in 1995 (revised 2006). Electronic copies: Available from the GINA Web site: www.ginasthma.com (Accessed 27 January 2007).
- Scottish Intercollegiate Guidelines Network (SIGN), British Thoracic Society. British guideline on the management of asthma. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2005. The original guideline was released in 2003 (revised 2005). Electronic copies: Available from the SIGN Web site: www.sign.ac.uk (Accessed 21 April 2006).
- Finnish Medical Society Duodecim. Long-term management of asthma. In: EBM Guidelines. Evidence-Based Medicine. Helsinki, Finland: Duodecim Medical Publications Ltd.; 2004. The original guideline was released in 2001 (revised 2004). This guideline is included in a CD-ROM titled "EBM Guidelines. Evidence-Based Medicine" available from Duodecim Medical Publications, Ltd, PO Box 713, 00101 Helsinki, Finland; e-mail: info@ebm-guidelines.com. Web site: www.ebm-guidelines.com (Accessed 21 April 2006).

The scientific value of the four selected evidence-based clinical practice guidelines on asthma was appraised with the AGREE appraisal tool. Results of this appraisal are summarized in *Appendix*.

In the following paragraphs, recommendations on the role of pulmonary function testing for the diagnosis and management of asthma in these guidelines are compared. For other aspects of diagnosis (i.e. definition and symptoms, medical history, assessment of asthma triggers, physical examination, additional diagnostic testing) and management of asthma, we refer to the original guideline documents.

Pulmonary function testing is considered in the initial diagnosis, assessment of asthma severity, acute asthma/asthma exacerbation, follow up, step care management of pharmacologic treatment and asthma education. Pulmonary function tests consist of spirometry, including measurements of forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), ratio of forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC), or peak expiratory flow (PEF).

6.2.3.2 *Spirometry*

The four guidelines agree on the importance of spirometry in the diagnosis of asthma, especially FEV_1, FVC, peak expiratory flow (PEF), and airway hyperresponsiveness. Particularly, demonstrating variability of pulmonary function abnormalities increases diagnostic confidence.

Although it is recognized that spirometry gives more accurate information on pulmonary function, three guidelines (GINA, SIGN, FMS) state that, alternatively or complementary to FEV_1 and FEV_1 variability, PEF and PEF variability may be useful in the diagnosis of asthma and in the assessment of severity of disease and follow-up.

6.2.3.3 *Peak Expiratory Flow (PEF) monitoring*

All guidelines consider PEF and PEF monitoring an important aid in the diagnosis and subsequent treatment of asthma. PEF and PEF monitoring is beyond the scope of this project. More detailed information from guidelines on PEF monitoring is provided in the original guideline documents.

6.2.3.4 *Assessing severity of disease*

ICSI and GINA recommend a severity classification system based on symptoms (frequency and severity) and FEV_1 and PEF values (table 4). ICSI identifies the type of evidence supporting their conclusion on asthma severity assessment as classes M (RCTs/meta-analysis) and R (expert consensus). GINA states that this type of asthma classification, based on severity, is important when decisions must be made about the initial management of the patient, because therapy involves a stepwise approach. In the 2006 update of GINA, emphasis is placed on whether the asthma is controlled, partially controlled or uncontrolled. This reflects an understanding that asthma severity involves not only the severity of the underlying disease but also its responsiveness to treatment, and that severity is not an unvarying feature of an individual patient's asthma but may change over months or years.

Table 4: Assessing severity of Asthma

ICSI (2005)	GINA (2006)
Step 1: Mild Intermittent • Symptoms twice a week or less • Asymptomatic and normal peak expiratory flow (PEF) between exacerbations • Exacerbations are brief (few hours to a few days) • Nighttime symptoms twice a month or less • FEV_1 or PEF 80% predicted or greater and PEF variability 20% predicted or less	**Controlled asthma** • No daytime symptoms • No limitations of physical activities • No nocturnal symptoms or awakenings • No • PEF or FEV1 normal • No exacerbations
Step 2: Mild Persistent • Symptoms twice a week or more but once a day or less • Exacerbations may affect activity • Nighttime symptoms twice a month or more • FEV_1 or PEF 80% predicted or greater and PEF variability 20 to 30% predicted	**Partially controlled asthma** • Daytime symptoms more than twice/week • Any limitations of physical activities • Any nocturnal symptoms or awakenings • Need for reliever of rescue treatment more than twice/week • PEF or FEV1 less than 80% predicted or personal best (if known) • Exacerbations one or more/year
Step 3: Moderate Persistent	**Uncontrolled asthma**

• Daily symptoms • Daily use of inhaled short-acting beta$_2$-agonists • Exacerbations affect activity • Exacerbations twice a week or more; may last days • Nighttime symptoms once a week or more or 4 times per month • FEV_1 or PEF between 60 and 80% predicted • PEF variability 30% or greater **Step 4: Severe Persistent** • Continual symptoms • Limited physical activity • Frequent exacerbations • Frequent nighttime symptoms • FEV_1 or PEF 60% predicted or less and PEF variability 30% predicted or greater	• Three of more features of partially controlled asthma in any week • Exacerbation one in any week

6.2.3.5 Bronchodilator Reversibility Testing

All guidelines agree that spirometry is essential in diagnosing asthma, particularly when variability of pulmonary function is measured, either spontaneously, after inhalation of a bronchodilator, or in response to a trial of glucocorticosteroid therapy.

Spirometry measurements (FEV_1, FVC, FEV_1/FVC) before and after the patient inhales a short-acting bronchodilator are recommended for patients in whom the diagnosis of asthma is considered. Significant reversibility is indicated by an increase of at least 12% (ICSI, GINA) or 15% (FMS, SIGN) and 200 ml in FEV_1 from the pre-bronchodilator value after inhaling a short-acting bronchodilator.

Alternatively or complementary to spirometric testing, diurnal variability of airway obstruction may be assessed with repeated PEF measurements. Although the normal level of diurnal variability is open to question, a diurnal variation in PEF of $\geq$ 20% is considered significant (GINA, SIGN, FMS). SIGN comments that many patients with asthma will demonstrate variability below 20%, making this a reasonable specific, but insensitive diagnostic test. That is, marked variability of peak flow and easily demonstrated reversibility confirms a diagnosis of asthma, but smaller changes do not necessarily exclude the diagnosis.

6.2.3.6 Bronchoprovocation Testing

The guidelines agree that additional studies tailored to the specific patient including bronchial provocation testing may provide useful information in patients with normal or near normal spirometry. Airway hyper-responsiveness may be assessed following inhalation of metacholine, histamine or on exercise testing. GINA and SIGN comment that these measurements are sensitive for a diagnosis of asthma, but have a low specificity. This means that a negative test is useful to rule out asthma, but a positive test is not sufficient to rule asthma in.

6.2.3.7 Asthma education and selfmanagement

All guidelines agree that asthma education and selfmanagement based on home PEF monitoring are essential in the management of asthma patients. These strategies, which also emphasize the need for regular follow up visits and asthma treatment adherence, have been shown effective from RCTs and a systematic review in reducing emergency department visits and hospitalizations and in improving pulmonary function in patients with moderate to severe persistent asthma or with a history of severe exacerbations.Acute asthma/asthma exacerbation

There is agreement among guidelines on the importance of spirometry (FEV_1) or PEF in an acute asthma episode to document and quantify a decrease in expiratory flow which is characteristic for acute asthma. A PEF less than 50% predicted indicates severe acute asthma and is a possible indication for emergency care. Two guidelines (GINA, SIGN) provide a formal severity classification system for acute asthma based on PEF values, symptoms and other indices of severity.

ICSI states that spirometry (FEV_1) or PEF may be helpful in assessing the response to treatment of acute asthma with a PEF or FEV greater than 70% predicted normal indicating a good response. A PEF or FEV_1 50 to 70% predicted normal indicates an incomplete response. A PEF or FEV_1 less than 50% predicted normal indicates a poor response. In case of an incomplete or poor response, an emergency care visit or hospitalisation may be appropriate.

Key points

- **Documentation of airflow limitation variability is essential in the initial diagnosis, reassessment and follow up of patients with asthma. Two guidelines (ICSI, GINA) also use airflow limitation measured by FEV_1 or PEF to classify asthma severity.**
- **All guidelines agree on the importance of spirometry (FEV_1) or PEF in an acute asthma episode to document and quantify a decrease in expiratory flow, to direct patient management and assess response to treatment.**
- **Bronchodilator reversibility testing may be helpful in confirming a diagnosis of asthma i.e. when significant reversibility of airflow limitation can be measured. However, a negative test does not exclude asthma.**
- **In selected patients, bronchoprovocation testing may assist in ruling out asthma.**
- **Guidelines agree on the value of patient asthma education and selfmanagement based on home PEF monitoring.**

6.3 PULMONARY FUNCTION TESTING IN RESTRICTIVE LUNG DISEASE

6.3.1 Extra-pulmonary conditions causing restrictive defects

Conditions causing a restrictive defect include muscular diseases, such as Duchenne's disease, amyotrophic lateral sclerosis, Guillain-Barre syndrome, and myasthenia gravis. Other conditions capable of inducing restrictive defects are thoracic wall disorders, such as scoliosis.

6.3.2 Diffuse parenchymal lung disease

Diffuse parenchymal lung diseases (DPLDs) comprise over 200 entities and include a wide spectrum of diseases, many uncommon and many of unknown aetiology. There is no universally agreed classification of DPLDs. Demedts et al. classify the diseases according to known or unknown etiology (Longfunctie. Demedts and Decramer) The British Thoracic Society classifies DPLDs in acute DPLD, episodic DPLD, all of which may present acutely, chronic DPLD due to occupational or environmental agents or drugs, chronic DPLD with evidence of systemic disease and chronic DPLD with no evidence of systemic disease.

Diffuse parenchymal lung disease (DPLD) is thought to be characterized by restrictive pulmonary function, by which is meant a reduction in lung volumes with preserved FEV_1/FVC together with a reduction in carbon monoxide transfer factor (DI_{CO}).

In order to summarize the evidence on the clinical efficacy of pulmonary function tests in the management of interstital lung disease, an iterative search strategy was developed. Guidelines were searched first, then systematic reviews and finally original research.

6.3.2.1 Methods

Guidelines were searched on the websites of AHRQ, National Guideline Clearinghouse, New Zealand Guidelines Group, NICE and Prodigy. Terms used were 'restrictive lung disease' OR 'interstitial lung disease' (search data 6/11/2006). One guideline on chronic cough was identified, which was not relevant to the research question, 1 guideline on static lung volumes and 1 guideline on body plethysmography. The latter two will be discussed in the test-based approach of this report.

Systematic reviews were searched in Medline, using the terms: "Lung Diseases, Interstitial"[MeSH] AND "Respiratory function tests"[MeSH] AND systematic[sb]

(search date 6/11/2006). Seven articles were identified, of which none was relevant for the research question.

Original studies were also searched in Medline, using the terms: ("Lung Diseases, Interstitial"[MeSH] AND "Respiratory Function Tests"[MeSH]) AND specificity[Title/Abstract]) (search date 6/11/2006). 57 articles were identified, of which 3 were considered potentially relevant, based on title and abstract.

Of the three articles identified in our search, one article was excluded because it did not provide diagnostic or prognostic evidence on pulmonary function tests in patients with restrictive lung disease. Two articles evaluated the prognostic value of pulmonary function tests for mortality in patients with Langerhans' cell granulomatosis in one article and for treatment response in patients with idiopathic pulmonary fibrosis in the second article. Using the quality appraisal tool of the Cochrane Collaboration for prognostic studies, the quality of both papers was poor and the results were subsequently not extracted.

Additional references were brought in by experts in the field: the British Thoracic Society Standards of Care Recommendations[69], American Thoracic Society Statement on Sarcoidosis[70], a prognostic study on the clinical course of idiopathic pulmonary fibrosis[71], ATS/ERS/WASOG statement on sarcoidosis[72].

6.3.2.2 Results

The BTS guideline has summarized the evidence systematically, and offers grading of their recommendations similar to that of the Scottish Intercollegiate Guidelines Network. The working group stated that pulmonary function tests are of limited usefulness in the diagnosis of DPLD. A restrictive pattern of pulmonary function is probably the most common pattern, but a proportion of patients have preserved pulmonary function or airflow obstruction. Such findings should not lead to the exclusion of DPLD. For assessing severity of disease, simple pulmonary function testing using lung volumes and gas transfer factor gives a reasonable measure of the extent of disease. For monitoring patients with DPLD, VC and DlCO are the most appropriate and simplest indicators of change in DPLD. The evidence is contradictory whether these measurements can predict survival. Inadequate data are available on the question of whether exercise testing offers additional information to VC and DlCO. Further prospective studies are required as to the most appropriate monitoring strategy for DPLD.

The American Thoracic Society Statement on Sarcoidosis specifically states it is based solely on expert opinion, as evidence on the subject is not supportive. According to this statement, for patients in which the diagnosis of sarcoidosis is established by history and clinical and radiological features, pulmonary function tests are important to measure initial lung impairment and to provide a baseline to assess improvement or deterioration of the lung disease. Therefore, they are indicated for all patients. Aberrations in pulmonary function tests are found in only 20% of patients with Stage I disease, compared with 40–70% of patients with Stage II, III, or IV disease. The most common parameters indicating functional impairment are the DI_{CO} and the VC. Both restrictive and obstructive pulmonary function abnormalities may be found.

Martinez et al. analysed the clinical course of patients suffering from idiopathic pulmonary fibrosis, which were enrolled in a randomized trial and allocated to the placebo treatment. During the 72-week follow-up period, 19% of patients died of IPF related causes. For patients who survived to week 72, the mean percentage predicted FVC decreased from 64.5% (SD 11.1%) to 61.0% (SD 14.1); the mean percentage predicted Dlco decreased from 37.8% (SD 11.1%), to 37.0% (SD 19.9%); and the mean alveolar–arterial gradient increased from 23.2 mm Hg (SD 10.9), to 26.9 mm Hg (SD 13.0). For patients who died during the trial, a general trend was observed toward increases in alveolar–arterial gradient and dyspnea and toward decreases in FVC and Dlco. Although dyspnea or alveolar–arterial gradient often increased sharply before a patient's death, significant intrapatient variability occurs over time. In addition, Martinez et al. found no difference in overall incidence in acute deteriorations leading to death in baseline measures of mean predicted FVC or Dlco[73].

Key points

- **No conclusive evidence was identified on the value of pulmonary function tests for the diagnosis, monitoring, treatment or prognosis of patients suffering from restrictive lung disease.**
- **In the absence of conclusive evidence, guidelines generally agree on the value of pulmonary function tests for diagnosis and monitoring of patients with interstitial lung disease, mainly focusing on VC and DIco (quality of evidence fair).**

6.4 PULMONARY FUNCTION TESTING IN PULMONARY VASCULAR DISEASE

Pulmonary arterial hypertension is defined as a group of diseases with a progressive increase of the mean pulmonary artery pressure. A new clinical classification of pulmonary hypertension was defined in 2003[74].

1 Pulmonary arterial hypertension (PAH)
  1.1 Idiopathic (IPAH)
  1.2 Familial (FPAH)
  1.3 Associated with (APAH):
    1.3.1 Connective tissue disease
    1.3.2 Congenital systemic to pulmonary shunts
    1.3.3 Portal hypertension
    1.3.4 HIV infection
    1.3.5 Drugs and toxins
    1.3.6 Other (thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary haemorrhagic telangiectasia, haemoglobinopathies, myeloproliferative disorders, splenectomy)
  1.4 Associated with significant venous or capillary involvement
    1.4.1 Pulmonary veno-occlusive disease (PVOD)
    1.4.2 Pulmonary capillary haemangiomatosis (PCH)
  1.5 Persistent pulmonary hypertension of the newborn (PPHN)
2 Pulmonary hypertension associated with left heart diseases
  2.1 Left-sided atrial or ventricular heart disease
  2.2 Left-sided valvular heart disease
3 Pulmonary hypertension associated with lung respiratory diseases and/or hypoxia
  3.1 Chronic obstructive pulmonary disease
  3.2 Interstitial lung disease
  3.3 Sleep disordered breathing
  3.4 Alveolar hypoventilation disorders
  3.5 Chronic exposure to high altitude
  3.6 Developmental abnormalities
4 Pulmonary hypertension due to chronic thrombotic and/or embolic disease

4.1 Thromboembolic obstruction of proximal pulmonary arteries

4.2 Thromboembolic obstruction of distal pulmonary arteries

4.3 Non-thrombotic pulmonary embolism (tumour, parasites, foreign material)

5 Miscellaneous: Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumour, fibrosing mediastinitis)

PAH is not a frequent condition. However, without management, the prognosis is poor. Treatments are available; if necessary, lung transplantation must be anticipated. A specific diagnosis and an assessment of the disease progression are essential.

This chapter concerns only the use of pulmonary function tests for patients whose a PAH is suspected or diagnosed. We do not consider all the testing needed for the diagnosis and the follow-up of PAH.

6.4.1 Methods

Guidelines were searched on the websites of AHRQ, National Guideline Clearinghouse, New Zealand Guidelines Group, NICE, Prodigy and Sumsearch. Terms used were pulmonary arterial hypertension, pulmonary vascular disease (search data 19/02/2007).

