NRS Roadmap Asthma 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

The team has made an inventory of Dutch asthma research over the last 5 years Search terms: "asthma OR (airways not COPD)".
This revealed: 1430 papers by Dutch researchers, of which 1184 original articles with on average 9,34 citations per item (Tables 1-5).

Summary
Top 10 most cited basic research initiated by Dutch groups 2008-2013, defined as that first and last author have a Dutch affiliation (Table 1).
- Immunology of allergy in mouse. (Hammad, Kool, Perros, Lambrecht).
- Immunotherapy in mouse. (Taher, Oosterhout)
- Steroid receptor in Zebrafish. (Schaaf, Richardson)
- Genetic mutations filaggrin. (Schuttelaar, Postma)
- RSV interaction with dendritic cells in mouse. (Lukens, van Bleek)
- Arginase inhibition is anti-inflammatory. (Maarsingh, Meurs)

Top 10 most cited clinical research initiated by Dutch groups 2008-2013 (Table 2).
- Telemonitoring in children. (De Jongste)
- Phenotyping by electronic nose. (Fens, Sterk)
- Adherence to ICS therapy. (Menckeberg, Bouvy)
- Small airways effect of ciclesonide. (Cohen, Postma)
- Telemonitoring in adults. (vd Meer, Sont)
- Birth cohort - risk of asthma. (Roduit, Scholtens, Willers, multicenter)
- Difficult asthma in adults. (v Veen, Bel)

2. Visibility Dutch research judged by international experts (see also appendix)

Areas with good visibility	**Areas with less visibility**
- Severe asthma	- Asthma in the elderly
- Genetics of asthma	- Translational research,
- Pediatric asthma	- Identification of novel biologicals
- Environment and asthma	- Mechanistic research
- Non-invasive detection	- Effectiveness research
- Phenotyping of asthma (biomarkers)	- Health economics
- Therapy medical	- Biologicals
- Biological mechanisms	- Developement and ageing
	- Data management

3. Research needs

Facts and Figures (2013)

- 54,000 patients with asthma, slightly more males than females (2007)[1]
- 69 patients died from asthma in 2011[1]
- 4th ranked for loss of DALYs, mainly due to exacerbations

Euro costs[2]

- Data on costs for asthma specifically are difficult to retrieve. Based on the LAN report[1], costs for asthma in 2007 are approximately € 331,600,000, and based on a recent publication € 287,000,000[3]
  Most costs relate to treatment (64%) and additionally to physiotherapy (11%), specialist care (10%) and hospitalizations (5%)[3].

Unmet needs (extracted from: LAN verkenning 2010[4])

- Asthma is underdiagnosed, especially in elderly subjects. More accurate diagnostic methods are needed.
- There are only limited diagnostic tests for children under 6 years of age. This leads to under- and overtreatment with potential adverse effects from treatment. Better diagnostic tools need to be developed.
- Asthma treatment is mainly symptomatic. Better understanding of etiologic mechanisms is needed to prevent or eventually cure asthma.
- Difficult-to-control asthma is heterogeneous. A better understanding of this disabling disease and how to avoid side effects of corticosteroid treatment is necessary.
- There are currently insufficient therapies for patients with difficult-to-control asthma. Existing therapies including high altitude treatment should be reimbursed.
- There is a high degree of nonadherence to treatment amongst patients with asthma. Better patient education and coaching are needed to improve adherence. Also should patients be better informed about medications and how to use them.
- Transition of care from paediatrician to pulmonologist is not well organized.
- Transition programs should be developed.

References

[1] Feiten en cijfers 2013 Chronische Longziekten, LAN 2013
[2] Maatschappelijke kosten voor astma, COPD en respiratoire allergie. RIVM Rapport 260544001/2012
[3] Nederlands Tijdschrift voor Geneeskunde 2013;157:2358-2365
[4] Feiten en cijfers chronische Longziekten, LAN 2010

4. Summary of SWOT analysis

Results of the web-based SWOT

Strengths	*Weaknesses*
1. Phenotyping and severity 2. Biological mechanisms 3. Diagnosis and monitoring	1. Biobanking
Opportunities	*Threats*
1. Phenotyping and severity 2. Implementation and care 3. Diagnosis and monitoring	1. Phenotyping and severity 2. Environment and lifestyle 3. Biobanking 4. Implementation and care

