NRS Roadmap COPD report

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1. Inventory of Dutch research efforts in this field over the past five years (2008-2013) by ISI web of knowledge

A search on ISI web of knowledge for the last five years revealed 918 papers by Dutch researchers.

Search terms:
TS=("COPD" OR "Chronic Obstructive Pulmonary Disease" OR "Chronic Obstructive Pulmonary Diseases" OR "Chronic Obstructive Lung Disease" OR "Chronic Obstructive Lung Diseases" OR "emphysema" OR "chronic bronchitis") AND (AD=("Netherlands" OR "Dutch") OR OG=("Netherlands" OR "Dutch") OR OO=("Netherlands" OR "Dutch") OR SG=("Netherlands" OR "Dutch") OR FO=("Netherlands" OR "Dutch") OR FT=("Netherlands" OR "Dutch")) AND PY=(2008 or 2009 or 2010 or 2011 or 2012 or 2013) NOT DT=meeting-abstract

In order to get a worthy overview both total number of citations and mean number of citations per year were searched.

Summary:
Best cited basic research initiated by Dutch groups 2008-2013, defined as that first and last author have a Dutch affiliation. (Table 1)
- Proteomics (Klein, Bischoff)
- Genetics (Lambrechts, Groen, van Klaveren, Verschakelen, Wijmenga, Postma)
- Systemic inflammation (Groenewegen, Postma, Hop, Wouters)
- Genetics (de Vries, van Hijum, Riesbeck, Hermans, Bootsma)
- Genetics (Dijkstra, Postma, Noordhoek, Lodewijk, ten Hacken, Timens)
- Inflammation (Mortaz, Kraneveld, Smit JJ, Kool, Lambrecht, Nijkamp, Folkerts)

Best cited clinical research initiated by Dutch groups 2008-2013. (Table 2)

- Diagnosis (Dragonieri, Annema, Schot, van der Schee, Sterk)
- Exacerbations (Rutten, Zuithoff, Hak, Grobbee, Hoes)
- Diagnosis (Fens, Zwinderman, vn der Schee, de Nijs, Dijkers, Cheung, Bel, Sterk)
- Mortality (van Gestel, Hoeks, Sin, Welten, Schouten, Witteveen, Mertens)
- Exercise capacity (Rietema, Holverda, Bogaard, Marcus, Smit HJ, Westerhof, Postmus, Boonstra, Vonk-Noordergraaf)
- Inhaled corticosteroids (Lapperre, Snoeck-Stroband, Gosman, Jansen DF, van Schadewijk, Thiadens, Vonk, Boezen, ten Hacken, Kerstjens, Hiemstra, Timens, Postma, Sterk)

Table 1 from the appendix shows the top 10 most and best cited basic research on COPD initiated by Dutch groups 2008-2013, defined as that first and last author have a Dutch affiliation. The top 10 best cited clinical research initiated by Dutch groups 2008-2013 is shown in Table 2. Table 3 and 4 show the top 10 for research by Dutch groups in collaboration with international groups. Table 5 shows the top 10 for reviews and/or guidelines.

2. Visibility Dutch research as judged by international experts and based on consensus (See also Appendix)

Areas with good visibility	**Less visible**
- Comorbidity	- Translational research
- Genetics	- International collaboration for basic research
- Diagnosis	– Telemonitoring and self-management
- Pharmacological treatment	
- Epidemiology	
- Phenotyping	
- Biomarkers	
- Exacerbations	

3. Research needs

Facts and Figures

- 323,619 patients with COPD, slightly more males than females (2007) [1]
- 6383 patients died from COPD (2011) [1]
- 6th rank as cause of death in NL; 5th rank as lost years; 7th rank as lost *Disability adjusted life years*[1]
- 25% with important co-morbidity[1]
- paid job 24-58% (compared to 71% in general population) [1]
- hospitalizations: (200) 21.342 occasions; 208,000 hospital days; 113 million

Euro costs

- total costs € 414,742,000 or € 1356 per patient (2007) [2]

Unmet needs (extracted from: Longziekten feiten en cijfers 2008[3])

A considerable level of know how is available within several institutes, but further collaborations will strengthen Dutch research:

- Outside respiratory but within local institute
- At a national level
- At an international level, also outside Europe

To achieve high-quality and safe research, and to strive for improvement in research processes, quality labels (like ISO quality management system) are necessary to be introduced in the field of respiratory research. This enables researchers to show internal and external stakeholders that quality of research processes is taken very serious and also focusing on constant improvements in safety, accessibility, efficiency and efficacy of research processes.