Systematic reviews and original studies were searched in Medline, using the terms: "Hypertension, pulmonary /di"[MeSH] AND "Respiratory function tests"[MeSH], Diseases /di "[MeSH] AND "Respiratory function tests"[MeSH], ("Hypertension, Pulmonary"[MeSH] AND "Respiratory Function Tests"[MeSH]) AND systematic[sb], "Hypertension, Pulmonary"[MeSH] AND "Respiratory Function Tests"[MeSH] AND "Sensitivity and Specificity"[MeSH], "Vascular Diseases"[MeSH] AND "Respiratory Function Tests"[MeSH] AND "Sensitivity and Specificity"[MeSH] (search date 19/02/2007).

Five publications were relevant for this topic; all on PAH:

- Mc Goon 2004[75]: ACCP Evidence-based guideline on screening, early detection and diagnosis; good quality guideline according to AGREE score
- Mc Laughlin 2004[76]: ACCP Evidence-based guideline prognosis; good quality guideline according to AGREE score
- Rubin 2004[77, 78]: ACCP introduction to the guideline: exclusion
- Galie 2004 [74]: Task Force European Society of Cardiology expert consensus guideline with levels of evidence, on diagnosis and treatment
- Sun 2003[79]: JACC Clinical trial

An additional reference was brought in by experts in the field: Barst 2004[80]: JACC experts review on diagnosis.

6.4.2 Results

6.4.2.1 Screening

Screening for PAH in relatives of patients with family PAH: ACCP recommends a genetic testing and counselling (based on expert opinion) (Mc Goon 2004) [75]. The use of pulmonary testing for the screening of family PAH is not recommended.

In patients with systemic sclerosis, pulmonary function testing with DLco should be performed periodically (every 6 to 12 months) to improve detection of pulmonary vascular or interstitial disease (ACCP guidelines: quality of evidence fair) (Mc Goon 2004) [75].

6.4.2.2 *Diagnosis*

PAH is suspected by symptoms, mainly exertion dyspnoea. But incidental findings are also possible [80, 74]

The three publications [80, 74, 75] (JACC, ACCP and European Task Force) developed a stepwise program for the diagnosis of PAH in symptomatic patients.

According to the JACC publication, in symptomatic patients PAH is diagnosed by physical examination, chest X-ray, electrocardiogram (ECG) and echocardiogram (based on experts' opinion). In case of suspicion of PAH, pulmonary function testing is then recommended to exclude or characterize the contribution of any underlying airway or parenchyma disease (based on experts' opinion) [80].

The ACCP guidelines also recommend the diagnosis of PAH by chest X-ray, ECG, Doppler ultrasound before the use of pulmonary function tests in patients with PAH (quality of evidence low) [75].

The Task Force of the European Society of Cardiology recommends a similar diagnostic strategy as the ACCP guideline: ECG, chest X-ray and transthoracic echocardiography for the detection, followed by pulmonary function tests as part of the PH class identification phase (experts consensus) [74] .

The study of Sun 2003[79] showed that patients with Primary Pulmonary Hypertension (PPH) commonly have abnormalities in Dlco levels, and to a lesser extent in lung volumes, that correlate significantly with disease severity.

6.4.2.3 *Follow-up and prognosis*

The natural history of the disease is heterogeneous. A follow-up is recommended by all the publications. Assessment of prognosis is important as it influences both medical therapy and referral for transplantation.

The ACCP diagnosis guideline recommends, in patients with PAH, serial determinations of functional class and exercise capacity assessed by the 6-min walk test to provide benchmarks for disease severity, response to therapy, and progression (quality of evidence good) [75]

The ACCP prognosis guideline recommends, in patients with scleroderma-associated PAH, reduced Dlco (< 45% of predicted) may be used to predict a worse prognosis (quality of evidence low) [76].

Key points

- **Pulmonary function testing is used in patients diagnosed with PAH to evaluate the presence of lung disease (quality of evidence low).**
- **A follow-up of patients with PAH is essential. Serial determinations of functional class and exercice capacity assessed by the 6-min walk test provide benchmarks for disease severity, response to therapy, and progression (quality of evidence good).**
- **In patients with scleroderma-associated PAH, reduced DLco (< 45% of predicted) may be used to predict a worse prognosis (quality of evidence low).**

7 PULMONARY FUNCTION TESTING: A TEST-BASED APPROACH

7.1 THE BRONCHODILATOR REVERSIBILITY TEST

In the guidelines on COPD and asthma, there was disagreement on the clinical utility of bronchodilator reversibility testing. In order to resolve some of the uncertainty on the value of bronchodilator testing, the evidence was systematically reviewed.

7.1.1 Methods

Two databases were searched, Medline and Embase. Search terms are given below; the search date was August 2006.

Medline search:

("Albuterol"[MeSH] OR salbutamol OR "Ipratropium"[MeSH] OR "Bronchodilator Agents"[MeSH] OR "Adrenergic beta Agonists"[MeSH] OR bronchodilator test) AND (sensitiv*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic *[MeSH:noexp] OR diagnosis,differential[MeSH:noexp] OR diagnosis[Subheading:noexp]) AND ("Lung Diseases, Obstructive"[MeSH] OR "Pulmonary Disease, Chronic Obstructive"[MeSH] OR COPD OR chronic bronchitis OR chronic obstructive pulmonary disease)

Embase search:

(('albuterol'/exp OR 'albuterol') OR ('ipratropium'/exp OR 'ipratropium') OR ('bronchodilator agents'/exp OR 'bronchodilator agents') OR ('adrenergic beta

agonists'/exp OR 'adrenergic beta agonists') OR ('bronchodilator'/exp OR 'bronchodilator') AND test) AND (sensitiv* OR sensitivity AND specificity OR diagnos* OR ('diagnosis'/exp OR 'diagnosis') OR diagnostic AND * OR diagnosis,differential OR ('diagnosis'/exp OR 'diagnosis')) AND (('lung diseases, obstructive'/exp OR 'lung diseases, obstructive') OR ('pulmonary disease, chronic obstructive'/exp OR 'pulmonary disease, chronic obstructive') OR ('copd'/exp OR 'copd') OR chronic AND ('bronchitis'/exp OR 'bronchitis') OR chronic AND obstructive AND pulmonary AND ('disease'/exp OR 'disease'))

Eligibility criteria for inclusion in the review were: reversibility test, adults, diagnostic study. The articles selected were subsequently retrieved in full text and assessed on quality using the QUADAS instrument[31]. QUADAS has been designed specifically for evaluating the quality of diagnostic accuracy studies. It is endorsed by the Cochrane Collaboration's new handbook on the methodology of diagnostic systematic reviews. Studies fulfilling at least 5 of the 14 quality criteria were included in the review. Other studies were excluded.

7.1.2 Results

The literature search in Medline yielded 2299 articles, 225 articles were found in Embase. Discarding duplicates, 2499 articles were screened on title and abstract. Based on the aforementioned selection criteria, 39 articles were selected for further assessment in full text: 17 studies were not a diagnostic accuracy study; three studies were excluded because they did not evaluate the reversibility test. One article could not be obtained from any of the collaborating libraries. This left 18 articles for quality assessment[81-94, 38, 95, 43, 96]. One article reported the results of two different studies[84], by which 19 different studies were evaluated for quality. Seven studies fulfilled at least 5 quality criteria and were included in the review. The remaining 12 studies were excluded.

Overall, the quality of the included studies remained poor: three studies fulfilled 6 quality criteria, the remaining 4 studies only 5. Details on study design, population included and index test are summarized in the evidence table (Appendix). There was marked heterogeneity between studies on the various items.

Only one study included a consecutive series of patients, which is considered the optimal design for assessing diagnostic accuracy[43]. A second cohort study did not specify whether patients were included consecutively[90]. Both studies, however, showed that the result of the reversibility test did not alter the probability of disease in a clinically meaningful way. Pre-test probability of COPD was 54% in the first study, and changed to 63% when the FEV_1 after bronchodilation increased less than 12% compared to the baseline value. Similar in the second study: the pre-test probability of asthma (84%) changed very little (87.5%) after a positive reversibility test. This small change in disease probability is reflected in the likelihood ratios of a negative or positive test, which are close to 1 in all cases.

All other studies had a case-control design, which has been shown to increase sensitivity and specificity. This is even more the case, when patients with mixed or unclear diagnosis are excluded from the study. Still, the test characteristics are not good: sensitivity ranges from 49% to 100%, specificity from 50% to 84%. Although some authors provided positive and negative predictive values, these can not be calculated from case-control studies as the ratio of cases and controls was chosen by the researchers and does not reflect the prevalence of disease. Likelihood ratios can be questioned as well, as the reference standard of the cases is not the same as that of the controls, by which ideally, the two strata should not be mixed. Considering this limitation, the likelihood ratios are higher than those reported in the cohort studies but still far from being clinically significant.

Two studies included patients with only minor airflow limitation, or even healthy subjects with a normal airflow. In these patients, reversibility can never be large, as baseline obstruction is yet small or non-existent. This finding emphasizes the general lack of evidence on the subject.

The results of this review are consistent with previous research by Calverley et al. in which COPD patients showed a significant increase in FEV1 with each bronchodilator, a response that was normally distributed. Using ATS criteria, 52.1% of patients changed responder status between visits[97]. In a population based study, reversibility expressed as a response of at least 9% of the predicted value was significantly related to respiratory symptoms, some of which attributable to asthma. But, 4.5% of subjects without asthma demonstrated significant reversibility too[98].

Key points

- **The reversibility test should not be used for distinguishing patients with asthma from patients with COPD, as its test characteristics are insufficient.**

7.2 (STATIC) LUNG VOLUMES

7.2.1 Methods

Similar as in previous section, we performed an iterative literature search.

Guidelines were searched on the websites of AHRQ, National Guideline Clearinghouse, New Zealand Guidelines Group, NICE and Prodigy. Terms used were 'body plethysmography' and 'lung volume' (search data 6/11/2006). Two guidelines previously cited in the review on interstitial lung disease were identified: one on body plethysmography[99] and one on static lung volumes[100].

Systematic reviews were searched in Medline, using the terms: ("Plethysmography, Whole Body"[MeSH] OR "Lung Volume Measurements"[MeSH]) AND systematic[sb] (search date 6/11/2006). 94 articles were identified, of which one was relevant based on title and abstract[101].

Original studies were also searched in Medline, using the terms: ("Plethysmography, Whole Body"[MeSH] OR "Lung Volume Measurements"[MeSH]) AND specificity[Title/Abstract] (search date6/11/2006). Here, 192 articles were identified, of which 2 were selected based on the following criteria: the evaluation of lung volumes in patients of 18 years or over, performed in ambulatory care. Studies were excluded if they used a paediatric population, hospitalized patients, if it were editorials or letters or did not relate to a test on lung volume.

7.2.2 Results

In the two guidelines, no details on their methodology were found. In addition, the website of the guideline developer did not provide more information on the methods used. Therefore, we did not include these guidelines in our review.

The article by Stocks and Quanjer provides reference values for residual volume, functional residual capacity and total lung capacity. Although this is an important aspect of pulmonary function testing, the article does not provide guidance on the clinical indications for these tests.

Finally, the two articles identified in the search for original studies were already discussed in the disease-based approach of interstitial lung disease[102, 103]. Neither was included due to insufficient quality.

Key points

- **No high quality evidence on the clinical value of lung volumes was identified.**

7.3 CO DIFFUSING CAPACITY

7.3.1 Introduction

The diffusing capacity for carbon monoxide (Dlco) is a measure of the capacity of the lung to transfer gas from the alveolar spaces into pulmonary capillary blood, or the gas exchanging capability of the lung. The process occurs by passive diffusion of carbon monoxide which is the gas used because of its high avidity for the haemoglobin. The method generally used and best standardized is the single breath method.

The Tlco (transferfactor for co) is a synonym of DLco. "The product Kco x Va has been termed transfer factor of the lung by the European community and diffusing capacity of the lung for co (Dlco) by the North American community" [104]. The Kco is the transfer coefficient for the CO (per unity of alveolar volume) or Krogh-factor. This coefficient is however not a constant independent of the lung volume [105]. The Va (alveolar volume) is

usually measured during a simple inhalation, with a known mass of a relative insoluble and inert gas such as Helium.

The limits and difficulties with the interpretation of the test are important. Many factors can influence the results;

- smoking during the last 24 hours (carboxyhaemoglobin)
- anaemia (haemoglobin) (that can be corrected by an appropriated equation)
- pulmonary volume inhaled restriction caused by muscular pathology, restrictive pathologies or airways obstruction
- alveolar volume measure technique
- patient's collaboration

In this review, we summarize the available evidence on the diagnostic value of the Dlco in different pathologies.

7.3.2 Methods

We searched for guidelines with the search term "pulmonary diffusing capacity", which is a MeSH term, in National Guidelines Clearinghouse, Guidelines finder, Protocol &Care pathways, Cochrane database for systematic reviews, CRD database and INAHTA. We searched Pubmed with Clinical Queries for systematic reviews and clinical studies (broad search). The search date was August 2006 and 128 references were found.

We searched also in Medline, using the search term 'Pulmonary Diffusing Capacity' as a MeSH term and applying a diagnostic filter. Search date was August 2006. This search was completed by references given by the experts and by reference tracking. A total of 289 references have been considered. A first selection was made on the basis of the titles and abstracts according to the PICO (Patient: symptomatic, Intervention: Dlco or transfer factor, Comparison: no test or another test, Outcome: screening, diagnosis, prognosis). We excluded the studies about pre or postoperative tests (previous KCE report) and studies with <20 patients. We also excluded retrospective studies.

The full text of 94 references was then considered for exclusion criteria. A further selection was made based on the QUADAS score for diagnostic accuracy studies and the Cochrane checklist for prognostic studies. The quality appraisal is described in the evidence table, see appendix. The quality of the studies is globally poor. Many studies date from several decades ago (30 or 40 years). The details of the methods of these studies are often not sufficient to be selected with the actual critical appraisal criteria.

We also considered the guidelines selected by critical appraisal (see appendix) and already considered in the other parts of this report for COPD (ICSI, GOLD, NICE, FMS) or asthma (ICSI, GINA, SIGN, FMS).

7.3.3 Indications for Dlco

Our systematic review found 3 guidelines or consensus statements (ATS/ERS task force 2005[104], AARC clinical practice guideline 1999[106] and the SBP/BVP 2001[107]) on diffusing capacity. All three were of poor methodological quality. Levels of evidence are not provided. A comparison on the various indications for Dlco according to the guidelines is made in table 5.

7.3.4 Idiopathic pulmonary fibrosis

7.3.4.1 Diagnosis and follow-up

An international consensus statement (ATS 2000[104]), adopted by the board of the ATS (American Thoracic Society) and the ERS (European Respiratory Society) focuses on diagnosis and treatment of idiopathic pulmonary fibrosis (IPF). The Dlco is proposed for

the diagnosis of IPF, the monitoring and the follow-up of the treatment. There is however no evidence level in this guideline, which is largely based on expert opinion developed. There is no information on the accuracy of the test.

A study of Xaubet[108] showed a good correlation between the extent of overall lung involvement in the high resolution computed tomography (HCRT) and DLco at diagnosis and during the time of follow-up (7.5months).

7.3.4.2 Prognosis

A prospective prognostic study of Erbes[109] concluded that parameters of gas exchange at presentation to the hospital were not predictive for survival.

The study of Flaherty [110] showed that in IPF patients with a baseline saturation ≤ 88% during a six-minute-walk-test, the strongest predictor of mortality was a serial change in DLco.

In the study of Rudd [111], the DLco measured prior to the treatment was not statistically correlated with response to treatment.

A recent study of Hamada[112] shows that DLco good predicted the prognosis in idiopathic pulmonary fibrosis patients. Nineteen of the 27 patients in the preserved DLco group (≥ 40%) survived for 5 years, versus only 20% of the low DLco group (< 40%). The relative risk of mortality in the low DLco group was 2.70 (95% CI 1.46-4.99).

Table 5: comparison of SBP/BVP 2001 indications with AARC 1999 and ATS/ERS 2005

Pathology	SBP/BVP 2001	AARC 1999	ATS/ERS 2005
Asthma	First evaluation	+	+
COPD	First evaluation		
Emphysema	+	evaluation and follow up	+
Interstitial lung diseases (eg IPF, sarcoidosis)	First evaluation and follow up	+	+
Systemic disease (eg rheumatoid arthritis, systemic lupus erythematosis)	+	+	+
Respiratory muscle weakness	+		+
Pulmonary Arterial Hypertension (PAH)	+	+	+
Cardiovascular disease and secondary PAH	+	+	+
Respiratory failure	+		
Sleep Apnea Syndrome	+		
Hypoventilation (eg obesity)	+		+
Hyperventilation	+		
Dyspnea	+		
Medication (eg bleomycin, amiodarone)	+	+	+

We don't consider the surgical context.
IPF Idiopathic pulmonary fibrosis

7.3.4.3 Referral for lung tansplantation

Mogulkoc [113] studied optimal scores for referring IPF patients to a waiting list for lung transplantation. In this study, the optimal points for discriminating between survivors and nonsurvivors after 2 years corresponded to 39% DLco percent predicted, and to a HRCT–fibrosis score of 2.25. The combination of these parameters yielded an optimal point with specificity and sensitivity of 84% and 82%, respectively.