Relevance of research judged by 5 international experts (order of importance):
See Table *Relevance of research judged by international experts* in appendix

	Mean
Phenotyping and Severity	4.80
Biological mechanisms	4.00
Environment and lifestyle	3.60
Development and ageing	2.00
Prevention	3.20
Diagnosis monitoring	3.80
Therapy medical	4.20
Therapy non-medical	2.40
Biobanking	2.60
Data management clinical studies	2.00
Implementation and care	3.20

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

The asthma research area has interfaces with the following other research fields in the Netherlands (number of papers last 5 years):

- Paediatric lung disease (593)
- Respiratory allergies (515)
- Infectious diseases (139)
- COPD (123)

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

Based on the unmet needs (point 2), research strengths (point 3), and prior research successes (point 1) our team proposes the following priorities for 2014 – 2019:

- To find better tools for diagnosing and phenotyping asthma, in particular in children under 6 and in adults patients and children with difficult-to-control severe asthma; use cohorts.
- To investigate the genetics, etiologic mechanisms and environmental risk factors of asthma to prevent the onset of disease in children and adults; use interface with allergy, immunology; epidemiology, asthma models.
- To investigate the basic underlying mechanisms of different phenotypes of asthma in order to develop better treatments; use biobanks.
- To investigate the genetics, mechanisms and risk factors of asthma chronicity and severity to improve long term prognosis; use interface with COPD research.
- To investigate factors leading to uncontrolled asthma, asthma exacerbations and asthma deaths; use tele-monitoring.

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

- Funding from local institutes (Universities), government (ZonMW), charities (Longfonds), and pharmaceutical companies. Funding should be in line with the burden of disease.
- Interdisciplinary collaborations within same institute, multicenter national collaborations (cohort studies), European collaborations in the context of Framework programs, IMI, Horizon 2020.
- Establishment of national biobanks.

8. What do patients want?

The lung foundation has asked focus groups of patients on what they thought was needed in research on asthma. This included the following aspects: Insights in genetic and etiologic factors for asthma; Insights in mechanisms contributing to improvement and deterioration of asthma symptoms; Research on underlying causes of asthma development instead of symptom management; Environmental, endogenous and lifestyle factors contributing to development of asthma (indoor and outdoor air pollution, overweight, smoking, stress and depression); Insights in the life-course of asthma and the contributing factors: co-morbidity, multimorbidity and fatigue; Hormonal influences on asthma (OAC, hormonal diseases, thyroid disease, menstrual periods, premenstrual syndrome, menopause); Interaction of asthma with other diseases; Research on how treatments affect composure and recovery (insomnia, comorbidity, over-tiredness, treatment side-effects); Research on the role of lung nurses / assistants in GP practices to support E-health; Research on the role of patient participation in E-health development; Active job participation while having the disease (office hours, office environment, no smoking, perfume smells in toilets and at the job etc); Research on the ability to cope independently (family management, support by fellow patients, disease management and acceptance); Active involvement of patients in treatment approaches.