References

[1] Longziekten feiten en cijfers 2013
[2] Maatschappelijke kosten voor astma, COPD en respiratoire allergie. RIVM Rapport 260544001/2012
[3] Longziekten feiten en cijfers 2008

4. Summary SWOT analysis

Results of the web-based SWOT

Strengths	*Weaknesses*
1. High output of peer-reviewed manuscripts in high-impact journals. 2. Several world-class scientists in the field of phenotying COPD, genetics and biomarkers. 3. Epidemiologic research (development and course of COPD). 4. Strong translational focus: from 'bench to bed side'. 5. Self-management and exacerbations of COPD /disease management, pulmonary rehabilitation and physical activity.	1. Not enough attention for efficacy of longer-term (treatment) interventions. 2. Not enough attention fundamental processes. 3. Few positions for young researchers at a post-doc or staff level. 4. Large gaps in evidence- based research in guidelines, a.o. optimal treatment of COPD comorbidities. 5. COPD has a low priority for research funding. In Europe, 12% for funding in Respiratory Research involves COPD. This is not in balance with much higher total health care costs of COPD.
Opportunities	*Threats*
1. Research on COPD could benefit by collaboration with leading immunologists. (strong research) 2. Systems biology (availability of large databases for epidemiological, genetic/epigenetic, and clinical research). 3. Telemedicine: e-health en telemonitoring. 4. Research on optimal patient coaching and lifestyle interventions. 5. Improve the position of COPD research in the priority of The Hague and Health Insurance Companies by better communicating the burden of this disease.	1. High pressure on young researchers by focusing (too) much on the individual output, i.e. number of publications as first or last author in high-impact journals. 2. Too many "following" research projects by the dogma that all research should have clinical implications on the short-term. 3. Decreasing possibilities for funding. In addition, the available funding is assigned to large consortia and is limited to a few research topics. This is a threat for the creativity career development, especially for younger researchers. 4. Loss of phase-2 and phase-3 clinical trials to countries outside Western Europe.

Relevance of research judged by international experts in appendix

	Mean
Biological mechanisms	4.80
Diagnosis monitoring	4.40
Phenotyping and Severity	4.20
Therapy non-medical	3.80
Therapy medical	3.60
Implementation and care	3.60
Environment and lifestyle	3.50
Development and ageing	3.50
Prevention	3.00
Biobanking	2.80
Data management clinical studies	2.80

With the current search studies with high quality in Primary care are less visible. Therefore we added information from two different point of views.

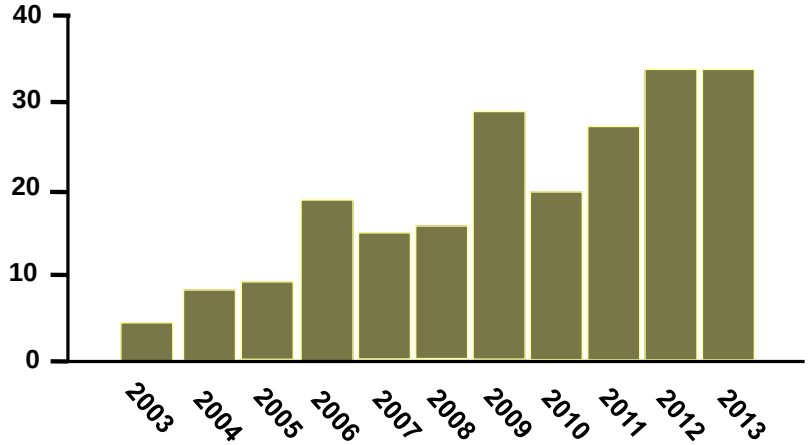
Relevant topics of research judged by experts from primary care

- implementation studies on COPD care
- trials on use of commonly applied medication schemes in hay fever and allergic rhinitis in primary care
- data on the effect of ehealth
- less hospital admissions
- less work impairment
- efficient treatment strategies
- less smoking young adults
- less mortality
- improvement of treatment of co-morbidity
- improvement
- early diagnostic, monitoring, screening

Increasing number of publications/year by GPs in the Netherlands

COPD: Number of publications/year by GPs in internationally refereed Pubmed articles