Key points

- **Correlation between Dlco and High-Resolution Computed Tomography (HRCT) for diagnosis and follow-up of idiopathic pulmonary fibrosis is good (low level of evidence).**
- **Dlco does not predict response to treatment (low level of evidence)**
- **Dlco % predicted is correlated with the prognosis in IPF patients (low level of evidence).**

7.3.5 Pulmonary arterial hypertension

7.3.5.1 Screening and diagnosis

The American College of Chest Physicians (ACCP) evidence-based clinical practice guideline [75] recommends a pulmonary function testing with Dlco in patients with systemic sclerosis periodically (every 6 to 12 months) to detect pulmonary vascular or interstitial disease (quality of evidence fair). On the other hand, the study of Mukerjee [114] showed that Dlco had a weak correlation with mean pulmonary arterial pressure in patients with systemic sclerosis. In addition, pulmonary function testing was less sensitive than clinical history in identifying patients with early pulmonary hypertension. The positive predictive value of currently used non-invasive tests was adequate for the diagnosis of advanced PAH provided sufficiently high thresholds (TG>45mmHg or Dlco <55% predicted) were used. These tests cannot be relied on to exclude pulmonary hypertension where pre-test probability is high.

The study of Romano[115] showed normal or slightly reduced Dlco in patients with precapillary pulmonary hypertension (either from chronic thrombo-embolic pulmonary hypertension or from idiopathic pulmonary hypertension); normal Dlco did not exclude the diagnosis of PPH.

The study of Sun[79] showed that patients with Primary Pulmonary Hypertension (PPH) commonly had abnormalities in Dlco levels that correlated significantly with disease severity.

7.3.5.2 Prognosis

The American College of Chest Physicians evidence-based clinical practice guidelines[76] considers Dlco for the prognosis of arterial pulmonary hypertension, because it influences both medical therapy and referral for transplantation. In patients with scleroderma-associated PAH, reduced Dlco (<45% predicted in the absence of interstitial fibrosis) may be used to predict a worse prognosis (quality of evidence low).

Key points

- **In patients with systemic sclerosis, Dlco is recommended for the screening and diagnosis of pulmonary arterial hypertension, despite lower sensitivity than clinical history (low level of evidence).**
- **Very low DLco (<45% predicted) may be used to predict a worse prognosis in patients with scleroderma-associated pulmonary arterial hypertension (low level of evidence)**
- **In patients with a diagnosis of advanced pulmonary arterial hypertension, Dlco results correlate significantly with disease severity (Low level of evidence).**

7.3.6 Systemic sclerosis

The study of Steen[116] on the prognosis of 815 patients with systemic sclerosis found that isolated reduction in Dlco was a frequent abnormality in SSc. Overall, it was associated with a good prognosis for survival and for pulmonary morbidity. A small subset of patients (11%) with a very low Dlco (<55% of predicted) developed isolated pulmonary hypertension, all of whom had limited scleroderma.

The study of Peters-Golden[117] showed that DLco ≤ 40% of the predicted reference value was associated with only 9% five-year cumulative survival rate compared with a 75% five-year cumulative survival rate in patients with a DLco > 40% of the predicted reference value. The study of Altman[118] showed that reduced pulmonary diffusing capacity for carbon monoxide (≤ 50% of predicted) was one of the best predicting reduced survival. The study of Taskhin[119] found that, in patients with SSc, cumulative survival may be related to the rate of decline in Dco, TLC, and FVC, but was not predicted by impairment in any measure of pulmonary function.

A prospective study of Wells[120] showed that the percent predicted Dlco best reflected the extent of fibrosing alveolitis, in patients with fibrosing alveolitis associated with SSc.

Key points

- **Isolated reduction in Dlco is a frequent abnormality in SSc patients and is associated with a good prognosis for survival and pulmonary morbidity.**
- **A very low DLco (< 55% of predicted) may be associated with isolated pulmonary hypertension in patients with limited scleroderma (low level of evidence).**
- **A very low DLco (≤ 50% of predicted) is predicts reduced survival in patients with systemic scleroderma.**
- **Dlco % predicted may reflect the extent of fibrosing alveolitis in patients with fibrosing alveolitis associated with SSc (low level of evidence).**

7.3.7 COPD

7.3.7.1 Guidelines

For the diagnosis of COPD, the NICE guideline recommends the use of Dlco in case symptoms seem disproportionate to the spirometric impairment or when diagnostic uncertainty remains (expert opinion). For the assessment of severity, the NICE guideline states that COPD is heterogeneous and that for the assessment of the true severity of the disease in an individual patient the degree of airflow obstruction and disability, the frequency of exacerbations and the following known prognostic factors may be needed: FEV_1, DI_{CO}, breathlessness (MRC scale), health status, exercise capacity, BMI, partial

pressure of oxygen in arterial blood (PaO2) and cor pulmonale. Likewise, GOLD states that diffusing capacity (Dlco) measurements are not needed in a routine assessment but can provide information on the overall impact of the disease and can be valuable in resolving diagnostic uncertainties and assessing patients for surgery.

FMS includes the diffusion capacity in the diagnostic strategy, without level of evidence. On the opposite, the guideline ICSI does not include the Dlco in the strategy necessary to establish diagnosis or severity of COPD.

7.3.7.2 Systematic search

The study of Owens[121] (48 patients with COPD) found that the diffusing capacity was more specific and sensitive than FEV_1 to predict the development of arterial desaturation during exercise in COPD patients. A diffusing capacity > 55% predicted was 100% specific for desaturation, as compared to a specificity of 82% for an FEV1 > 55% predicted. Using this cut-off point, the sensitivity of the diffusing capacity was 68% as compared to 46% for the FEV_1.

The study of Dubois[122] found that, in severely hypoxemic patients (PaO2 ≤ 55 mmHg) selected for long term oxygen therapy, lower Dlco % predicted is one factor that independently predicted reduced survival.

The Cochrane systematic review of Tiong Lu on surgical lung volume reduction for diffuse emphysema found that patients identified post hoc as being of high risk of death from surgery were those with particularly impaired lung function and poor diffusing capacity and/or homogenous emphysema.

Key points

- **Recommendations disagree on the use of DLco for the diagnosis or the assessment of severity.**
- **DLco is recommended to investigate symptoms that seem disproportionate to the spirometric impairment, to evaluate the overall impact of the disease, to resolve diagnostic uncertainties, and to assess patients for surgery (based on expert's opinion).**
- **DLco >55% is more sensitive than FEV_1 to exclude an arterial desaturation during exercise (Low level of evidence)**
- **Lower Dlco % predicted independently predicts reduced survival in patients receiving long term oxygen therapy (low level of evidence)**
- **A poor diffusing capacity is a predictor of mortality in patients undergoing a surgical lung volume reduction (low level of evidence).**

7.3.8 Sarcoidosis

The study of Dunn[123] compared patients with sarcoidosis to patients with idiopathic pulmonary fibrosis. Resting and exercise gas exchange tended to be relatively normal and the diffusing capacity was higher in patients with sarcoidosis than in those with IPF.

Barros et al.[124] studied the role of clinical, radiographic and functional variables in predicting gas exchange impairment during moderate exercise in patients with sarcoidosis. They concluded that conventional chest X-ray and Dlco were sufficient to estimate the individual risk. DLco correlated best with gas exchange impairment: Dlco single breath ≤ 70% predicted had a sensitivity of 81.8% and specificity of 70%, the positive predictive value was 50%, the negative predictive value 91% and the likelihood ratio + 2.72. Dlco single breath ≤ 50% predicted had a sensitivity of 45%, specificity 96.6%, positive predictive value 83%, negative predictive value 83% and likelihood ratio + 13.35.

Key points

- **Dlco is correlated with gas exchange impairment during moderate exercise in patients with sarcoidosis (low level of evidence)**

7.3.9 Bleomycin effects

In the study of McKeage[125], six of 81 patients developed clinically significant bleomycin lung and the Dlco predicted its development in only one patient (sensitivity 16.7%). 75 of 81 patients did not develop clinically significant bleomycin lung and 12 of these showed a major reduction (≥ 35% pre-treatment level) in Dlco (specificity 63 of 75 patients: 84,0%). In this study, Dlco failed to predict the development of serious bleomycin lung toxicity in all but one case.

Key points

- **Dlco failed to predict Bleomycin pulmonary pneumonitis or serious lung toxicity (low level of evidence).**

7.3.10 Heart failure prognosis

Guazzi et al.[126] found that impaired alveolar-capillary membrane gas conductance is a powerful independent predictor of worse prognosis in stable chronic heart failure. In contrast, FEV_1, FVC, maximum voluntary ventilation and Dlco were not independent predictors of a worse prognosis.

Key points

- **Impaired alveolar-capillary membrane gas conductance is an independent predictor of worse prognosis in stable chronic heart failure but Dlco is not (low level of evidence).**

7.3.11 HIV/AIDS

The cohort study of Kvale[127] found that a decline of Dlco without concomitant respiratory symptoms or new chest X-ray abnormalities did not warrant further evaluation. Moreover, serial measurements of Dlco should not be performed to screen HIV-infected persons for lung disease. In 1995 Rosen[128] reviewed the same study and concluded that patients with advanced HIV infection all have reduced Dlco measurements.

Key points

- **Dlco is not a good test to screen HIV-infected persons for lung disease (low level of evidence).**

7.3.12 Asthma

None of the four guidelines (ICSI, GINA, SIGN, FMS) recommends the use of Dlco for the diagnosis, assessment of the disease severity or follow-up of asthma. SIGN specifies that failure to respond to asthma treatment should prompt a search for an alternative, or additional, diagnosis (based on expert's opinion).

Our systematic search did not find studies to support the use of Dlco in this topic.

Key points

- **There is no evidence to use the DLco for the diagnosis, the assessment of disease severity or the follow-up of asthma.**

7.3.13 Miscellaneous

Our systematic search found no article that satisfied to our inclusion and exclusion criteria. Evidence for other possible indications of Dlco (such as respiratory muscle weakness, respiratory failure, sleep apnoea syndrome, hypoventilation, hyperventilation or dyspnoea) is not supported by the results of our search.

Key points

- **There is no evidence to support other possible use of Dlco such as respiratory muscle weakness, respiratory failure, sleep apnoea syndrome, hypoventilation, hyperventilation or dyspnoea.**

7.4 AIRWAYS RESISTANCE

7.4.1 Guidelines

Using the term 'body plethysmography' in the databases of the National Guideline Clearinghouse (US), Scottish Intercollegiate Guidelines Network (UK), New Zealand Guideline Group (New Zealand), National Library of Health (UK), NICE (UK), two guidelines were found, both cited above in the section on lung volumes: the AARC guideline on body plethysmography and the AARC guideline on static lung volumes. As already mentioned earlier, no details are given on the methodology, by which they were not included in the review.

7.4.2 Systematic reviews

Using the search terms: (("Plethysmography, Whole Body"[MeSH]) AND systematic[sb]) in PubMed, only 3 articles were identified. The first two were not relevant for our research question (2 articles relating to infants) and the last article was the AARC guideline, cited above and not included due to lack of details on the methodology.

7.4.3 Original studies

Using the search terms: ("Plethysmography, Whole Body"[MeSH]) AND (specificity[Title/Abstract]) in PubMed, 13 articles were identified. Not one article satisfied our inclusion and exclusion criteria, by which no article was included in our review.

Key points

- **No evidence on the value of airways resistance was identified in our review.**

7.5 RESPIRATORY RESISTANCE (FORCED OSCILLATION TECHNIQUE AND INTERRUPTER TECHNIQUE)

In this review, the available evidence on the diagnostic value of the forced oscillation technique and interrupter technique was summarized. The review was limited to clinical studies in adults in an ambulatory setting. An iterative search strategy was developed. Guidelines on the use and indications of respiratory resistance were sought first.

Subsequently systematic reviews and meta-analyses were searched and finally original studies were identified.

7.5.1 Guidelines:

The following sites were searched: National Guideline Clearinghouse (US), Scottish Intercollegiate Guidelines Network (UK), New Zealand Guideline Group (New Zealand), National Library of Health (UK), NICE (UK). Search terms were 'Airway resistance', 'forced oscillation technique', 'interrupter technique'.

Results: 8 guidelines were identified that were possibly relevant, only four of which contained statements regarding the tests under review. Three of these guidelines were of low quality by the criteria of AGREE: the methods of evidence gathering were not specified, nor the methods of evidence selection and appraisal; in addition, there was no information on whether levels of evidence were used and which grades of recommendation.

Only one guideline was of medium quality according to the AGREE criteria: the GOLD guideline[28]. In this guideline, flow-volume loops, diffusion capacity and lung volumes are not considered necessary in routine assessment of patients with COPD. However, they can be considered when the physician wants to provide information on the overall impact of the condition on the patient's health, to resolve diagnostic uncertainty and to assess patients for surgery. More detailed information on these indications, levels of evidence or grades or recommendation to specify these statements were not given.

7.5.2 Systematic reviews

Two databases were searched for systematic reviews or meta-analyses: Medline using Clinical Queries and the CRD database. The following search terms were used: 'airway resistance [MeSH]', forced oscillation technique, interrupter technique, plethysmography. Medline yielded 20 articles of which one was potentially relevant[12]. CRD yielded 85 articles, of which none was potentially relevant.

When assessing the review by Miller et al. in full text, it did not prove a systematic review.

Consequently, no systematic reviews were included in this report.

7.5.3 Original studies

7.5.3.1 Methods

Two databases were searched: Medline and Embase.

Medline was searched from 1966 to August 2006, with the following search string:

("Respiratory Mechanics"[MeSH] OR (forced[All Fields] AND oscillation[All Fields] AND technique[All Fields]) OR fot[All Fields] OR interrupter[All Fields] OR "Airway Resistance"[MeSH]) AND specificity[Title/Abstract]

In Embase, a similar search string was used:

'lung resistance'/exp OR 'airway resistance'/exp OR forced AND 'oscillation'/exp AND 'technique'/exp OR fot OR interrupter AND [embase]/lim AND [1966

2006]/py

All articles were selected for assessment on full text according to the following criteria:

Inclusion criteria: population included: adults; all tests related to forced oscillation technique or interrupter technique; clinical studies; ambulatory setting

Exclusion criteria: population included: children; ventilated patients; hospitalized patients; studies on healthy volunteers; studies of less than 20 patients; narrative reviews; editorials, letters

Those articles satisfying the inclusion and exclusion criteria were then assessed on quality using the QUADAS instrument.

In this review on tests of airway resistance, studies were included in the final review if they fulfilled at least 5 items of the 14 QUADAS items, and had a maximum of 6 items that were not fulfilled.

Data were extracted from the studies of medium or high quality, and summarized in evidence tables.

7.5.3.2 Results

The search in Medline yielded 198 articles, in Embase 391 articles. Discarding duplicates, a total of 574 articles were assessed on title and abstract for eligibility.

Of these 574 articles, 35 were selected for assessment on full text. After obtaining the full text, 16 articles were not eligible, because they were not evaluating a test of airway resistance, included hospitalized patients or were a narrative review. Finally, 19 articles reporting 20 studies were assessed on quality using the QUADAS instrument[129-131, 17, 132, 133, 88, 134-145]. Only 7 studies were of medium or high quality (summarized in the evidence table, see appendix), the remaining 13 studies were excluded due to insufficient quality.

The results of the studies included in this review are scattered. No two studies evaluated exactly the same index test in a comparable population for the same target condition or agreement with another measuring method. In general, studies are fairly small, leading to low precision of the results. However, confidence intervals are seldom provided.

Measurements before and after provocation seem to give the most diagnostic information in terms of altering the pre-test probability of asthma.

Key points

- **No definitive answer on the diagnostic value of forced oscillation technique or the interrupter technique can be given, based on the evidence summarized in this review.**

8 RECOMMENDATIONS

Disclaimer

It is by no means the intention that the recommendations in this report would be strictly adhered to in every individual patient. Recommendations are based on the available evidence and can change as new evidence comes forward. Therefore, the recommendations should be considered as guidance. Adhering to the recommendations does not guarantee success in every patient. In addition, they can not be considered the only appropriate clinical approach and thereby exclude other approaches that strive for the same result. The ultimate decision to use a certain clinical procedure or treatment is the responsibility of the treating physician, taking all clinical information of the patient and the available diagnostic and therapeutic measures into account. It is to be expected that these recommendations are adapted to the local context after discussion in peer groups.

8.1 METHODOLOGY

Based on the evidence gathered for the disease-based and the test-based approach, a panel of physicians working in the field has formulated clinical practice guidelines. The panel consisted of several pneumologists and general practitioners.

Each recommendation has been assigned a grade of recommendation, based on the guidelines of the GRADE working group. The GRADE guidelines are centred on 2 axes: the level of evidence obtained for a certain clinical question, and the balance between benefit and harm that is expected for the patient. The level of evidence is denoted with A, B or C, referring to high, moderate or low level of evidence. The balance between benefit and harm is denoted with 1 and 2, referring to a strong recommendation and a weak recommendation respectively.

It should be noted that guidance is only given on the use of the specified pulmonary function tests, and should not be considered as an exhaustive guidance on the clinical management of the patient. Other tests such as exhaled NO, arterial blood gases, or tests for muscle strength may be warranted in certain situations but are not considered here.