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

Theme	Article	Citations	
		Total	Mean/ yr
Origins of allergy	Hammad et al. House dust mite allergen induces asthma via Toll-like receptor 4 triggering of airway structural cells. Nat Med 2009; 15: 410-416.	285	57.0
Origins of allergy	Hammad et al. Inflammatory dendritic cells-not basophils-are necessary and sufficient for induction of Th2 immunity to inhaled house dust mite allergen. J Exp Med 2010; 207:2097-2111.	119	29.8
Origins of allergy	Kool M, et al. An unexpected role for uric acid as an inducer of T helper 2 cell immunity to inhaled antigens and inflammatory mediator of allergic asthma. Immunity. 2011; 34(4):527-40.	56	18.7
Immunotherapy	Taher et al. 1 alpha,25-dihydroxyvitamin D(3) potentiates the beneficial effects of allergen immunotherapy in a mouse model of allergic asthma: Role for IL-10 and TGF-beta. J Immunol 2008: 5211-5221.	73	12.2
Genetics / Filaggrin	Schuttelaar ML, et al. Filaggrin mutations in the onset of eczema, sensitization, asthma, hay fever and the interaction with cat exposure. Allergy. 2009; 64(12):1758-65.	45	9.0
Corticosteroids / Genetics	Schaaf et al. Discovery of a functional glucocorticoid receptor beta-isoform in zebrafish . Endocrinol 2008; 149 :1591-1599.	53	8.8
Dendritic cells	Kool M, et al. An anti-inflammatory role for plasmacytoid dendritic cells in allergic airway inflammation. J Immunol. 2009; 183(2):1074-82.	43	8.6
Virus – dendritic cells	Lukens MV, et al. Respiratory syncytial virus-induced activation and migration of respiratory dendritic cells and subsequent antigen presentation in the lung-draining lymph node. J Virol. 2009; 83(14):7235-43.	43	8.6
Arginase	Maarsingh H, et al. Arginase inhibition protects against allergen-induced airway obstruction, hyperresponsiveness, and inflammation. Am J Respir Crit. Care Med. 2008; 178(6):565-73.	48	8.0
Dendritic cells	Perros F, et al Blockade of CCR4 in a humanized model of asthma reveals a critical role for DC-derived CCL17 and CCL22 in attracting Th2 cells and inducing airway inflammation. Allergy. 2009; 64(7):995-1002.	36	7.2

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

Theme	Article	Citations	
		Total	Mean/ yr
Monitoring	De Jongste et al. Daily Telemonitoring of Exhaled Nitric Oxide and Symptoms in the Treatment of Childhood Asthma Am. J Respir Cirt Care Med 2009: 179: 93-97.	85	17.0
Adherence	Menckeberg et al. Beliefs about medicines predict refill adherence to inhaled corticosteroids. J Psychosom Res 2008; 64:47-54.	81	13.5
Phenotyping	Fens et al. Exhaled Breath Profiling Enables Discrimination of Chronic Obstructive Pulmonary Disease and Asthma Author(s): Am. J Respir Crit Care Med 2009; 180:1076-1082.	65	13.0
Tele monitoring	van der Meer V, Internet-based self-management plus education compared with usual care in asthma: a randomized trial. Ann Intern Med. 2009; 151(2):110-20.	47	9.4
Small airways	Cohen et al. Ciclesonide improves measures of small airway involvement in asthma Eur J respir J. 2008; 31:1213-1220.	54	9.0
Severe asthma	Van Veen et al. Airway inflammation in obese and nonobese patients with difficult-to-treat asthma Allergy 2008; 63:570-574.	54	9.0
Risk asthma	Roduit C, et al Asthma at 8 years of age in children born by caesarean section. Thorax. 2009; 64(2):107-13.	41	8.2
Risk asthma	Scholtens S, et al. Overweight and changes in weight status during childhood in relation to asthma symptoms at 8 years of age. J Allergy Clin Immunol. 2009; 123(6):1312-8.e2.	39	7.8
Severe asthma	Van Veen et al. Exhaled nitric oxide predicts lung function decline in difficult-to-treat asthma Eur Respir J 2008: 344-349.	46	7.7
Risk asthma	Willers SM, et al. Maternal food consumption during pregnancy and the longitudinal development of childhood asthma. Am J Respir Crit Care Med. 2008; 178(2):124-31.	38	6.3