Numbers: 4-8-9-21-16-17-29-20-27-33-33



5. Description of the interface of COPD with other Roadmap areas

It is becoming increasingly clear that different chronic inflammatory diseases are in part mediated by generic immune mechanisms. This leads to the realization that large differences in phenotypes of inflammatory diseases are for an important part mediated by tissue dependent factors. An example is that neutrophilic inflammation as seen in COPD leads to a specific clinical picture in the lung, but is also present in many other inflammatory diseases in different tissues. Therefore, important research questions regarding inflammation can be obtained from these other tissues; particularly in the event that these tissues are better suitable for specific research questions. Therefore, a clear synergy will be present when these research questions are approached from a higher level in different tissues and not only in the context of COPD.

Research focused on COPD will greatly benefit when more collaborations are initiated with researchers working on similar diseases in other tissues. In addition, it is important that COPD research is presented more and evaluated at meetings of

organization that focus on generic immune mechanisms such as the Dutch Society of Immunology. COPD research will greatly benefit from the cross-talk with all these different research fields. This is very important because of the enormous complexity of the pathogenesis of COPD.

Interface with specific area's	
- Comorbidity	asthma, allergy, infectious diseases, cardiovascular disease, psychological diseases, obesity
- Genetics	asthma, ILD, lung cancer, infectious diseases
- Diagnosis	asthma
- Pharmacological treatment	asthma, ILD, lung cancer, infectious diseases
- Epidemiology	asthma, lung cancer
- Phenotyping	asthma, allergy, infectious diseases
- Biomarkers	asthma, ILD, lung cancer, infectious diseases
- Telemonitoring and self-management	asthma, other chronic disease
- Exacerbations - Alpha-1-anttrypsin deficiency	asthma, infectious diseases asthma, ILD, lung cancer, infectious diseases

6. Priorities for Dutch research in the area of COPD 2014-2019

General Facilitating young talented researchers.

- Translational research by stimulating collaboration between different disciplines, i.e. pulmonary diseases, epidemiology/genetics, pathology, cell biology, clinical immunology, molecular pharmacology.
- Fundamental research to facilitate translational research.

In general, it has become harder over the past years to receive grants. This provides less opportunities for young researchers. Many calls for grants demand consortia, leading to an increased percentage of grants for well-established researchers.
Knowledge on fundamental research is still limited and there is urgent need for novel therapies and genetic techniques.

Focus on COPD
Better positioning of COPD within the priorities of The Hague.

- Systems biology en Telemedicine (e-health and telemonitoring).
- Personalized COPD management based on accurate phenotyping of the disease.

5-10 % of adults aged over 40 years have COPD. Patients have symptoms as well as exacerbations that aggravates when diseases progresses. Treatment includes smoking cessation, medical treatment with bronchodilators as well as

inhibitors of inflammation, physical exercise and oxygen therapy. With the growing aging of the population COPD will have an enormous impact on society from both a health and economic perspective (http://www.erswhitebook.org).

There is need for improvement of evidence based medicine for patients with COPD in Primary Care. Good scientists in Primary Care in the Netherlands should become more visible. To be able to improve research in Primary Care topics such as 'Implementation and care' should get higher priority.

In the Netherlands many researchers focus on phenotyping of COPD (for example Fens N COPD 2013, van den Berge M Thorax 2013, Agusti PloS one 2012). At this moment COPD is characterized by spirometry. This should be extended by the focus of research on more in depth characterization of COPD by novel imaging techniques and biomarkers. In addition, the Netherlands possess a well registered electronic data registration system for all clinical data from patients with COPD. This provides the opportunity to examine and implement clinical phenotyping in daily practice. The basic registration systems are quickly developing and provide an important basis for different health and telemonitoring programs.

7. What is needed to let the research priorities listed be successful?

To achieve the abovementioned COPD research priorities, additional funding, relevant collaborations and quality management systems are needed:
Additional funding:

- Additional local funding to facilitate research by young, talented researchers
- Additional national funding to facilitate interdisciplinary research
- Additional international funding to facilitate systems biology and personalized medicine (genotyping and clinical phenotyping, including comorbidities)
- Long-term funding to study and understand long-term outcomes as relevant in a chronic persistent disease
- Long-term, comprehensive studies/trials, will have spin-off as will international and industrial partners (including the pharmaceutical industry) to do joint studies.