In the recommendations, the term ‘referred patients’ is used to denote all patients that present themselves to secondary, specialist care after initial evaluation in primary care. It is not the intention of the expert panel to describe when and how patients should be referred. The term is merely used to describe a selected group of patients, in whom clinical presentation, duration of illness, differential diagnoses etc, are different from those seen in primary care. On average, patients in secondary care present with a different spectrum of disease: rare illnesses are more prevalent, patients present with more advanced stages of the disease, respond less well to therapy and present with co-morbidities more often.

8.1.1 Asthma diagnosis

Patients presenting with signs and symptoms suggestive of asthma, variability in airflow limitation should be documented, either by spirometry (grade of recommendation 1A) or by other means such as peak flow measurements. In a selected group of patients in which diagnostic doubt remains, reversibility testing, TLC, airways resistance or provocation tests may be indicated (grade of recommendation 1C). DI_{CO} is not indicated, unless there is a suspicion of COPD, by which these patients also fall into the ‘COPD diagnosis’ category (grade of recommendation 1C).

8.1.2 Asthma follow-up

Patients diagnosed with asthma should have spirometry during follow-up (grade of recommendation 1A). The optimal interval between tests depends on the clinical presentation of the patient. Reversibility testing is recommended by the expert panel in case of obstruction despite therapy (grade of recommendation 2C). In case there is a suspicion of small airway disease, a TLC is indicated (grade of recommendation 1C). Airways resistance can be tested in those patients with an abnormal test result at diagnosis (grade of recommendation 2C). In general, a provocation test is not indicated in the follow-up of patients with asthma, except in patients with seasonal asthma with symptoms outside the pollen season (grade of recommendation 1B). DI_{CO} is not indicated (grade of recommendation 1C).

8.1.3 Asthma exacerbation

The same tests are indicated in patients suffering from an asthma exacerbation, except for the provocation test which is not indicated here (grade of recommendation 1C).

8.1.4 Screening for COPD

No evidence was found in favour of screening for COPD in the general population. In addition, the hypothesis that documenting airflow obstruction might increase smoking cessation rates has been rejected in several randomized trials. Therefore, screening in asymptomatic subjects is not recommended (grade of recommendation 1A).

8.1.5 Case finding of COPD

Case finding is defined as actively diagnosing a target disorder in patients experiencing symptoms without seeking medical advice for those symptoms. For example, general practitioners might question patients on respiratory symptoms while in fact the patient is consulting for another reason. Randomised trials showing improved patient outcome are not available. But, studies have shown that case finding detects patients with early stage COPD, and that therapy might be efficacious in these patients. Therefore, case finding for COPD is recommended (grade of recommendation 1B).

8.1.6 COPD diagnosis

Patients suspected of COPD based on their signs and symptoms should have a spirometry (grade of recommendation 1A). Reversibility testing is reserved for those patients in whom diagnostic doubt remains (grade of recommendation 1C). TLC and thoracic gas volume are not indicated in primary care, but may be indicated in patients referred to secondary care because of the prognostic impact of an abnormal test result (grade of recommendation 2B and 2C respectively). The same applies for the DI_{CO} which should be done in patients referred to secondary care or patients with signs and symptoms disproportionate to the spirometry result (grade of recommendation 2B). Airways resistance and provocation tests are not indicated, as they do not offer any additional information based on current evidence (grade of recommendation 1C).

8.1.7 COPD follow-up

Spirometry is indicated in the follow-up of a patient diagnosed with COPD (grade of recommendation 1A). Again, the optimal interval depends on the clinical presentation. No other pulmonary function tests are necessary (grade of recommendation 1C), except thoracic gas volume in case the symptoms are disproportionate to the spirometry result and there is a suspicion of hyperinflation (grade of recommendation 1B). In patients scheduled for reductive surgery or receiving oxygen therapy, the results of a diffusion capacity test have a prognostic value (grade of recommendation 1C).

8.1.8 COPD exacerbation

Patients hospitalised because of a COPD exacerbation should have a spirometry, although the expert panel acknowledged that it may not be feasible in the acute phase (grade of recommendation 2C). Other pulmonary function tests are not indicated (grade of recommendation 1C).

8.1.9 Interstitial lung disease, systemic disease and primary pulmonary hypertension, diagnosis

At initial presentation, patients should have a spirometry and a TLC (grade of recommendation 1A), as they are part of the definition of the disease. Patients diagnosed with scleroderma should have a DI_{CO} (grade of recommendation 1B). DI_{CO} provides prognostic information in the remaining patients (grade of recommendation 1C). No other pulmonary function tests are recommended (grade of recommendation 1C).

8.1.10 Interstitial lung disease, systemic disease and primary pulmonary hypertension, follow-up

Parallel to the diagnosis, spirometry and TLC are indicated (grade of recommendation 1A). DI_{CO} is indicated for prognostic reasons in patients with ILD, scleroderma and pulmonary hypertension (grade of recommendation 1B).

8.1.11 Thoracic wall pathology, diagnosis

All patients suspected of thoracic wall pathology should have a spirometry and TLC (grade of recommendation 1A and 1B respectively). No other pulmonary function tests are indicated.

8.1.12 Dyspnoea

Those patients that are suspected of asthma or COPD based on their signs and symptoms, fall in that category and are not considered here.

Every patient suffering from dyspnoea should have a spirometry (grade of recommendation 1A), TLC (grade of recommendation 1C), and a DI_{CO} (grade of recommendation 1C). A provocation test is indicated in case diagnostic uncertainty remains after the previous tests (grade of recommendation 1C).

8.1.13 Chronic cough

As in the patients with dyspnoea, those patients suspected of asthma or COPD based on their signs and symptoms are not considered here.

Every patient with chronic cough should have a spirometry (grade of recommendation 1A) and a TLC (grade of recommendation 1C). Similar as above, a provocation test is indicated in case diagnostic certainty remains (grade of recommendation 1C).

	Asthma diagnosis	Asthma follow-up	Asthma exacerbation	COPD diagnosis	COPD follow-up	COPD exacerbation	ILD diagnosis	ILD follow-up	Dyspnoea	Chronic cough
Spirometry	+ (1A)	+ (1A)	+ (1A)	+ (1A)	+ (1A)	+ (2C) hospitalised patients	+ (1A)	+ (1A)	+ (1A)	+ (1A)
Reversibility test	+ (1C) selected patients	+ (1C) insufficient response to therapy	+ (1C) insufficient response to therapy	+ (1C) selected patients	- (1C)	- (1C)	- (1C)	- (1C)	- (1C)	- (1C)
TLC	+ (1C) selected patients	+ (1C) small airway disease	+ (1C) small airway disease	+ (2B) referred patients	+ (1B) hyperinflation	- (1C)	+ (1A)	+ (1A)	+ (1C)	+ (1C)
Thoracic gas volume	- (1C)	- (1C)	- (1C)	+ (2C) referred patients	+ (1B) hyperinflation	- (1C)	- (1C)	- (1C)	- (1C)	- (1C)
Airways resistance	+ (1C) selected patients	+ (2C) abnormal result at diagnosis	+ (2C) abnormal result at diagnosis	- (1C)	- (1C)	- (1C)	- (1C)	- (1C)	- (1C)	- (1C)
Provocation test	+ (1C) selected patients	+ (1B) seasonal asthma with symptoms outside season	- (1B)	- (1C)	- (1C)	- (1C)	- (1C)	- (1C)	+ (1C) selected patients	+ (1C) selected patients
Diffusion capacity	- (1C)	- (1C)	- (1C)	+ (2B) referred patients	- (1C)	- (1C)	+ (1B) scleroderma patients + (1C)	+ (1B)	+ (1C)	- (1C)

9 CONCLUSIONS AND RECOMMENDATIONS

- Pulmonary function tests are increasingly performed in ambulatory care. More than half of all patients receiving at least one lung function test are submitted to a vast combination of tests.
- The Belgian nomenclature on pulmonary function testing is outdated, and corresponds poorly to the scientific literature both in names attributed to tests as in clinical indications. Especially the code for 'ventilation mechanics' is unclear and may give rise to inappropriate use.
- The reimbursement of pulmonary function tests individually acts as a financial incentive for combined and repetitive testing.
- Global reimbursement of diagnostic testing on lung function would decrease the financial incentive, and add flexibility to the introduction of new techniques, e.g. exhaled NO. This should not preclude the independent assessment of new techniques before introducing these in clinical practice.
- Quality control and standardisation is essential for the proper use of pulmonary function tests. Quality indicators should be developed and audited to guarantee and maintain quality and standardisation of tests.
- The reimbursement of some interventions, such as long-acting beta-agonists or respiratory revalidation, also requires the results of pulmonary function tests. Consistency between guidelines and requirements ought to be pursued.
- The scientific community has a responsibility in broadening the evidence base for what they consider to be an integral part of their clinical work. Studies addressing some of the gaps identified in this report should be set up.
- The clinical recommendations that have been formulated in this report should be the basis of a comprehensive program aimed at improving clinical practice. Other interventions that may be included in such a program are feedback reports to physicians in which their test requesting behaviour is compared to either their peers or to guidelines, peer review groups discussing and adapting the recommendations to the local context, or financial incentives aimed at reducing the numbers of unnecessary tests.

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11 APPENDICES

ABBREVIATIONS

- ATS: American Thoracic Society
- BTS: Belgian Thoracic Society
- COPD: chronic obstructive pulmonary disease
- Dlco: carbon monoxide diffusion capacity
- ECG: electrocardiogram
- ERS: European Respiratory Society
- FEV1: forced expiratory volume in 1 second
- FMS: Finnish Medical Society
- FRC: functional residual capacity
- FVC: forced vital capacity
- GOLD: Global initiative for chronic Obstructive Lung Disease
- HTA: health technology assessment
- ICSI: Institute for Clinical Systems Improvement
- IMA: intermutualistisch agentschap
- INAMI: Institut National d'Assurance Maladie-Invalidité
- KCE: Federal Health care Knowledge Center
- NICE: National Institute for Health and Clinical Excellence
- PEF: peak expiratory flow
- PEFR: peak expiratory flow rate
- PFT: pulmonary function testing
- Raw: airways resistance
- RIZIV: Federal Health Insurance Institute
- Rrs: respiratory resistance
- RV: residual volume
- TLC: total lung capacity
- Va: alveolar volume
- VC: vital capacity

NOMENCLATURE CODES AND RULES

Nomenclatuur	Beschrijving	Description
471251/471262	Volledige spirografie met bepalen van maximum adem minuten volume	Spirographie globale avec détermination du volume expiratoire maximum seconde
471273/471284	Spirografie met bronchodilatatieproef	Spirographie avec épreuve de bronchodilatation
471295/471306	Spirografie met pharmacodynamische provocatieproef al dan niet gevolgd van bronchodilatatie	Spirographie avec épreuve pharmaco-dynamique, de provocation, suivie ou non de bronchodilatation
471310/471321	Bepalen van het residuair volume	Détermination du volume résiduel
471354/471365	Meten van diffusiecapaciteit	Mesure de la capacité de diffusion
471376/471380	Studie van de ventilatiemechaniek	Etude de la mécanique ventilatoire

Nummer	Beschrijving	Description
02	VRAAG	QUESTION
	Mag verstrekking nr. 471295 - 471306 ** K 35 verscheidene keren per zitting worden aangerekend omdat het onderzoek verscheidene proeven bij inspanning omvat ?	Peut-on porter en compte plusieurs fois par séance la prestation n° 471295 - 471306 ** K 35 parce que l'examen comporte plusieurs épreuves d'effort ?
	ANTWOORD	REPONSE
	Verstrekking nr. 471295 - 471306 ** Spirografie met farmacodynamische provocatieproef, al dan niet gevolgd van bronchodilatatie K 35 mag éénmaal per zitting worden geattesteerd. De verstrekking beoogt de volledige proef en mag niet worden toegepast per geprovoceerde inspanning.	La prestation n° 471295 - 471306 ** Spirographie avec épreuve pharmaco-dynamique de provocation, suivie ou non de broncho-dilatation K 35 peut être attestée une fois par séance. La prestation vise l'ensemble de l'épreuve et ne peut s'appliquer par effort provoqué.
	Staatsblad datum : 13/03/2002	Date du moniteur : 13/03/2002
	Inwerkingtreding datum : 13/03/2002	Date de prise d'effet : 13/03/2002
	Artikels : 20-§ 1b ;	Articles : 20-§ 1b ;
	Nomenclatuurnummer : 471295 ; 471306 ;	Numéro de nomenclature : 471295 ; 471306 ;
03	VRAAG	QUESTION
	Bepalen van de kennelijke longcompliantie door slokdarmcatheterisme, plus, dezelfde	Détermination de la compliance apparente pulmonaire par cathétérisme oesophagien,

Nummer	Beschrijving	Description
	dag, een studie van de dynamische weerstand en van de functionele residuaire capaciteit door plethysmografie van het lichaam. Mag men 2 x nr. 471376 - 471380 ** Studie van de ventilatiemechaniek K 40 tariferen (die onderzoeken worden afzonderlijk verricht met een aparte apparatuur) ?	plus, le même jour, une étude des résistances dynamiques et de la capacité résiduelle fonctionnelle par pléthysmographie corporelle. Peut-on tarifer 2 x 471376 - 471380 ** Etude de la mécanique ventilatoire K 40 (ces examens se pratiquent séparément avec un appareillage distinct) ?
	ANTWOORD	REPONSE
	Verstrekking nr. 471376 - 471380 ** K 40 mag geen tweemaal worden geattesteerd voor het bepalen van de longcompliantie en weerstand aangezien die verstrekkingen tot doel hebben de ventilatiemechaniek te waarderen en dat hun tarifering niet wijzigt, ongeacht de aard en het aantal aangewende technieken.	La prestation n° 471376 - 471380 ** K 40 ne peut être attestée deux fois pour la détermination de la compliance et des résistances pulmonaires vu qu'elles ont pour but d'apprécier la mécanique ventilatoire et que leur tarification ne change pas quels que soient la nature et le nombre des
	Staatsblad datum : 13/03/2002	techniques mises en oeuvre.
	Inwerkingtreding datum : 13/03/2002	Date du moniteur : 13/03/2002
	Artikels : 20-§ 1b ;	Date de prise d'effet : 13/03/2002
	Nomenclatuurnummer : 471376 ; 471380 ;	Articles : 20-§ 1b ;
		Numéro de nomenclature : 471376 ; 471380 ;
04	VRAAG	QUESTION
	Hoe moeten de volgende onderzoekingen inzake pneumologie worden getarifeerd :	En matière de pneumologie comment faut-il tarifer les examens suivants :
	1) Meten van de volumes + M.A.M.V.	1) Mesure des volumes + V.E.M.S.
	2) Meten van de volumes + M.A.M.V. + R.V.	2) Mesure des volumes + V.E.M.S. + V.R.
	3) Meten van de volumes + M.A.M.V. + R.V. + farmacodynamische proeven ?	3) Mesure des volumes + V.E.M.S. + V.R. + épreuves pharmacodynamiques ?
	ANTWOORD	REPONSE
	1. Meten van de volumes + M.A.M.V. : 471251 - 471262 ** Volledige spirografie met bepalen van maximum adem minuten volume K 10.	1. Mesure des volumes + V.E.M.S. : 471251 - 471262 ** Spirographie globale avec détermination du volume expiratoire maximum seconde K 10.
	2. Meten van de volumes + M.A.M.V. + residuair volume : 471251 - 471262 ** K 10 + 471310 - 471321 ** Bepalen van het residuair volume K 40.	2. Mesure des volumes + V.E.M.S. + volume résiduel : 471251 - 471262 ** K 10 + 471310 - 471321 ** Détermination du volume résiduel K 40.
	3. Meten van de volumes + M.A.M.V. + R.V. + farmacodynamische proeven : (471273 – 471284 ** Spirografie met bronchodilatatieproef K 20) of (471295 - 471306 ** Spirografie met farmacodynamische provocatieproef, al dan niet gevolgd van bronchodilatatie K 35) + 471310 - 471321 ** K 40. Te noteren is dat het eigenlijk gaat om "dynamische volumes", gemeten tijdens de spirografie.	3. Mesure des volumes + V.E.M.S. + V.R. + épreuves pharmacodynamiques : (471273 – 471284 ** Spirographie avec épreuve de bronchodilatation K 20) ou (471295 - 471306 ** Spirographie avec épreuve pharmacodynamique de provocation, suivie ou non de bronchodilatation K 35) + 471310 - 471321 ** K 40. A noter qu'il s'agit en réalité de "volumes dynamiques", mesurés pendant la spirographie.
	Staatsblad datum : 13/03/2002	Date du moniteur : 13/03/2002