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

Theme	Article	Citations	
		Total	Mean/ yr
Genetics IL^{1}RL^{1}	Gudbjartsson, Koppelman, Boezen, Postma…et al. Sequence variants affecting eosinophil numbers associate with asthma and myocardial infarction Author(s): Nat Genet 2009: 41:342-347.	250	50.0
Macrophages	Kurowska-Stolarska, van Rooijen et al. IL-33 Amplifies the Polarization of Alternatively Activated Macrophages That Contribute to Airway Inflammation Author(s): J Immunol 2009; 183:6469-6477.	124	24.8
Genetics / Filaggrin	Brown SJ, Pasmans et al. Loss-of-function variants in the filaggrin gene are a significant risk factor for peanut allergy. J Allergy Clin Immunol. 2011; 127(3):661-7.	65	21.7
Mucus production	Chen et al. SPDEF is required for mouse pulmonary goblet cell differentiation and regulates a network of genes associated with mucus production. J Clin Invest 2009: 119:2914-2924.	74	14.8
Influenza	Chang YJ, Appelmelk et al. Influenza infection in suckling mice expands an NKT cell subset that protects against airway hyperreactivity. J Clin Invest. 2011; 121(1):57-69.	42	14.0
Genetics IL^{6} R	Ferreira MA, Willemsen et al. Identification of IL6R and chromosome 11q13.5 as risk loci for asthma. Lancet. 2011; 378(9795):1006-14.	42	14.0
Dendritic cells	Bedoret D, Van Rooijen et al. Lung interstitial macrophages alter dendritic cell functions to prevent airway allergy in mice. J Clin Invest. 2009; 119(12):3723-38.	61	12.2
Genetics / TLR	Smit LA et al. CD14 and toll-like receptor gene polymorphisms, country living, and asthma in adults. Am J. Respir Crit Care Med. 2009; 179(5):363-8.	52	10.4
Influenza	Tate MD, van Rooijen N, et al. Critical role of airway macrophages in modulating disease severity during influenza virus infection of mice. J Virol. 2010; 84(15):7569-80.	41	10.3
Smooth muscle	Araujo Lindeman. Extracellular matrix components and regulators in the airway smooth muscle in asthma. Eur Respir J. 2008; 32(1):61-9.	61	10.2

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

Theme	Article	Citations	
		Total	Mean/yr
Farming	Ege, Heederi et al. Exposure to Environmental Microorganisms and Childhood Asthma . N Engl J Med 2011: 364: 701-709.	143	47.7
Severe asthma	Wenzel, Rabe et al. A Randomized, Double-blind, Placebo-controlled Study of Tumor Necrosis Factor-alpha Blockade in Severe Persistent Asthma. Am J Respir Crit Care Med 2009: 179:549-558.	144	28.8
Severe asthma	Castro M, Ten Hacken et al. AIR2 Trial Study Group. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. Am J Respir Crit Care Med. 2010; 181(2):116-24.	104	26.0
Farming	Ege MJ, Heederik D et al. Gene-environment interaction for childhood asthma and exposure to farming in Central Europe. J Allergy Clin Immunol. 2011; 127(1):138-44, 144.e1-4.	40	13.3
Immunotherapy	Dahl, De Monchet al. Sublingual grass allergen tablet immunotherapy provides sustained clinical benefit with progressive immunologic changes over 2 years Author(s): J Allergy Clin Immuinol 2008: 121: 512-518.	77	12.8
Probiotics	Kalliomäki M, Rijkers et al. Guidance for substantiating the evidence for beneficial effects of probiotics: prevention and management of allergic diseases by probiotics. J Nutr. 2010; 140(3):713S-21S.	48	12.0
Virus	Thomsen SF, van der Sluis S et al. Exploring the association between severe respiratory syncytial virus infection and asthma: a registry-based twin study. Am J Respir Crit Care Med. 2009; 179(12):1091-7.	50	10.0
Genetics 17921	Halapi E, Koppelman et al. A sequence variant on 17q21 is associated with age at onset and severity of asthma. Eur J Hum Genet. 2010; 18(8):902-8.	40	10.0
Farming	Ege MJ, Brunekreef et al. Protection Against Allergy Study in Rural Environments (PASTURE) Study group. Prenatal exposure to a farm environment modifies atopic sensitization at birth. J Allergy Clin Immunol. 2008; 122(2):407-12, 412.e1-4.	56	9.3
Phenotyping	Schultz A, Brand PL. The transient value of classifying preschool wheeze into episodic viral wheeze and multiple trigger wheeze. Acta Paediatr. 2010; 99(1):56-60.	34	8.5