8. What do patients want?

We attempted to involve patients in the evaluation and prioritizing process via the Lung Foundation (Long Fonds). This was welcomed as a good idea, but unfortunately, the timelines involved were too short to find suitable candidates.

Table 1 . Top 10 most cited basic research initiated by a Dutch group:

Theme	Article	Citations	
		Total	Mean/yr
Proteomics	Klein T, Bischoff R. Physiology and pathophysiology of matrix metalloproteases. AMINO ACIDS 2011; 41(2);271-90.	31	10.3
Genetics	Lambrechts D, et al. The 15q24/25 Susceptibility Variant for Lung Cancer and Chronic Obstructive Pulmonary Disease Is Associated with Emphysema American Journal of Respiratory and Critical Care Medicine 2010; 181(5);486-93.	32	8.0
Systemic inflammation	Groenewegen KH, et al. Increased systemic inflammation is a risk factor for COPD exacerbations. Chest 2008; 133(2);350-7.	41	6.8
Genetics	de Vries SPW, et al. Genome Analysis of Moraxella catarrhalis Strain RH4, a Human Respiratory Tract Pathogen Journal of Bacteriology 2010; 192(14);3574-83.	21	5.3
Genetics	Dijkstra A, et al. Expression of ADAMs ("a disintegrin and metalloprotease") in the human lung Virchows Archiv 2009; 454(4);441-9.	24	4.8
Inflammation	van Durme YMTA, et al. C-Reactive Protein Levels, Haplotypes, and the Risk of Incident Chronic Obstructive Pulmonary Disease American Journal of Respiratory and Critical Care medicine 2009; 179(5);375-82.	23	4.6
Alpha-1-antitrypsine	Fregonese L, et al. Hereditary alpha-I-antitrypsin deficiency and its clinical consequences. Orphanet Journal of Rare Diseases 2008; 3;Article Number 16.	27	4.5
Arginine	van Houwelingen, AH, et al. Induction of lung emphysema is prevented by L-arginine-threonine-arginine Faseb Journal 2008; 22(9);3403-8.	26	4.3
Inflammation	Geraets L, et al. Inhibition of LPS-induced pulmonary inflammation by specific flavonoids Biochemical and Biophysical Research Communications 2009; 382(3);598-603.	21	4.2
Genetics	Siedlinski M, et al. Lung Function Loss, Smoking, Vitamin C Intake, and Polymorphisms of the Glutamate-Cysteine Ligase Genes American Journal of Respiratory and Critical Care Medicine 2008; 178(1);13-19	25	4.2

Table 2. Top 10 most cited clinical research initiated by a Dutch group:

Theme	Article	Citations	
		Total	Mean/yr
Diagnosis	Dragonieri S, et al. An electronic nose in the discrimination of patients with non-small cell lung cancer and COPD. Lung Cancer 2009; 64(2);166-70.	70	14.0
Exacerbations	Rutten FH, et al. beta-Blockers May Reduce Mortality and Risk of Exacerbations in Patients With Chronic Obstructive Pulmonary Disease Archives of Internal Medicine 2010; 170(10);880-7.	53	13.3
Diagnosis	Fens N, et al. Exhaled Breath Profiling Enables Discrimination of Chronic Obstructive Pulmonary Disease and Asthma. American Journal of Respiratory and Critical Care Medicine 2009; 180(11); 1076-1082	48	9.6
Mortality	van Gestel YRBM, et al. Impact of cardioselective beta-blockers on mortality in patients with chronic obstructive pulmonary disease and atherosclerosis American Journal of Respiratory and Critical Care Medicine 2008; 178(7);695-700.	47	7.8
Exercise capacity	Rietema H, et al. Sildenafil treatment in COPD does not affect stroke volume or exercise capacity European Respiratory Journal 2008; 31(4);759-64.	45	7.5
Comorbidity	Galal W, et al. The Obesity Paradox in Patients With Peripheral Arterial Disease Chest 2008; 134(5);925-30.	44	7.3
Treatment Inhaled corticosteroids	Lapperre TS, et al. Effect of Fluticasone With and Without Salmeterol on Pulmonary Outcomes in Chronic Obstructive Pulmonary Disease A Randomized Trial Annals of Internal Medicine 2009; 151(8)517-U20.	37	7.4
Comorbidity	de Voogd JN, et al. Depressive Symptoms as Predictors of Mortality in Patients With COPD. Chest 2009; 135(3);619-25.	35	7.0
Lung function	Schermer T, et al. Current clinical guideline definitions of airflow obstruction and COPD overdiagnosis in primary care. European Respiratory. Journal 2008; 32(4);945-52.	34	5.7