Nummer	Beschrijving	Description
	Inwerkingtreding datum : 13/03/2002	Date de prise d'effet : 13/03/2002
	Artikels : 20-§ 1b ;	Articles : 20-§ 1b ;
	Nomenclatuurnummer : 471251 ; 471262 ; 471273 ; 471284 ; 471295 ; 471306 ; 471310 ;	Numéro de nomenclature : 471251 ; 471262 ; 471273 ; 471284 ; 471295 ; 471306 ; 471310 ;
	471321 ;	471321 ;
05	VRAAG	QUESTION
	Broncho-pulmonale provocatietest in het raam van het opzoeken van de extrinsieke allergische pneumopathie, die een klassieke studie van de ademhalingsfunctie door spirografie impliceert en die na + 1 uur, + 3 uur, + 5 uur en + 7 uren wordt herhaald.	Test de provocation broncho-pulmonaire dans le cadre de la recherche de pneumopathie extrinsique allergique, ce qui implique une étude classique de la fonction respiratoire par
	ANTWOORD	spirographie répétée après + 1 heure, + 3 heures, + 5 heures et + 7 heures.
	Zoals het is beschreven moet het onderzoek worden geattesteerd onder het nr. 471295 – 471306 ** Spirografie met farmacodynamische provocatieproef, al dan niet gevolgd van bronchodilatatie K 35, ongeacht het aantal spirografieën die in de loop van de proef worden verricht.	REPONSE
		L'examen tel qu'il est décrit doit être attesté sous le n° 471295 - 471306 ** Spirographie avec épreuve pharmaco-dynamique de provocation, suivie ou non de broncho-dilatation K 35, quel que soit le nombre de spirographies effectuées au cours de l'épreuve.
	Staatsblad datum : 13/03/2002	Date du moniteur : 13/03/2002
	Inwerkingtreding datum : 13/03/2002	Date de prise d'effet : 13/03/2002
	Artikels : 20-§ 1b ;	Articles : 20-§ 1b ;
	Nomenclatuurnummer : 471295 ; 471306 ;	Numéro de nomenclature : 471295 ; 471306 ;
06	VRAAG	QUESTION
	Mag verstrekking nr. 471251 - 471262 ** Volledige spirografie met bepalen van maximum adem minuten volume K 10 worden geattesteerd wanneer men met een elektronische spirometer met thermistor en digitale afleesschaal de volgende verstrekkingen verricht :	La prestation n° 471251 - 471262 ** Spirographie globale avec détermination du volume expiratoire maximum seconde K 10 peut-elle être attestée lorsqu'on effectue, à l'aide d'un
		spiromètre électronique avec thermistor et cadran à lecture digitale, les prestations suivantes :
	- vitale capaciteit;	- la capacité vitale;
	- het M.A.M.V.;	- le V.E.M.S.;
	- het maximum uitademingsdebiet (peak flow);	- le débit expiratoire maximum (Peak Flow);
	- de maximum vrijwillige ventilatie ?	- la ventilation volontaire maximum ?
	ANTWOORD	

Nummer	Beschrijving	Description
	De opgesomde spirometrische onderzoekingen komen niet voor in de nomenclatuur van de geneeskundige verstrekkingen en daarvoor wordt geen verzekeringstegemoetkoming toegekend. Wanneer een volledige spirometrie met bepaling van FEV1 met een dergelijke electronische spirometer wordt gemeten kan wel nr. 471251 - 471262 ** K 10 worden geattesteerd.	REPONSE Les examens spirométriques cités ne sont pas prévus à la nomenclature des prestations de santé et ne donnent pas lieu à intervention de l'assurance. Quand une spirométrie complète avec détermination du FEV1 est effectuée avec un tel spiromètre électronique, le n° 471251 – 471262 ** K 10 peut toutefois être attesté.
	Staatsblad datum : 13/03/2002	Date du moniteur : 13/03/2002
	Inwerkingtreding datum : 13/03/2002	Date de prise d'effet : 13/03/2002
	Artikels : 20-§ 1b ;	Articles : 20-§ 1b ;
	Nomenclatuurnummer : 471251 ; 471262 ;	Numéro de nomenclature : 471251 ; 471262 ;
07	VRAAG	QUESTION
	Bepalen van de resistentie van de luchtwegen en van het residuair volume door plethysmografie.	Détermination de la résistance des voies aériennes et du volume résiduel par pléthysmographie corporelle.
	ANTWOORD	REPONSE
	Deze onderzoeken mogen aangerekend worden onder respectievelijk de nrs. 471376 - 471380 ** Studie van de ventilatiemechaniek K 40 en 471310 - 471321 ** Bepalen van het residuair volume K 40.	Ces examens peuvent être attestés respectivement sous les numéros 471376 - 471380 ** Etude de la mécanique ventilatoire K 40 et 471310 - 471321 ** Détermination du volume résiduel K 40.
	Staatsblad datum : 13/03/2002	Date du moniteur : 13/03/2002
	Inwerkingtreding datum : 13/03/2002	Date de prise d'effet : 13/03/2002
	Artikels : 20-§ 1b ;	Articles : 20-§ 1b ;
	Nomenclatuurnummer : 471310 ; 471321 ; 471376 ; 471380 ;	Numéro de nomenclature : 471310 ; 471321 ; 471376 ; 471380 ;
08	VRAAG	QUESTION
	Gedurende een functionele ademhalingstest wordt de diffusiecapaciteit bij rust bepaald door de techniek van de inspiratoire apnoea. De diffusiecapaciteit wordt ook bepaald door de methode, in stabiele toestand, bij rust en bij inspanning. Mag verstrekking nr. 471354 - 471365 ** K 40 meermaals worden geattesteerd als die studies dezelfde dag worden uitgevoerd ?	Au cours d'un bilan fonctionnel respiratoire, la capacité de diffusion est déterminée au repos par la technique de l'apnée inspiratoire. La capacité de diffusion est également déterminée par la méthode en état stable, au repos et à l'effort. La prestation n° 471354 - 471365 ** K 40 peut-elle être attestée plusieurs fois si ces études sont réalisées le même jour ?
	ANTWOORD	REPONSE
	Verstrekking nr. 471354 - 471365 ** Meten van diffusiecapaciteit K 40 mag slechts eenmaal worden geattesteerd ongeacht de aangewende technieken of methoden.	La prestation n° 471354 - 471365 ** Mesure de la capacité de diffusion K 40 ne peut être attestée qu'une fois quelles que soient les techniques ou les méthodes mises en oeuvre.

Nummer	Beschrijving	Description
	Staatsblad datum : 13/03/2002	Date du moniteur : 13/03/2002
	Inwerkingtreding datum : 13/03/2002	Date de prise d'effet : 13/03/2002
	Artikels : 20-§ 1b ;	Articles : 20-§ 1b ;
	Nomenclatuurnummer : 471354 ; 471365 ;	Numéro de nomenclature : 471354 ; 471365 ;
11	VRAAG	QUESTION
	Bepalen van de "debiet-volume"-curve bij maximaal inademen of uitademen.	Détermination de la courbe « débit-volume » à l'inspiration ou expiration maximale.
	ANTWOORD	REPONSE
	De techniek mag aangerekend worden onder nr. 471251 - 471262 ** Volledige spirografie met bepalen van maximum adem minuten volume K 10.	La technique peut être portée en compte sous le n° 471251 - 471262 ** Spirographie globale avec détermination du volume expiratoire maximum seconde K 10.
	Staatsblad datum : 13/03/2002	Date du moniteur : 13/03/2002
	Inwerkingtreding datum : 13/03/2002	Date de prise d'effet : 13/03/2002
	Artikels : 20-§ 1b ;	Articles : 20-§ 1b ;
	Nomenclatuurnummer : 471251 ; 471262 ;	Numéro de nomenclature : 471251 ; 471262 ;

DEFINITION OF SPECIALISMS

specialism category	number	specialism
Anaesthetics-reanimation	100	Anaesthetics-reanimation
Anatomy-pathology	870	Anatomy-pathology
Cardiology	730	Cardiology
	734	Cardiology + functional and professional revalidation of handicapped persons
Clinical biology	860	Clinical biology
	862	Clinical biology + special competence in nuclear in vitro medicine
Dermatology-venerology	550	Dermatology-venerology
Gastroenterology	650	Gastroenterology
General practioners	1	General practioners
	2	General practioners + ECG
	3	Acknowledged general practitioners
	4	Acknowledged general practitioners + ECG
	5	General practioners in training
	6	General practioners in training + ECG
	7	General practioners + functional and professional revalidation of handicapped persons
	8	General practioners + ECG + functional and professional revalidation of handicapped persons
Gynaecology-obstetrics	340	Gynaecology-obstetrics
Internal medicine	58	Internal medicine in training
	580	Internal medicine
	582	Internal medicine + special competence in nuclear in vivo medicine
	584	Internal medicine + functional and professional revalidation of handicapped persons
	591	Internal medicine + cardiology
	597	Internal medicine + clinical biology
Neurology	770	Neurology
	774	Neurology + functional and professional revalidation of handicapped persons
Neurosurgery	170	Neurosurgery
	174	Neurosurgery + functional and professional revalidation of handicapped persons
Neurpsychiatry	760	Neurpsychiatry
	764	Neurpsychiatry + functional and professional revalidation of handicapped persons
Nuclear medicine	970	Nuclear medicine
	972	Nuclear medicine + surgery
	978	Nuclear medicine + gynaecology-obstetrics
	985	Nuclear medicine + internal medicine
	987	Nuclear medicine + gastroenterology

	988	Nuclear medicine + paediatrics
	989	Nuclear medicine + cardiology
	991	Nuclear medicine + rheumatology
	992	Nuclear medicine + physical medicine + revalidation
	994	Nuclear medicine + radio-diagnostics
	995	Nuclear medicine + radiotherapy-oncology
	997	Nuclear medicine + radio-diagnostics + radiotherapy-oncology
Ophthalmology	370	Ophthalmology
	374	Ophthalmology + functional and professional revalidation of handicapped persons
Orthopaedic surgery	480	Orthopaedic surgery
	494	Orthopaedic surgery + functional and professional revalidation of handicapped persons
Oto-rhino-laryngology	410	Oto-rhino-laryngology
	414	Oto-rhino-laryngology + functional and professional revalidation of handicapped persons
Paediatrics	690	Paediatrics
	694	Paediatrics + functional and professional revalidation of handicapped persons
Physical Medicine	795	Physical Medicine + revalidation + rheumatology + functional and professional revalidation of handicapped persons
	830	Physical Medicine + revalidation
	834	Physical Medicine + functional and professional revalidation of handicapped persons
Plastic surgery	210	Plastic surgery
Pneumology	620	Pneumology
	624	Pneumology + functional and professional revalidation of handicapped persons
	629	Pneumology + paediatrics
Psychiatry	780	Psychiatry
	784	Psychiatry + functional and professional revalidation of handicapped persons
Radio-diagnostics	930	Radio-diagnostics
Radiotherapy-oncology	960	Radiotherapy-oncology
	964	Radiotherapy-oncology + functional and professional revalidation of handicapped persons
Rheumatology	790	Rheumatology
	794	Rheumatology + functional and professional revalidation of handicapped persons
Stomatology	520	Stomatology
Surgery	140	Surgery
	153	Surgery + functional and professional revalidation of handicapped persons
Urology	450	Urology
	454	Urology + functional and professional revalidation of handicapped persons

TEST COMBINATIONS: FREQUENCIES AND RECURRENCES IN IMA SAMPLE

	Ambulatory			In hospital		
	Number of tests	Percent	Cumulative percent	Number of tests	Percent	Cumulative percent
Spirography + bronchodilation;Residual volume;Diffusion capacity;Ventilatory mechanics;	3647	29.39%	29.39%	1445	25.77%	25.77%
Complete spirography;Residual volume;Diffusion capacity;Ventilatory mechanics;	2133	17.19%	46.58%	1193	21.27%	47.04%
Complete spirography;	1317	10.61%	57.19%	301	5.37%	52.41%
Complete spirography;Residual volume;Diffusion capacity;	620	5.00%	62.18%	336	5.99%	58.40%
Complete spirography;Residual volume;Ventilatory mechanics;	605	4.88%	67.06%	204	3.64%	62.04%
Spirography + bronchodilation;Residual volume;Ventilatory mechanics;	508	4.09%	71.15%	205	3.66%	65.69%
Spirography + bronchodilation;Residual volume;Diffusion capacity;	500	4.03%	75.18%	263	4.69%	70.38%
Spirography + bronchodilation;	485	3.91%	79.09%	226	4.03%	74.41%
Complete spirography;Ventilatory mechanics;	359	2.89%	81.98%	184	3.28%	77.69%
Spirography + bronchodilation;Ventilatory mechanics;	303	2.44%	84.42%	70	1.25%	78.94%
Spirography + provocation;Residual volume;Diffusion capacity;Ventilatory mechanics;	283	2.28%	86.70%	43	0.77%	79.71%
Spirography + bronchodilation;Residual volume;	204	1.64%	88.35%	55	0.98%	80.69%
Complete spirography;Residual volume;	200	1.61%	89.96%	126	2.25%	82.94%
Ventilatory mechanics;	179	1.44%	91.40%	669	11.93%	94.86%
Spirography + bronchodilation;Diffusion capacity;Ventilatory mechanics;	160	1.29%	92.69%	36	0.64%	95.51%
Complete spirography;Spirography + bronchodilation;Residual volume;Diffusion capacity;Ventilatory mechanics;	146	1.18%	93.87%	48	0.86%	96.36%
Spirography + provocation;	124	1.00%	94.87%	13	0.23%	96.59%
Complete spirography;Diffusion capacity;	118	0.95%	95.82%	45	0.80%	97.40%
Complete spirography;Diffusion capacity;Ventilatory mechanics;	67	0.54%	96.36%	33	0.59%	97.99%
Spirography + provocation;Ventilatory mechanics;	64	0.52%	96.87%	1	0.02%	98.00%
Spirography + bronchodilation;Diffusion capacity;	57	0.46%	97.33%	23	0.41%	98.41%
Complete spirography;Spirography + bronchodilation;Residual volume;Ventilatory mechanics;	53	0.43%	97.76%	19	0.34%	98.75%
Spirography + provocation;Residual volume;Diffusion capacity;	50	0.40%	98.16%	1	0.02%	98.77%
Spirography + provocation;Residual volume;Ventilatory mechanics;	39	0.31%	98.48%	3	0.05%	98.82%
Complete spirography;Spirography + provocation;Residual volume;Diffusion capacity;Ventilatory mechanics;	25	0.20%	98.68%	4	0.07%	98.89%
Diffusion capacity;	23	0.19%	98.86%	18	0.32%	99.22%
Complete spirography;Spirography + bronchodilation;	20	0.16%	99.02%	6	0.11%	99.32%
Spirography + provocation;Residual volume;	19	0.15%	99.18%			99.32%
Residual volume;Diffusion capacity;Ventilatory mechanics;	15	0.12%	99.30%	6	0.11%	99.43%
Complete spirography;Spirography + provocation;Residual volume;Diffusion capacity;	11	0.09%	99.39%	3	0.05%	99.48%
Spirography + bronchodilation;Spirography + provocation;Residual volume;Diffusion capacity;Ventilatory mechanics;	10	0.08%	99.47%	2	0.04%	99.52%
Complete spirography;Spirography + bronchodilation;Residual volume;Diffusion capacity;	9	0.07%	99.54%	7	0.12%	99.64%
Complete spirography;Spirography + bronchodilation;Ventilatory mechanics;	9	0.07%	99.61%	1	0.02%	99.66%
Residual volume;Ventilatory mechanics;	8	0.06%	99.68%	4	0.07%	99.73%
Complete spirography;Spirography + provocation;Residual volume;Ventilatory mechanics;	6	0.05%	99.73%			99.73%
Complete spirography;Spirography + provocation;	5	0.04%	99.77%	2	0.04%	99.77%
Spirography + provocation;Diffusion capacity;	5	0.04%	99.81%			99.77%
Diffusion capacity;Ventilatory mechanics;	4	0.03%	99.84%	2	0.04%	99.80%
Spirography + bronchodilation;Spirography + provocation;Ventilatory mechanics;	4	0.03%	99.87%			99.80%
Complete spirography;Spirography + bronchodilation;Residual volume;	3	0.02%	99.90%	1	0.02%	99.82%
Spirography + provocation;Diffusion capacity;Ventilatory mechanics;	3	0.02%	99.92%	1	0.02%	99.84%
Residual volume;	2	0.02%	99.94%	5	0.09%	99.93%
Residual volume;Diffusion capacity;	2	0.02%	99.95%	1	0.02%	99.95%
Complete spirography;Spirography + provocation;Residual volume;	2	0.02%	99.97%			99.95%
Complete spirography;Spirography + bronchodilation;Spirography + provocation;Residual volume;Diffusion capacity;	1	0.01%	99.98%			99.95%
Complete spirography;Spirography + provocation;Ventilatory mechanics;	1	0.01%	99.98%			99.95%
Spirography + bronchodilation;Spirography + provocation;Residual volume;Diffusion capacity;	1	0.01%	99.99%			99.95%
Spirography + bronchodilation;Spirography + provocation;Residual volume;Ventilatory mechanics;	1	0.01%	100.00%			99.95%
Complete spirography;Spirography + bronchodilation;Diffusion capacity;Ventilatory mechanics;				3	0.05%	100.00%