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

Theme	Article	Citations	
		Total	Mean/ yr
Fluctuations	Scheffer M, et al Early-warning signals for critical transitions. Nature. 2009; 461(7260):53-9.	354	70.8
ARIA guidelines	Brozek Gerth van Wijk et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol. 2010; 126(3):466-76.	170	42.5
Pneumonia	Van der Poll et al. Pathogenesis, treatment, and prevention of pneumococcal pneumonia. Lancet. 2009; 374(9700):1543-56.	127	25.4
Severe asthma guideline	Bousquet J, Rabe. et al. Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. J Allergy Clin Immunol. 2010; 126(5):926-38.	100	25.0
Guideline severe asthma	Taylor, Sterk et al. A new perspective on concepts of asthma severity and control. Eur Respir J. 2008; 32(3):545-54.	134	22.3
HATs drugs	Dekker & Haisma. Histone acetyl transferases as emerging drug targets. Drug Discov Today. 2009; 14(19-20):942-8.	85	17.0
Severe asthma	Bel EH. et al Diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI). Thorax. 2011; 66(10):910-7.	51	17.0
Notch signalling	Amsen D et al. The different faces of Notch in T-helper-cell differentiation. Nat Rev Immunol. 2009; 9(2):116-24. doi: 10.1038/nri2488. Review.	66	13.2
Occupational asthma	Quirce, Gerth van Wijck et al. Noninvasive methods for assessment of airway inflammation in occupational settings. Allergy. 2010; 65(4):445-58.	38	9.5
Dendritic cells	GeurtsvanKessel CH, Lambrecht BN. Division of labor between dendritic cell subsets of the lung. Mucosal Immunol. 2008; 1(6):442-50.	5	0.8

APPENDIX

Opinions of international key opinion leaders

Questions were sent to international experts in the field about the visibility of Dutch asthma research.

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

Expert 1

- Severe Asthma research in Amsterdam, AMC (E. Bel, P. Sterk): U- BIOPRED.
- Genetics of Asthma in Groningen, GRIAC/UMCG (D. Postma, G. Koppelman, H.M. Boezen).
- Asthma in Children (cohort studies: Generation R, PIAMA) in Rotterdam (J. De Jongste).
- Role of environment in allergy and asthma (exposure studies) in Utrecht (B. Brunekreef).

Expert 2

Top ranking:
- Pediatric asthma & prevention
- Diagnosis & monitoring of asthma
- Pharmacological treatment, asthma genetics, severe asthma, and basic asthma research

Expert 3

Clinical Research
Cohorts
Network
Biomarkers
Genetics
Excellent clinical trials
Academic and drugs associated studies

European leadership

- Amsterdam
- Groningen
- Leiden

Expert 4

- Overall gene/environmental interactions
- Epidemiology
- Therapeutic interventions

Expert 5

From my point of view the Netherlands have a high visibility regarding asthma research in these areas:
- Severe asthma (E. Bel)
- Asthma models (C. Taube)
- Non-invasive detection of asthma related inflammation (P. Sterk)

The two groups with the greatest international impact in asthma are the Groningen group of Prof. Postma and the Amsterdam group of Prof. Bel and Prof. Sterk. The areas of strength are translational research in asthma, severe asthma phenotypes, genetics of asthma, overlap between asthma and COPD.

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

Expert 1

- Asthma in the elderly (Rotterdam Study) in Rotterdam (A. Hofman, B. Stricker).

Expert 2

See attached spreadsheet

Expert 3

- Mechanisms
- Biologicals
- Translational research

Expert 4

- Mechanistic research
- Effectiveness research
- Health economics
- Identification of novel therapeutics.

Expert 5

I do believe that groups in the Netherlands cover the currently most interesting areas of asthma research. I am not aware of major gaps.

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

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

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

	1	2	3	4	5	Mean
Phenotyping and Severity	5	5	4	5	5	4.80
Biological mechanisms	3	4	5	4	4	4.00
Environment and lifestyle	4	3	3	4	4	3.60
Development and ageing	4	1	0	2	3	2.00
Prevention	3	2	5	4	2	3.20
Diagnosis monitoring	5	3	4	2	5	3.80
Therapy medical	4	4	5	3	5	4.20
Therapy non-medical	4	3	1	2	2	2.40
Biobanking	3	5	0	4	1	2.60
Data management clinical studies	4	3	0	2	1	2.00
Implementation and care	4	2	3	4	3	3.20