Table 3. Top 10 most cited collaborative international basic research (excl. reviews, guidelines):

Theme	Article	Citations	
		Total	Mean/yr
Genetics	Patel BP, Wouters EF, et al. Airway wall thickening and emphysema show independent familial aggregation in chronic obstructive pulmonary disease American Journal of Respiratory and Critical Care Medicine 2008; 178(5);500-5.	84	14.0
Systemic inflammation	Agusti A, Wouters EFM, et al. Persistent Systemic Inflammation is Associated with Poor Clinical Outcomes in COPD: A Novel Phenotype Plos One 2012; 7(5)Article Number: e37483	23	11.5
Cytokines	Barreiro E, Gosker HR, et al. Cytokine profile in quadriceps muscles of patients with severe COPD Thorax 2008; 63(2);100-7.	58	9.7
Biomarkers	Celli BR, Wouters EFM, et al. Inflammatory Biomarkers Improve Clinical Prediction of Mortality in Chronic Obstructive Pulmonary Disease American Journal of Respiratory and Critical Care Medicine 2012; 185(10);1065-72	15	7.5
Signal transduction	Grandoch M, Roscioni SS, Schmidt M. The role of Epac proteins, novel cAMP mediators, in the regulation of immune, lung and neuronal function British Journal of Pharmacology 2010; 159(2);265-84.	29	7.3
Treatment PDE-4	Diamant Z, Spina D. PDE4-inhibitors: A novel, targeted therapy for obstructive airways disease. Pulmonary Pharmacology & Therapeutics 2011; 24(4);353-360	17	5.7
Lymphoid follicles	Brusselle GG, Brandsma CA, Timens W. Lymphoid follicles in (very) severe COPD: beneficial or harmful? European Respiratory 2009; 34;(1);219-30.	28	5.6
Biomarkers	O'Reilly P, Blalock JE. N-alpha-PGP and PGP, potential biomarkers and therapeutic targets for COPD. Respiratory Research 2009; 10; Article Number 38	24	4.8
Inflammation	Chappell S, Hiemstra PS, et al. Genetic variants of microsomal epoxide hydrolase and	19	3.2

	glutamate-cysteine ligase in COPD. European Respiratory Journal 2008; 32(4);931-7.		

Table 4. Top 10 Most cited collaborative international clinical research (excl, reviews, guidelines):

Theme	Article	Citations	
		Total	Mean/yr
Exacerbation	Hurst JR, Wouters EFM, et al. Susceptibility to Exacerbation in Chronic Obstructive Pulmonary Disease. New England Journal of Medicine 2010; 363(12);1128-38.	194	48.5
Treatment PDE-4	Calverley PMA, Rabe KF, et al. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials Lancet 2009; 374(9691);685-94.	151	30.2
Treatment PDE-4	Fabbri LMRabe KF. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials 2009; 374(9691)695-703	135	27.0
Composit measurement	Puhan MA ter Riet GMoons KGM, Kessels AG, et al. Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated Bode index and the Ado index Lancet 2009; 374(9691);704-11.	100	20.0
Ph/Fenotype	Agusti A, Wouters EFM, et al. Characterisation of COPD heterogeneity in the Eclipse cohort Respiratory Research 2010; 11;Article Number 122.	86	21.5
Treatment Bronchodilator	Vogelmeier C, Rutten-van Molke MPMH,…Rabe K,et al. Tiotropium versus Salmeterol for the Prevention of Exacerbations of COPD. New England Journal of Medicine 2011; 364(12);1093-1103.	62	20.7
Lung function	Vestbo J, et al. Changes in Forced Expiratory Volume in 1 Second over Time in COPD. New England Journal of Medicine 2011; 365(13); 1184-92.	58	19.3
Treatment Bronchodilator	Rennard S, Bantje T, et al. A dose-ranging study of indacaterol in obstructive airways disease, with a tiotropium comparison. Respiratory Medicine 2008; 102(7);1033-44.	53	8.8
Inhalers	Lavorini F, Dekhuijzen R, et al. Effect of incorrect use of dry powder inhalers on	49	8.2

	management of patients with asthma and COPD Respiratory Medicine 2008; 102(4);593-604.		
Treatment Bronchodilator	Vogelmeier C, Gans SJM, et al. Formoterol mono- and combination therapy with tiotropium in patients with COPD: A 6-month study Respiratory Medicine 2008; 102(11);1511-20.	44	7.3