Test combination	Recurrence of test combination	Number of patients Ambulatory	In hospital
Complete spirography;	1	799	225
Complete spirography;	2	134	18
Complete spirography;	3	33	5
Complete spirography;	4	18	2
Complete spirography;	5	5	2
Complete spirography;	7	2	1
Complete spirography;	19		1
Complete spirography;Diffusion capacity;	1	85	39
Complete spirography;Diffusion capacity;	2	9	3
Complete spirography;Diffusion capacity;Ventilatory mechanics;	1	67	33
Complete spirography;Residual volume;	1	155	77
Complete spirography;Residual volume;	2	9	3
Complete spirography;Residual volume;	3	2	2
Complete spirography;Residual volume;	4	1	2
Complete spirography;Residual volume;	5	2	2
Complete spirography;Residual volume;Diffusion capacity;	1	431	235
Complete spirography;Residual volume;Diffusion capacity;	2	56	20
Complete spirography;Residual volume;Diffusion capacity;	3	15	3
Complete spirography;Residual volume;Diffusion capacity;	4	4	3
Complete spirography;Residual volume;Diffusion capacity;	6	1	1
Complete spirography;Residual volume;Diffusion capacity;	9		1
Complete spirography;Residual volume;Diffusion capacity;	11		1
Complete spirography;Residual volume;Diffusion capacity;	14		1
Complete spirography;Residual volume;Diffusion capacity;Ventilatory mechanics;	1	1696	1045
Complete spirography;Residual volume;Diffusion capacity;Ventilatory mechanics;	2	142	61
Complete spirography;Residual volume;Diffusion capacity;Ventilatory mechanics;	3	20	6
Complete spirography;Residual volume;Diffusion capacity;Ventilatory mechanics;	4	7	2
Complete spirography;Residual volume;Ventilatory mechanics;	1	361	169
Complete spirography;Residual volume;Ventilatory mechanics;	2	81	9
Complete spirography;Residual volume;Ventilatory mechanics;	3	15	3
Complete spirography;Residual volume;Ventilatory mechanics;	4	5	2
Complete spirography;Spirography + bronchodilation;	1	14	6
Complete spirography;Spirography + bronchodilation;Diffusion capacity;Ventilatory mechanics;	1		3
Complete spirography;Spirography + bronchodilation;Residual volume;	1	3	1
Complete spirography;Spirography + bronchodilation;Residual volume;Diffusion capacity;	1	9	7
omplete spirography;Spirography + bronchodilation;Residual volume;Diffusion capacity;Ventilatory mechanics;	1	88	43
omplete spirography;Spirography + bronchodilation;Residual volume;Diffusion capacity;Ventilatory mechanics;	2	16	1
omplete spirography;Spirography + bronchodilation;Residual volume;Diffusion capacity;Ventilatory mechanics;	3	4	1
Complete spirography;Spirography + bronchodilation;Residual volume;Ventilatory mechanics;	1	31	19
Complete spirography;Spirography + bronchodilation;Ventilatory mechanics;	1	7	1
Complete spirography;Spirography + provocation;	1	5	2
Complete spirography;Spirography + provocation;Residual volume;Diffusion capacity;	1	11	3
Complete spirography;Spirography + provocation;Residual volume;Diffusion capacity;Ventilatory mechanics;	1	25	4
Complete spirography;Ventilatory mechanics;	1	227	92
Complete spirography;Ventilatory mechanics;	2	28	15
Complete spirography;Ventilatory mechanics;	3	10	9
Complete spirography;Ventilatory mechanics;	4	3	4
Complete spirography;Ventilatory mechanics;	5		1
Complete spirography;Ventilatory mechanics;	7	1	2
Diffusion capacity;	1	11	15
Diffusion capacity;	3	2	1
Diffusion capacity;Ventilatory mechanics;	1	4	2
Residual volume;	1	2	5
Residual volume;Diffusion capacity;	1	2	1
Residual volume;Diffusion capacity;Ventilatory mechanics;	1	15	6
Residual volume;Ventilatory mechanics;	1	8	4
Spirography + bronchodilation;	1	253	145
Spirography + bronchodilation;	2	58	23
Spirography + bronchodilation;	3	18	5
Spirography + bronchodilation;	4	7	3
Spirography + bronchodilation;	8		1

Test combination	Recurrence of test combination	Number of patients Ambulatory	In hospital
Spirography + bronchodilation;Diffusion capacity;	1	37	23
Spirography + bronchodilation;Diffusion capacity;Ventilatory mechanics;	1	119	36
Spirography + bronchodilation;Residual volume;	1	116	37
Spirography + bronchodilation;Residual volume;	2	25	1
Spirography + bronchodilation;Residual volume;	3	8	4
Spirography + bronchodilation;Residual volume;	4	1	1
Spirography + bronchodilation;Residual volume;Diffusion capacity;	1	338	195
Spirography + bronchodilation;Residual volume;Diffusion capacity;	2	61	26
Spirography + bronchodilation;Residual volume;Diffusion capacity;	3	7	4
Spirography + bronchodilation;Residual volume;Diffusion capacity;	4	2	1
Spirography + bronchodilation;Residual volume;Diffusion capacity;Ventilatory mechanics;	1	2182	1081
Spirography + bronchodilation;Residual volume;Diffusion capacity;Ventilatory mechanics;	2	412	108
Spirography + bronchodilation;Residual volume;Diffusion capacity;Ventilatory mechanics;	3	112	33
Spirography + bronchodilation;Residual volume;Diffusion capacity;Ventilatory mechanics;	4	43	4
Spirography + bronchodilation;Residual volume;Diffusion capacity;Ventilatory mechanics;	5	13	4
Spirography + bronchodilation;Residual volume;Diffusion capacity;Ventilatory mechanics;	6	4	1
Spirography + bronchodilation;Residual volume;Diffusion capacity;Ventilatory mechanics;	7	2	1
Spirography + bronchodilation;Residual volume;Ventilatory mechanics;	1	342	185
Spirography + bronchodilation;Residual volume;Ventilatory mechanics;	2	48	7
Spirography + bronchodilation;Residual volume;Ventilatory mechanics;	3	14	2
graphy + bronchodilation;Spirography + provocation;Residual volume;Diffusion capacity;Ventilatory mechanics;	1	10	2
Spirography + bronchodilation;Ventilatory mechanics;	1	175	49
Spirography + bronchodilation;Ventilatory mechanics;	2	38	4
Spirography + bronchodilation;Ventilatory mechanics;	3	13	3
Spirography + bronchodilation;Ventilatory mechanics;	4		1
Spirography + provocation;	1	107	13
Spirography + provocation;Diffusion capacity;Ventilatory mechanics;	1	3	1
Spirography + provocation;Residual volume;Diffusion capacity;	1	48	1
Spirography + provocation;Residual volume;Diffusion capacity;Ventilatory mechanics;	1	243	30
Spirography + provocation;Residual volume;Diffusion capacity;Ventilatory mechanics;	2	13	3
Spirography + provocation;Residual volume;Diffusion capacity;Ventilatory mechanics;	7		1
Spirography + provocation;Residual volume;Ventilatory mechanics;	1	39	3
Spirography + provocation;Ventilatory mechanics;	1	59	1
Ventilatory mechanics;	1	81	41
Ventilatory mechanics;	2	22	15
Ventilatory mechanics;	3	14	8
Ventilatory mechanics;	4		8
Ventilatory mechanics;	5	1	3
Ventilatory mechanics;	6		7
Ventilatory mechanics;	7	1	3
Ventilatory mechanics;	8		3
Ventilatory mechanics;	9		1
Ventilatory mechanics;	10		1
Ventilatory mechanics;	13		1
Ventilatory mechanics;	14		2
Ventilatory mechanics;	15		2
Ventilatory mechanics;	16		1
Ventilatory mechanics;	17		1
Ventilatory mechanics;	19		1
Ventilatory mechanics;	24		1
Ventilatory mechanics;	27		1
Ventilatory mechanics;	29		1
Ventilatory mechanics;	30		1
Ventilatory mechanics;	41		1
Ventilatory mechanics;	44		2
Ventilatory mechanics;	59		1

QUALITY APPRAISAL OF GUIDELINES

Appraisal of Guidelines on Pulmonary Function Testing

Guideline developer	Source/Reference	Quality appraisal*	Comments
BTS 2001	Belgian Thoracic Society 2001. Lung Function Testing: Quality, Indications and Standardization. Consensusreport. www.webweaver.be/pneumo/	As the document provides no methodology on clinical indications for PFTs, a guideline appraisal is either not applicable or would inevitably yield a too low score in the domain of "rigor of development" (7/28 domain score).	Consensus-based guideline on technical performance, quality, standardization and indications of PFTs, intended for use by Belgian pulmonologists.

Appraisal of Clinical Guidelines on COPD

Guideline developer	Source/Reference	Quality appraisal*	Comments
ICSI 2005	Institute for Clinical Systems Improvement 2005. Chronic obstructive pulmonary disease. www.icsi.org	scope and purpose: 10/12 stakeholders involvement: 8/16 rigor of development: 14/28 clarity and presentation: 12/16 applicability: 6/12 editorial independence: 6/8	Evidence-based
GOLD 2005	Global Initiative for Chronic Obstructive Lung Disease 2005. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. http://goldcopd.com/	scope and purpose: 9/12 stakeholders involvement: 8/16 rigor of development: 19/28 clarity and presentation: 12/16 applicability: 6/12 editorial independence:3/8	Evidence-based
NCCCC/ NICE 2004	National Collaborating Centre for Chronic Conditions/ National Institute for Health and Clinical Excellence 2004. National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. Thorax 2004 Feb; 59 Suppl 1:1-232.	scope and purpose: 9/12 stakeholders involvement:10/16 rigor of development: 26/28	Evidence-based

		clarity and presentation:14/16 applicability: 8/12 editorial independence: 7/8	
FMS 2005	Finnish Medical Society Duodecim. Chronic obstructive pulmonary disease (COPD). www.ebm-guidelines.com	scope and purpose: 9 /12 stakeholders involvement: 7/16 rigor of development: 17/28 clarity and presentation: 11/16 applicability: 3/12 editorial independence: 3/8	Evidence-based

Appraisal of Clinical Guidelines on Asthma

Guideline developer	Source/Reference	Quality appraisal*	Comments
ICSI 2005	Institute for Clinical Systems Improvement 2005. Diagnosis and outpatient management of of asthma. www.icsi.org	scope and purpose: 10/12 stakeholders involvement: 8/16 rigor of development: 14/28 clarity and presentation: 12/16 applicability: 6/12 editorial independence: 11/8	Evidence-based
GINA 2005	Global Initiative for Asthma (GINA), National Heart, Lung and Blood Institute (NHBLI) 2005. Global strategy for asthma management and prevention. www.ginasthma.com	scope and purpose: 11/12 stakeholders involvement: 7/16 rigor of development: 22/28 clarity and presentation: 12/16 applicability: 7/12 editorial independence: 3/8	Evidence-based
SIGN 2005	Scottish Intercollegiate Guidelines Network (SIGN), British Thoracic Society 2005. British guideline on the management of asthma. A national clinical guideline. www.sign.ac.uk	scope and purpose: 9/12 stakeholders involvement:10/16 rigor of development: 22/28 clarity and presentation: 15/16 applicability: 6/12 editorial independence: 7/8	Evidence-based
FMS 2005	Finnish Medical Society Duodecim. Long-term management of asthma 2004. www.ebm-guidelines.com	scope and purpose: 9/12 stakeholders involvement: 7/16 rigor of development: 18/28 clarity and presentation: 12/16 applicability: 3/12 editorial independence: 3/8	Evidence-based

guideline appraisal with the AGREE instrument, www.agreecollaboration.org. Domain scores are calculated by summing up all the scores of the individual items in a domain and by expressing the total score obtained relative to the maximum possible score for that domain

EVIDENCE TABLES

Table1: evidence table of the HTA report on lung function testing for COPD

Study	Study type	Setting	Literature search	Outcome	Index test Reference standard
Wilt 2005	HTAreport	Mainly community-based and primary care	Medline, Cochrane Library up until May 2005 English literature	Diagnosis of COPD Effectiveness on smoking cessation Effectiveness on COPD therapy Prognosis	Spirometry

Table 2: evidence tables of primary studies on COPD published after the literature search of the HTA report

Study	Type of study	Setting	Participants	Outcome	Index test/ Reference standard
Miravitlles 2005	Prevalence study	Community	Random sample of subjects between 49 and 69 years old	Diagnosis of COPD	Portable spirometer
Murtagh 2005	Prevalence study	Community	Random sample of subject between 40 and 69 years old	Airflow obstruction	Spirometry $FEV_1/FVC<0.7$ and FEV_1 <80% of predicted normal with reversibility
Geijer 2005	Prevalence study	Community	Middle-aged smokers without lung medication or diagnosed lung disease	Undetected airflow obstruction	Hand-held spirometry
Vandevoorde 2005	Diagnostic accuracy study	Lung function laboratory	Consecutive patients referred for lung function testing	Airflow obstruction	Spirometry FEV_1/FEV_6 -FEV_1/FVC
Chhabra 2005	Diagnostic accuracy study	Outpatients	Patients with COPD: >10 pack years + cough with expectoration and dyspnoea on exertion Patients with asthma: history of recurrent wheezing and breathlessness, with seasonal and diurnal variations and any identifiable triggers	Bronchodilator response	Rolling seal spirometer
Dales 2005	Study on influence on physician related outcome	Primary care practices	Consecutive patients ≥35 years and ≥20 packages of cigarettes	Diagnosis of airflow obstruction by GP and planned management by GP	Portable spirometer
Anthonisen 2005	Randomized controlled trial	Community volunteers	Smokers aged 35-59 yrs with $FEV_1/FVC<0.7$ and FEV_1 55-90% of predicted normal	Bronchodilator response	Rolling seal spirometer
Simmons 2005	Randomized controlled trial	Community volunteers	Smokers aged 35-59 yrs with $FEV_1/FVC<0.7$ and FEV_1 55-90% of predicted normal	Rate of decline of FEV_1	Rolling seal spirometer
Casanova 2005	Prognostic study	Respiratory clinics	Outpatients with >20 pack years and $FEV_1/FVC<0.7$	Mortality	Information from family members confirmed by medical records
Buffels 2005 (Abstract – Epub ahead)	Randomized controlled trial	General practice	Patients willing to stop smoking selected from 16 general practices	Single office spirometry as a tool for enhancing smoking cessation	Unclear from the abstract

Table 3:Included studies for the reversibility test

Study	Design	Population	Indextest	Results
Kurashima 2005[30]	Prospective Cohort, consecutive QUADAS 6Y/2N/6U	516 patients with respiratory symptoms for at least 2 months; prevalence of COPD 54% baseline FEV1% pred: 58.6±1.0 FVC% pred: 85.3 ±0.9 FEV1/FVC % pred: 48.2 ±0.6	Salbutamol, dose not specified, 30 minutes interval, <12% increase in baseline FEV1 for diagnosis of COPD	Sensitivity 90.0% (86.5-93.5) Specificity 37.3% (31.1-43.5) PPV 63% (58.3-67.7) NPV 75.9% (68.1-83.6) LR+ 1.44 (1.29-1.60) LR- 0.27 (0.18-0.40) OR 5.35 (3.34-8.57)
Goldstein 2001[56]	Prospective Cohort QUADAS 6Y/3N/5U	57 patients, referred or self-referred for asthma-like symptoms of at least 3 months; prevalence of asthma 84% baseline FEV1% pred ≥80 FVC% pred ≥80	Two puffs of maxair autohaler, 15-20 minutes interval, ≥ 12% increase in baseline FEV 1	Sensitivity 7.1% (0.0-14.4) Specificity 95.0% (81.5-100.0) PPV 87.5% (55.1-100.0) NPV 17.3% (7.3-27.3) LR+ 1.43 (0.08-25.5) LR- 0.98 (0.83-1.15) OR 1.46 (0.07-30.7)
Hunter 2002[57]	Prospective Case-control QUADAS 5Y/6N/3U	69 patients with asthma (A), 21 patients with pseudoasthma (B) and 20 volunteers (C) baseline FEV1% pred A: 85.0 (1.7) B: 100.0 (2.3) C: 103.5 (1.7) FEV1/FVC%pred A: 73.4 (1.0) B: 79.6 (1.7) C: 85.4 (1.1)	200 µg albuterol, 10 minutes interval, > 3% increase in FEV1 baseline	Sensitivity 49% (37-61) Specificity 70% (50-90) LR+ 1.6 LR- 0.7
Sin 2006[53]	Prospective	51 patients over 60y: 27 asthma (A) + 24 COPD (B)	200 µg salbutamol,	26.0% +/-11.3 in asthma patients

	Case-control QUADAS 5Y/7N/2U	baseline FEV1% pred A: 63.5 ± 15.8 B: 43.8 ± 20.1 FEV1/FVC% pred A: 64.4 ± 11.3 B: 56.1 ± 14.4	interval unclear, ≥ 200 ml or 12% increase in baseline FEV 1	10.5% +/-2.2 in COPD patients, p<0.05
Meslier 1989a[60]	Prospective Case-control QUADAS 5Y/3N/6U	32 asthma patients (A) and 20 chronic bronchitis patients (B) baseline FEV1% pred A: 43.6 ± 15.7 B: 41.3 ± 16.8	0.2 mg + 0.8 mg salbutamol, 15 minutes interval, > 200 ml absolute difference, >5% change predicted, >20% change baseline FEV1	Sensitivity 100%; 97%; 97% Specificity 55%; 50%; 65% LR+ 2,2; 1,9; 2,8
Quadrelli 1999[62]	Prospective Case-control QUADAS 6Y/2N/6U	142 patients with asthma (A), 58 with COPD (B) baseline FEV1% pred A: 59.4 ± 19.1 B: 39.7 ± 14.7	200 µg salbutamol, 20 minutes interval, > 200 ml increase, >15% increase baseline, > 9% increase predicted, > 50% increase max FEV1 (other cut-offs available in article)	Sensitivity 70.4%; 85.2%; 67.2%; 6.5% Specificity 70.6%; 50.0%; 70.6%; 98.2%
Chhabra 2005[27]	Prospective Case-control QUADAS 5Y/4N/5U	200 patients with asthma (A) and 154 with COPD (B) baseline FEV1% pred A: 57.2 ± 21.7 B: 42.7 ± 18.7 FVC% pred A: 83.2 ± 23.9 B: 73.0 ± 21.6	200 µg salbutamol, 20 minutes interval, > 200 ml absolute change, 12% increase baseline, 9% increase predicted FEV1	Sensitivity 73%; 75%; 63% Specificity 80%; 60%; 84% LR+ 3.6; 1.88; 4.03

Table 4: Evidence table for CO diffusing

References	Description	Critical appraisal	Comment
	General guideline		
AARC clinical practice guideline. Single-breath carbon monoxide diffusing capacity, 1999 Update{AARC., 1999 #3124}.	Dlco: Indications, limitations, quality…	Expert panel guideline No described methodology (nothing about methodology on the society site)	Poor methodological quality
Macintyre N, Crapo RO, Viegi G and al. ATS/ERS task force: Standardisation of the single-breath determination of carbon monoxide uptake in the lung. 2005{Macintyre, 2005 #3172}	Dlco General equipment, technique standardisation, adjustments to interpretation	Consensus opinion of both societies No described methodology (nothing about methodology on the society site)	Poor methodological quality
SBP/BVP 2001. Normes de qualité, indications et standardisation des épreuves fonctionnelles respiratoires. Document de consensus de la société belge de pneumologie http://www.bvp-sbp.org/{SBP/BVP, 2001 #3197}	Indications pour les épreuves fonctionnelles respiratoires Standardisation : facteur de transfert (TLco) ou capacité de diffusion (Dlco)	Consensus of Belgian experts No described methodology	Poor methodological quality
	Diagnosis of pulmonary arterial hypertension in patients with systemic sclerosis		
ACCP 2004. (McGoon) Screening, early detection, and diagnosis of pulmonary arterial hypertension{McGoon, 2004 #3173}:	Patients with clinical suspicion of pulmonary arterial hypertension or patients at high risk	Guideline AGREE: score = 65	Only patients with systemic sclerodermy
ACCP 2004 (McLaughlin) Prognosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines{McLaughlin, 2004 #3175}.	Patients with pulmonary arterial hypertension Prognosis	Guideline AGREE: score = 54	Reduced Dlco (<45% of predicted)used for prognosis
Mukerjee 2004 Echocardiography and lung functionas screening tests for pulmonary arterial hypertension in systemic sclerosis{Mukerjee, 2004 #3180}.	52 patients with and 85 without pulmonary fibrosis To compare echography and lung function (Dlco) with cardiac catheterization in discriminating	study QUADAS: 6Y, 2U, 6N	Patients with systemic sclerosis

Launay 2001 Dépistage de l'hypertension artérielle pulmonaire au cours de la sclérodermie systémique: étude d'une cohorte de 67 patients{Launay, 2001 #3170}.	Patients (67) with systemic sclerodermy	Retrospective cohort study	Exclusion (retrospective)
	Systemic sclerosis		
Dujic 1994 Increase of pulmonary diffusing capacity in systemic sclerosis{Dujic, 1994 #3145}	29 non smoking systemic sclerosis patients	Physiological study No diagnostic accuracy study:	Excluded
Wells 1997 Fibrosing alveolitis in systemic sclerosis. Indices of lung function in relation to extent of disease on computed tomography{Wells, 1997 #3213}.	64 patients with fibrosing alveolitis in systemic sclerosis.	Prospective study QUADAS 9Y, 3U, 2N	Relationship between thin section computed tomography (CT) and static and exercise pulmonary function
Steen 1992 Isolated diffusing capacity reduction in systemic sclerosis{Steen, 1992 #3201}.	815 patients with systemic sclerosis	Prognosis study Validation Cochrane prognosis study: 6Y, 1U, 2N.	Comparison for prognosis of developing of pulmonary isolated hypertension and reduction of survival rates
Witt C 1999 Pulmonary involvement in diffuse cutaneous systemic sclerosis{Witt, 1999 #3215}	51 consecutive patients with SSc and clinical signs of pulmonary involvement Study about bronchoalveolar lage fluid (BALF) and not really about DLco	Prognosis study Validation Cochrane prognosis studies: 6Y 3U	Bronchoalveolar lage fluid (BALF) granulocytosis is associated with a progression of fibrosing alveolitis with a decrease DLco BALF normal or lymphocytosis is associated with stable pulmonary function parameters
Altman RD 1991 Predictors of survival in systemic sclerosis{Altman, 1991 #3126}	264 patients with SSc 5 years follow up 12% lost to follow up	Prognosis study Validation Cochrane prognosis studies:3Y, 3U, 3N	By survival tree analysis, the individual entry variables best predicting reduced survival include older age (>64 years), reduced renal function, anemia, reduced pulmonary diffusing capacity for carbon monoxide (≤ 50% of predicted) reduced total serum protein level and reduced pulmonary reserve.
Owens G 1987 Cardiopulmonary manifestations of systemic sclerosis{Owens, 1987 #3187}			Exclusion: narrative review
Tashkin D 1994 Interelationship between pulmonary and extra pulmonary involvement in systemic sclerosis{Tashkin, 1994 #3205}	62 non smoking SSc patients	Prognosis study Validation Cochrane prognosis study: 7Y, 2U	*"Cumulative survival may be related to the rate of decline in Dco, TLC, and FVC, but was not predicted by impairment in any measure of pulmonary function."*

Peters-Golden M 1984 Carbon monoxide diffusing capacity as predictor of outcome in systemic sclerosis{Peters-Golden, 1984 #3188}	71 patients with systemic sclerosis follow up of 5 years after pulmonary function testing	Prospective prognosis study 6Y, 2U, 1N	DLco ≤ 40% of the predicted reference value was associated with only 9% five year cumulative survival rate compared with a 75% five year cumulative survival rate in patients with a DLco > 40% of the predicted reference value.
	Idiopathic pulmonary fibrosis		
ATS 2000 International consensus statement. Idiopathic pulmonary fibrosis: diagnosis and treatment{ATS, 2000 #3128}.	Diagnosis and management of idiopathic pulmonary fibrosis	Guideline AGREE: 58	Guideline based on consensus experts
Schwartz 1994 Determinants of progression in idiopathic pulmonary fibrosis{Schwartz, 1994 #3198}.		No diagnostic accuracy study	Not selected
Collard 2003 Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis{Collard, 2003 #3137}	One group of 81 patients Comparison for prognostic values of the results	Prognosis cohort study Validation Cochrane prognosis study: 4Y, 4N, 1U	No discussion about the specific role of Dlco: Exclusion
Latsi 2003 Fibrotic idiopathic interstitial pneumonia: The prognosis value of longitudinal functional trends{Latsi, 2003 #3169}	One group of 31 patients dying within 2 years and one group of 31 patients dying after more than two years	Prognosis retrospective cohort study	Exclusion
Flaherty 2003 Prognostic implications of physiologic and radiographic changes in idiopathic interstitial pneumonia{Flaherty, 2003 #3149}	80 patients with usual interstitial pneumonia and 29 patients with non specific interstitial pneumonia	Prognosisretrrospective cohort study Exclusion	Exclusion
Wells AU 1997 Lone cryptogenic fibrosis: a functional-morphologic correlation based on extend of the disease on thin-section computed tomography{Wells, 1997 #3213}	68 patients		Exclusion= meme etude que l'autre etude de Wells déjà incluse (sous groupe)
Erbes R 1997 Lung function tests in patients with idiopathic pulmonary fibrosis{Erbes, 1997 #3147}	99 patients with IPF Extensive pulmonary function tests	Prognosis prospective cohort Validation Cochrane prognosis study: 7Y, 2U	*"Diminished survival was associated with an age older than 50 years, a reduced value to more than 2 SDs below the predicted values of both, TLC alone, or in combination with a reduced vital capacity. Factors not influencing survival were gender, parameters of gas exchange at rest (including DLco/Va), and PaO2 at rest and during bicycle exercise."*

Nagai 1998 Idiopathic non specific interstitial pneumonia/fibrosis: comparisons with IPF and BOOP{Nagai, 1998 #3181}	Differential diagnosis 64 IPF (idiopathic pulmonary fibrosis), 16 BOOP (bronchiolitis obliterans organizing pneumonia and 31 NSIP (non specific interstitial prneumonia/fibrosis	Diagnose study Quadas: 4Y, 6U, 4N	Exclusion (Quadas)
Nicholson 2000 The prognostic significance of the htopathologic pattern of interstitial pneumonia in patients presenting with the clinical entity of cryptogenic fibrosing alveolitis{Nicholson, 2000 #3184}	78 patients with clinico pathologic diagnosis of CFA (cryptogenic fibrosing alveolitis)	Prognosis prospective cohort	Exclusion: not a study about DLco
Bjoraker 1998 Prognostic significance of histopathological classification of idiopathic interstitial pneumonia{Bjoraker, 1998 #3132}			Exclusion: not a study about DLco
Flaherty 2006 Idiopathic pulmonary fibrosis: prognostic values of changes in physiology ans six-minutes walk tests (6MWT){Flaherty, 2006 #3150}	197 patients with idiopathic pulmonary fibrosis	Prognosis prospective study Validation Cochrane prognosis study: 6Y, 3U	*"For patients with a baseline saturation ≤ 88% during a 6MWT, the strongest observed predictor of mortality was serial change in diffusing capacity for carbon monoxide.* *For patients with saturation >88% during their baseline walk test, serial decreases in FVC and increases in desaturation area significantly predicted subsequent mortality, whereas decreases in walk distance and in diffusing capacity for carbon monoxide displayed less consistent statistical evidence of increasing mortality in our patients."*
Flaherty 2002 Clinical significance of histological classification of idiopathic interstitial pneumonia{Flaherty, 2002 #3222}			Exclusion: not a study about DLco
Daniil Z 1999 A histologic pattern of non specific interstitial pneumonia is associated with a better prognosis than usual interstitial prognosis in patients with cryptogenic fibrosing alveolitis {Daniil, 1999 #3140}			Exclusion: DLCO is here a part of pulmonary function test but this is not a study over DLco

Xaubet A 1998 Pulmonary function tests and CT Scan in the management of idiopathic pulmonary fibrosis{Xaubet, 1998 #3217}.	39 untreated patients with IPF correlation between HCRT (high resolution computed tomography) and pulpmonary function testing 23 patients with Follow up 7.5 months	Diagnosis study QUADAS 8Y, 4U 1N	*"At diagnosis, the extent of overall lung involvement in the HRCT scans showed a moderate but significant correlation only with FVC (r = 0.46, p = 0.003) and DLCO (r =0.40, p= 0.03).* *Changes over time (7.5 months) in the total extent of the disease evaluated with HRCT scans were also related to those observed in DLCO and in FVC (r= 0.57, p= 0.01, and r= 0.51, p= 0.01, respectively)."*
Mogulkoc 2001 Pulmonary function in idiopathic pulmonary fibrosis and referral for lung transplantation{Mogulkoc, 2001 #3177}	115 IPF patients with UIP (Interstitial Usual pneumonia) younger tha 65 years of age Predictor of 2 years survival (waiting list for transplantation) DLco percent predict and HRCT-fibrosis	Prognsosis study Validation Cochrane prognosis study: 7Y, 2U	*"DLco percent predicted and HRCT–fibrosis score were found to be independent predictors of survival and in combination gave the best prognostic prediction. The optimal points on the receiver operating characteristic (ROC) curves for discriminating between survivors and nonsurvivors corresponded to 39% DLco percent predicted, and to a HRCT–fibrosis score of 2.25. The combination of these parameters yielded an optimal point with a specificity and a sensitivity of 84% and 82%, respectively. A model based on a combination of DLco percent predicted and HRCT–fibrosis score may optimize the timing of referral for transplantation."*
Jezek 1980 The prognostic significance of fuctional tests in cryptogenic fibrosing alveolitis{Jezek, 1980 #3162}.	56 patients with kryptogenic fibrosing alveolitis follow up 6.3 years predictors of the survival	Prognosis study	*Exclusion: pas de texte complet trouvé*
Tukiainen 1983 Prognosis of cryptogenic fibrosing alveolitis{Tukiainen, 1983 #3208}	100 consecutive patients with cryptogenic fibrosing alveolitis treated with corticosteroids followed for at least 3 years	Retrospective prognosis study	exclusion
Mogulkoc N 2001 Pulmonary 99mTc-DTPA aerosol clearance in usual interstitial pneumonia (UIP){Mogulkoc, 2001 #3178}			Exclusion: DLco is not the index test

Rudd 1981 Cryptogenic fibrosing alveolitis{Rudd, 1981 #3194}	120 patients treated for cryptogenic fibrosing alveolitis 3 groups according to response to treatement (no response, response on FVC alone or response on FVC and DLCO)	Prognosis study Cochrane: 3Y, 6U	No statistical correlation in DLco prior to treatment and response to treatment
King 2001{King, 2001 #3163}	238 patients with idiopathic pulmonary fibrosis median survival 35 months	Prognosis study Cochrane: 2Y, 3U, 4N	Exclusion
	Emphysema		
Govaerts 1993 Total respiratory impedance and early emphysema{Govaerts, 1993 #3153}		Prospective study	No diagnostic accuracy study: Exclusion
Morrisson 1989 Comparison of single breath carbon monoxide diffusing capacity and pressure-volume curves in detecting emphysema{Morrison, 1989 #3179}.	73 patients admitted for investigation and treatment of suspected lung carcinoma.	Prospective study QUADAS: 4Y, 2U, 8N	Excluded: only 4 yes in QUADAS
Baldi 2001{Baldi, 2001 #3129}	24 patients with COPD	Prospective study QUADAS 2Y, 7U, 5N	Excluded: low QUADAS score
Sandek 2002{Sandek, 2002 #3195}	20 patients with COPD	Prospective study QUADAS: 3Y, 5U, 6N	Excluded: low QUADAS score
National emphysema treatment trial research group 2001{National Emphysema Treatment Trial Research, 2001 #3182}	1033 patients with severe airflow obstruction	RCT	Excluded
Teculescu 1970 Carbon monoxide transfer factor for the lung in silicosis{Teculescu, 1970 #3206}	37 patients with moderate or severe obstructive lung disease three subgroup: bronchitis, emphysema or intermediate	Prospective study QUADAS 3Y, 7U, 4N	Excluded: low QUADAS score
Gonzalez 1968 The value of single breath diffusing capacity in separating chronic bronchitis from pulmonary emphysema{Gonzalez, 1968 #3152}	30 patients 2 subgroups: predominant chronic bronchitis or predominant emphysema		Exclusion: DLco is used as group characteristic This is not a study about DLco testing
Hamada K 2007{Hamada, 2007 #3225} Significance of pulmonary arterial pressure and diffusion capacity of the lung as prognosticator in patients with idiopathic pulmonary fibrosis	78 patients with IPF complicated with pulmonary arterial hypertension follow up for a maximum of 14 years	Prognosis study Cochrane: 6Y, 2U, 1N	

Nathan S 2007{Nathan, 2007 #3226} Pulmonary hypertension and pulmonary function testing in idiopathic pulmonary fibrosis		Retrospective review	Exclusion: retrospective review of data
	COPD		
Owens 1984 The diffusing capacity as a predictor of arterial oxygen desaturation during exercise in patients with chronic obstructive pulmonary disease{Owens, 1984 #3076}.	48 patients with COPD: moderate to severe disease and oxygen tension values greater than 55mmHg at rest all cigarettes smokers	Cohort study QUADAS: 5Y, 3U, 6N	Inclusion Single breath diffusing capacity performed in duplicate; valid if the results differed by less than 10%; the mean value is presented
Delaunois 1976 Diagnostic differential des bronchjopneumopathies obstructives chroniques{Delaunois, 1976 #3141}.	65 patients with chronic bronchitis, emphysema or chronic asthma.	Prospective study QUADAS: 4Y, 6U, 4N	Excluded: only 4 yes in QUADAS
Cerveri 2004{Cerveri, 2004 #3134}	39 patients with COPD	Prospective study QUADAS 2Y/6U/6N	Excluded: low QUADAS score
Fabbri 2003 Differences in airway inflammation in patients with fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease{Fabbri, 2003 #3148}	46 patients with fixed airflow obstruction (post bronchodilatator FEV1/FVC < 70%) 27 with history of COPD 19 with history odf asthma		Exclusion: study about airway inflammation parameters and not over co diffusing DLco is one of the characteristic used to define the patients
Newton 2002 Response of lung volumes to inhaled salbutamol in a large population of patients with severe hyperinflation {Newton, 2002 #3183}			Exclusion: retrospective review of data
Gray-Donald 1996 Nutritional staus and mortality in chronic obstructive pulmonary disease {Gray-Donald, 1996 #3154}	348 subjects with severe COPD (grade 4 or 5 of dyspnea) recruited for a study of negative pressure ventilation Subgroup of 184 (hospitalized) who has baseline measures of diffusing capacity	Cohort prospective prognosis study 1Y, 4U, 4N	Exclusion : critical appraisal only 1 yes
	Sarcoidosis		
Lamberto 2004 Membrane and capillary blood components of diffusion capacity of the lung for carbon monoxide in pulmonary sarcoidosis{Lamberto, 2004 #3167}	24 patients with pulmonary sarcoidosis separated into 2 group of severity according to chest radiographic findings	Prospective analysis	Not selected: Not a clinical accuracy study