Table 5: Top 10 best cited review and guideline papers with Dutch collaborators:

Theme	Article	Citations	
		Total	Mean/yr
Biomarkers	Cazzola M, Wouters EF, et al. Outcomes for COPD pharmacological trials: from lung function to biomarkers. European Respiratory Journal 2008; 31(2);416-468	229	38.2
Comorbidity	Fabbri LM, Rabe KF, et al. Complex chronic comorbidities of COPD. European Respiratory Journal 2008; 31(1); 204-12.	146	24.3
Ph/fenotype	Han MK, Wouters EF et al. Chronic Obstructive Pulmonary Disease Phenotypes The Future of COPD. American Journal of Respiratory and Critical Care Medicine 2010; 182(5);598-604.	125	31.3
Integrins	Margadant C, Sonnenberg A et al. Integrin-TGF-beta crosstalk in fibrosis, cancer and wound healing. Embo Reports. 2010; 11(2);97-105.	86	21.5
Pathology	Hogg, James C, Timens, Wim. The Pathology of Chronic Obstructive Pulmonary Disease. Annual Review of Pathology-Mechanisms of Disease 2009; 4;435-59.	90	18.0
HATs	Dekker FJ, Haisma HJ. Histone acetyl transferases as emerging drug targets. Drug Discovery Today 2009; 14(19-20);942-8.	69	13.8
Early intervention	Decramer M, Wouters E, et al. COPD as a Lung Disease with Systemic Consequences - Clinical Impact, Mechanisms, and Potential for Early Intervention. COPD-Journal of Chronic Obstructive Pulmonary 2008; 5(4);235-56.	64	10.7
Comorbidity	Franssen FME, et al. Obesity and the lung: 5 . Obesity and COPD Thorax 2008; 63(12);1110-17.	40	6.7
Lung function	Derom E, van Weel C, Schermer T, Lammers E, Wouters E…et al. Primary care spirometry. European Respiratory Journal 2008; 31(1);197-203	39	6.5
System biology	Auffray, Sterk PJ. An Integrative Systems Biology Approach to Understanding Pulmonary Diseases. Chest 2010; 137(6);1410-16.	34	8.5

Appendix

Opinions of international key opinion leaders

Question 1
Which research topics and groups in COPD research are visible and have impact on pulmonary physicians and researchers outside the Netherland?

Expert 1
- Groningen (Postma et al). Translational research (inflammation)
- Amsterdam (Sterk et al) (Systems medicine, e-nose)
- Maastricht (Wouters et al) (co morbidities, integrated care)

I hope I have not forgotten any significant one. If so, please, excuse me!

Expert 2

In COPD the Groningen group (Postma, Timens) have a high profile on genetics, phenotyping, mechanisms., physiology, pathology
Amsterdam (Sterk) in monitoring.
Leiden (Hiemstra) in basic mechanisms

Expert 3
- Groningen: epidemiology, genetics, translational research
- Maastricht: rehab/physical activity, co morbidities
- Rotterdam/Rotterdam study: epidemiology/pharma co epidemiology
- Amsterdam: translational research, UBIOPRED
- Utrecht: imaging

Expert 4
- Groningen
- Maastricht (COPD)

Expert 5

Question 2
Which research topics in COPD research are less visible to physicians and researchers outside the Netherland?

Expert 1

Expert 2

Expert 3
Clinical trial participation less visible than a few years ago

Expert 4

Expert 5

Relevance of research judged by international experts (order of importance)

Research performed in the Netherlands in the field of **COPD**

0= no relevant research
5= excellent research international top level

	1	2	3	4	5	Mean
Phenotyping and Severity	4	4	4	5	4	4.20
Biological mechanisms	5	4	5	5	5	4.80
Environment and lifestyle	3	3	3	5		3.50
Development and ageing	3	2	4	5		3.50
Prevention	3	2	2	5	3	3.00
Diagnosis monitoring	4	4	4	5	5	4.40
Therapy medical	4	3	2	5	4	3.60
Therapy non-medical	5	3	3	3	5	3.80
Biobanking	3	1	2	5	3	2.80
Data management clinical studies	3	1	2	4	4	2.80
Implementation and care	4	3	3	5	3	3.60