Winterbauer 1980 Use of lung function tests in the management of sarcoidosis{Winterbauer, 1980 #3214}.		Revue (non systematique) de synthèse de publications antérieures	Not a diagnostic accuracy study: not selected
	Sarcoidosis versus idiopathic pulmonary fibrosis		
Dunn 1988 Gas exchange at a given degree of volume restriction is different in sarcoidosis and idiopathic pulmonary fibrosis{Dunn, 1988 #3146}.	21 idiopathic fibrosis patients 20 sarcoidosis	Etude prospective QUADAS: 6Y, 2U, 6N	Comparison of the single breath diffusing capacity for CO and gas exchange at rest and during exercise.
Barros 2004{Barros, 2004 #3130}	66 patients with biopsy-proven sarcoidosis	Prospective study QUADAS 6Y, 6U, 2N	Prospective cohort, consecutive patient inclusion Setting unclear single breath: ≤70% predicted/≤50% predicted pulmonary involvement: radiographical stages 1-4 sensitivity 82/45%; specificity 70/97%; PPV 50/83%; NPV 91/83%; LR+ 2,72/13,35 OR 0,97/4,80
	Autoimmune/ rheumatic disease		
Kono 2003. Visualization and functional consequence of pulmonary vascular impairment in patients with rheumatic diseases{Kono, 2003 #3164}.	72 patients with rheumatic diseases	Prospective study	Not selected: No clinical accuracy study
	Rare interstitial diseases		

Delobbe 1996{Delobbe, 1996 #3142}	45 patients with pulmonary Langerhans' cell granulomatosis	Prognostic study Cochrane quality checklist: not valid (selection bias, unclear definition of outcome, unclear blinding, loss to follow-up, confounders)	excluded
	Amiodarone effects		
Singh 1997 Pulmonary effect of Amiodarone in patients with heart failure{Singh, 1997 #3199}.	Patients with heart failure, patients with COPD and patients undergoing a surgical procedure	Prospective double blind placebo controlled trial to determine the effect of anti-arrhythmic drug therapy	Not a diagnostic accuracy study
Kudenchuk 1984 Prospective evaluation of Amiodarone pulmonary toxicity{Kudenchuk, 1984 #3165}.			No diagnostic accuracy study : exclusion
	Bleomycin effects		
McKeage 1990 Carbon monoxide diffusing capacity is a poor predictor of clinically significant bleomycin lung{McKeage, 1990 #3174}.	81 patients receiving bleomycin (mean total dose 230U)	Retrospective study QUADAS : 6Y, 4U, 4N	to determine the accuracy of carbon monoxide diffusing capacity (Dlco) as a predictor of clinically significant bleomycin lung
Wolkowicz 1992 Bleomycin-induced lung function abnormalities{Wolkowicz, 1992 #3216}.	59 men with non seminomatous testicular carcinoma and bleomycin (average dose of 555.5 units)	Cohort study with retrospective research architecture QUADAS : 4Y, 9U, 1N	Exclusion
	Mitomycin effects		
Castro 1996{Castro, 1996 #3133}	133 patients receiving mitomycin	RCT: prognostic analysis Cochrane quality checklist: not valid (selection bias, unclear outcome definition, unclear blinding, loss to follow up)	excluded
	Primary pulmonary hypertension		
Sun 2003 Lung function in primary pulmonary hypertension{Sun, 2003 #3204}.	79 patients with classical diagnostic criteria of PPH and who had no evidence of secondary causes of pulmonary hypertension versus control group.	Prospective case control study Validation QUADAS : 6Y, 5U, 3N	Findings correlate with severity of disease as assessed by cardiac catheterization, New York heart Association Class (NYHA) and cardiopulmonary exercise testing

Steenhuis 2000 Diffusion capacity and haemodynamics in primary and chronic thromboembolic pulmonary hypertension{Steenhuis, 2000 #3202}	Comparison 19 patients with PPH and 8 patients with chronic thrombo embolic pulmonary hypertension (CTEPH),	Prospective study QUADAS : 7Y, 4U, 3N	all patients considered for lung transplantation
Romano 1993 Respiratory function in precapillary pulmonary hypertension{Romano, 1993 #3190}	34 patients with precapillary pulmonary hypertension either form chronic thrombo embolic pulmonary hypertension or from idiopathic pulmonary hypertension	Retrospective study QUADAS : 6Y, 3U, 5N	Selected diagnosis : right heart catheterisation
	Restrictive lung disease		
Stam 2002 Evaluation of diffusing capacity in patients with a restrictive lung disease{Stam, 2000 #3200}			No selected Study about less than 20 patients
	Asbestos		
Oliver 1988 Asbestos-related pleural plaques and lung function{Oliver, 1988 #3185}	383 railroad workers: 81 with pleural plaques and 278 without plaques	Cross sectional morbidity study QUADAS : 7Y, 3U, 4N	The single breath Dlco was similar in the groups with and without plaques (p= 0.0550)
	Respiratory muscle weakness		
Hart 2002 Effect of pattern and severity of respiratory muscle weakness on carbon monoxide gas transfert and lung volumes{Hart, 2002 #3157}	129 patients referred for respiratory muscle function assessment: 27 identified as suitable for analysis		No selected No clinical diagnostic accuracy study
Mier-Jedrzejowicz 1988 Assessment of diaphragm weakness{Mier-Jedrzejowicz, 1988 #3176}	30 patients with breathlessness and diaphragm weakness Mesure of Transdiaphragmatic pressures and pulmonary fuction		Exclusion: not a diagnosis accuracy study
Laroche 1988 The value of sniff oesophageal pressures in the assessment of global inspiratory muscle strength{Laroche, 1988 #3168}	61 patients referred for investigation of respiratory muscle function comparison oesophageal pressur(sniff Pes) and mouth pressure (Pimax)		Exclusion not a study about DLco.
Demedts M 1982 Pulmonary function in moderate muscular disease without pulmonary complaints{Demedts, 1982 #3223}	29 patients with moderate neuromuscular disease without respiratory complaints		Subdivised in 2 groups depending on radiologically estimated diaphragmatic function (less than 4 cm displacement): gold standard?
	Heart failure		

Guazzi 2002 Alveolar-capillary membrane gas conductance: a novel prognostic indicator in chronic health failure{Guazzi, 2002 #3156}	106 stable chronic heart failure patients 17 died from cardiac reasons comparison results survivors with non survivors	Prognosis study Validation with Cochrane table for prognosis studies: 7Y, 2U	
Al-Rawas 2000 Exercise intolerance following heart transplantation: the role of pulmonary diffusing capacity impairment{Al-Rawas, 2000 #3125}			Exclusion Case-control study with two contrasted groups: healthy volunteers versus heart transplantation
	Intrapulmonary haemorrhage		
Greening 1981 Serial estimations of carbon monoxide diffusing capacity in intrapulmonary haemorrhage{Greening, 1981 #3155}.			Exclusion: Not a diagnostic accuracy study
	HIV/AIDS		
Kvale 1993 A decline in the pulmonary diffusing capacity does not indicate opportunistic lung disease in asymptomatic persons infected with the huyman immunodeficiency virus{Kvale, 1993 #3166}.	1353 subjects with HIV infection	Cohort prospective study QUADAS: 5Y, 3U, 6N	pulmonary complications and feasibility of detecting pulmonary infections in asymptomatic members of the group
Rosen 1995 the pulmonary complications of HIV infection study group{Rosen, 1995 #3191}.			Other publication of the same study as Kvale
	Severe hypoxemia		
Prediletto 1993 The assessment of respiratory function in a patient with dypnoea and severe hypoxaemia{Prediletto, 1993 #3189}	One patient	Case study	Exclusion: not a diagnostic accuracy study
Dubois 1994 Prognosis of severely hypoxemic patients receiving long term oxygen therapy{Dubois, 1994 #3144}	270 severely hypoxemic ($PaO_2 \leq 55$ mmHg) selected for long term oxygen therapy	Prognosis study Validation with Cochrane table for prognosis studies: 3Y, 4U, 2N	Lower CO coefficient transfer is one factor that independently predicts reduced survival.
	Popul refer to pulm labo		
van der Lee 2006 Pattern of diffusion disturbance related to clinical diagnosis: the Kco has no diagnostic value next the Dlco{van der Lee, 2006 #3209}.	460 patients referred to the pulmonary functionlaboratory	Prospective study QUADAS: 4Y, 4U, 6N	Exclusion: Quadas
Saydain G 2004 Clinical significance of elevated diffusing capacity{Saydain, 2004 #3196}	245 patients with high Dlco (<140% predicted) matched with 245 patients with		Not selected Not a clinical accuracy study

	normal Dlco (85 to 115% predicted)		
	General population sample		
Viegi 1990 Carbon monoxide diffusing capacity, others indices of lung function, and respiratory symptoms in a general population sample{Viegi, 1990 #3210}.	To assess the relationships among single-breath diffusing capacity for CO, respiratory symptoms and cigarette smoking in a general sample population.	Epidemiological study	Not clinical, not selected
Viegi 2001 An 8-year follow-up of carbon monoxide diffusing capacity in a general population sample of Northern Italy{Viegi, 2001 #3212}.	Temporal trends in Dlco to determine the effects of smoking and changes in smoking habits	Cohort longitudinal epidemiological study	Not selected: not clinical
Sue 1987 Diffusing capacity for carbon monoxide as a predictor of gas exchange during exercise{Sue, 1987 #3203}.	276 current and former shipyard workers		Not selected (Not clinical)
	Tests, standardisation, quality		
Chinn 1996 Transfer factor (diffusing capacity) standardized for alveolar volume: validation, reference values and applications of a new linear model to replace Kco (TL/VA){Chinn, 1996 #3136}	Asymptomatics non smoking subjects		Not selected Not a diagnostic accuracy study
Izquierdo-Alonzo JL 1996 Utility of complete dead space washout by real time gas analysis in the measurement of transfer factor in patients with chronic airflow limitation{Izquierdo-Alonso, 1996 #3159}.	152 COPD patients at different stages of severity Comparison of results if measurement of TLco by using standard criteria and after complete dead washout	Diagnose study QUADAS: 3Y, 5U, 6N	Not selected: less than 5 yes in QUADAS score
Viegi 1998 Single breath diffusing capacity for carbon monoxide: effects of adjustment for inspired volume dead space, carbon dioxide, haemoglobin and carboxyhemoglobin{Viegi, 1998 #3211}	Evaluation of the applying of all the corrections recommended by the 1987 ATS document on Dlcosb standardization	Study on data from previous measurement	Not selected Not a clinical accuracy study
Jensen and Crapo 2003 Diffusing capacity: how to get it right?{Jensen, 2003 #3161}	Quality of the test Calibrating the equipment, Optimizing the test procedure	Narrative review	Not selected
Jansons 1998 Re-breathing vs single-breath TLco in patients with unequal ventilation and diffusion{Jansons, 1998 #3160}	10 healthy subjects and 35 COPD	Diagnose study QUADAS: 3Y, 6U, 5N	Exclusion Quadas

Chinn 1992 Standardization of single-breath transfer factor (TLco); derivation of breathholding time{Chinn, 1992 #3135}.	18 adults with labile airflow obstruction		Not selected: less than 20 patients
Ameratunga 1988 The alveolar carbon monoxide uptake fraction: a simple, alternative measure of carbon monoxide transfer{Ameratunga, 1988 #3127}.			Not a diagnostic accuracy study: exclusion
Crapo 1989 Carbon monoxide diffusing capacity{Crapo, 1989 #3138}		Narrative review	Exclusion
Macintyre NR 1997 Diffusing capacity of the lung for carbon monoxide{MacIntyre, 1997 #3171}		Narrative review	Exclusion
Macintyre 2003 Lung function testing: coding and billing issues{MacIntyre, 2003 #3224}			Not a clinical accuracy study
Hsia CCW 2002 Recruitment of lung diffusing capacity: update of concept and application{Hsia, 2002 #3158}			Not a clinical accuracy study

Table 5: included studies for airways resistance

Study	Design	Population	Indextest	Results
Bohadana 1999[74]	Prospective Cohort, consecutive QUADAS 8Y/1U/5N	71 patients referred for bronchial challenge test with 5 cumulative doses of 320 µg carbachol; 32% prevalence of bronchial responsiveness (≥20% fall in FEV1)	Forced oscillation technique	96% rise of Rm after 1,600 µg carbachol: sensitivity 93%; specificity 81.2% Δ%Rm=56%: sensitivity 86.9% specificity 52.1% 106% rise of R10 after 1600 µg carbachol: sensitivity 91.3% specificity 95.8% Δ%R10=51%: sensitivity 91.3% specificity 58.3%
Descatha 2005[77]	Prospective Cohort, consecutive QUADAS 9Y/3U/2N	77 patients referred for suspicion of occupational asthma; 45% prevalence of occupational asthma (≥20% fall in FEV1 after metacholine)	Forced oscillation technique	ΔR0 ≥61%: sensitivity 74% specificity 67% positive predictive value 65% negative predictive value 76% R0hmd ≥240%: sensitivity 80% specificity 76% positive predictive value 74% negative predictive value 82%
Di Mango 2006[78]	Prospective Case-control, not consecutive QUADAS 6Y/6U/2N	Healthy volunteers (n=21) and COPD patients (n=79)	Forced oscillation technique	Significant difference of mean R0 and Rm between normal subjects and COPD subjects
Pairon 1994[83]	Prospective Cohort QUADAS	119 volunteers, recruited at the workplace: 48 blue collar workers 71 white collar workers	Forced oscillation technique	65% increase of ΔR0: sensitivity 75% specificity 76%

Study	Design	Population	Indextest	Results
	7Y/2U/5N	10% prevalence of bronchial hyperresponsiveness (≥20% fall in FEV1 after metacholine)		
Schmekel 1997[87]	Prospective Cohort, randomly selected QUADAS 7Y/1U/6N	20 patients with asthma, 100% prevalence (clinical diagnosis of asthma)	Impulse oscillation system before and after isocapnic hyperventilation of dry cold air	*Fres* at 2 SD units: sensitivity 89% specificity 100% *R5* at 2 SD units: sensitivity 88% specificity 89% FEV1 at 2 SD units sensitivity 73% specificity 88%
Chowienczyk 1991[88]	Prospective Cohort QUADAS 7Y/1U/6N	43 adults with varying degree of airflow obstruction Prevalence not applicable	Interrupter technique	Mean difference with body plethysmography 0.10 kPa/l.s Coefficient of variation 16.3%
Madsen 1986[90]	Prospective, Cohort, consecutive QUADAS 11Y/3U/0N	133 patients referred from other hospitals or GPs to outpatient allergy department Prevalence of asthma 62% (≥15% variability in PEF or on anamnestic grounds)	Interrupter method before and after various doses of histamine challenge	Positive predictive values: 66-85% Negative predictive values: 39-75% (for various doses of histamine)

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Wettelijk depot : D/2007/10.273/27

KCE reports

1. Effectiviteit en kosten-effectiviteit van behandelingen voor rookstop. D/2004/10.273/1.
2. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid (fase 1). D/2004/10.273/2.
3. Antibioticagebruik in ziekenhuizen bij acute pyelonefritis. D/2004/10.273/5.
4. Leukoreductie. Een mogelijke maatregel in het kader van een nationaal beleid voor bloedtransfusieveiligheid. D/2004/10.273/7.
5. Het preoperatief onderzoek. D/2004/10.273/9.
6. Validatie van het rapport van de Onderzoekscommissie over de onderfinanciering van de ziekenhuizen. D/2004/10.273/11.
7. Nationale richtlijn prenatale zorg. Een basis voor een klinisch pad voor de opvolging van zwangerschappen. D/2004/10.273/13.
8. Financieringssystemen van ziekenhuisgeneesmiddelen: een beschrijvende studie van een aantal Europese landen en Canada. D/2004/10.273/15.
9. Feedback: onderzoek naar de impact en barrières bij implementatie – Onderzoeksrapport: deel 1. D/2005/10.273/01.
10. De kost van tandprothesen. D/2005/10.273/03.
11. Borstkankerscreening. D/2005/10.273/05.
12. Studie naar een alternatieve financiering van bloed en labiele bloedderivaten in de ziekenhuizen. D/2005/10.273/07.
13. Endovasculaire behandeling van Carotisstenose. D/2005/10.273/09.
14. Variaties in de ziekenhuispraktijk bij acuut myocardinfarct in België. D/2005/10.273/11.
15. Evolutie van de uitgaven voor gezondheidszorg. D/2005/10.273/13.
16. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid. Fase II : ontwikkeling van een actuarieel model en eerste schattingen. D/2005/10.273/15.
17. Evaluatie van de referentiebedragen. D/2005/10.273/17.
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29. Nationale Richtlijnen College voor Oncologie: A. algemeen kader oncologisch kwaliteitshandboek B. wetenschappelijke basis voor klinische paden voor diagnose en behandeling colorectale kanker en testiskanker. D2006/10.273/12.
30. Inventaris van databanken gezondheidszorg. D2006/10.273/14.
31. Health Technology Assessment prostate-specific-antigen (PSA) voor prostaatkankerscreening. D2006/10.273/17.
32. Feedback : onderzoek naar de impact en barrières bij implementatie – Onderzoeksrapport : deel II. D/2006/10.273/19.
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