NRS Roadmap ILD report

Team members Coline van Moorsel (captain),
c.van.moorsel@antoniusziekenhuis.nl
René Jonkers, r.e.jonkers@amc.uva.nl.
Marlies Wijsenbeek, m.wijsenbeek-lourens@erasmusmc.nl

1. Inventory of Dutch research efforts in this field over the past five years

Search terms:
The inventory was based on the following search terms in the period 2008-may 2013:
Topic= (interstitial lung disease) AND Address=(netherlands): 78 items, 41 selected
Topic= (idiopathic pulmonary fibrosis) AND Address=(netherlands): 54 items, 31 selected
Topic=(sarcoidosis) AND Address= (netherlands): 142 items, 101 selected
Topic=(non-specific interstitial) AND Address=(netherlands): 7 items, 3 selected
Topic=(interstitial pneumonitis) AND Address=(netherlands): 21 items, 11 selected
Topic=(pulmonary fibrosis) AND Address=(netherlands): 83 items, 25 selected

Summary
Excluding overlap, in total 132 items were listed. From this list, papers describing original research with a focus on ILD or pathogenesis important to ILD were selected, resulting in 21 reviews, 3 letters without original data, 14 case reports and 94 original articles. 39 different Dutch scientific or medical institutes contributed to the articles. On average 2 Dutch institutes were involved. In total 38 articles were the product of international collaboration, of which 15 had a first and last author from institutes abroad.

To investigate visibility of Dutch research on ILD we summarized statistics for 79 articles with a first and last author from the Netherlands for sarcoidosis and interstitial pneumonia/fibrosis.
Most articles focussed on biological mechanisms (25), disease monitoring (18) and phenotyping (11).

Due to limited number of publications, only top 5 articles based on average time cited (between brackets) are given in each category (see appendix):

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

Areas with good visibility	Areas less visibility
- Sarcoidosis diagnosis and treatment	- Inflammation in ILD
- Fatigue in sarcoidosis	- Matrix modulation in ILD
- Anti-oxidants in ILD	- Biomarkers
- Imaging in ILD	- Implementation and care
- Genetics in ILD/pulmonary fibrosis	
- Translational research	
- Bronchoalveolar lavage in ILD	

Review of the literature shows that best cited articles on sarcoidosis concern specific non-pulmonary phenotypes of sarcoidosis. Articles on treatment, quality of life and imaging score highest and have direct consequences for clinical practice. Articles on interstitial pneumonia/fibrosis are more of a basic kind of science and involve biological mechanisms, risk factors and disease monitoring.

3. Research needs

Facts and Figures (2013[1])
Epidemiological research on incidence and prevalence of ILD has not been performed in The Netherlands, therefore all numbers described below are estimations based on numbers in other western countries or local observations. Furthermore, only numbers on the most common form of ILD "sarcoidosis" and the most lethal form of ILD "pulmonary fibrosis- not further specified" are provided.

- It is estimated that 20,000 patients have a form of ILD in The Netherlands
- Most common is sarcoidosis with an estimated prevalence of 500 – 800 patients.
- Incidence per year is approximately 3000 patients with an average age of 20-40 years.
- In up to 30% of the patient population the disease is chronic (>2 years) and ultimately 27 patients died in 2010 from sarcoidosis, while secondary cause of death in another 31 patients was sarcoidosis.
- The prevalence of pulmonary fibrosis is based on estimations regarding IPFand estimated
  to be 3200, with an incidence of 800-1600 a year.
- There is strong male predominance and patients are between 40 and 70 years of age.
- In 2010 in The Netherlands 412 patients died from pulmonary fibrosis, while another 98 patients had pulmonary fibrosis as a second cause of death.

Unmet needs according to LAN report 2010[2]:

- Treatment that cures sarcoidosis or IPF is not available. In case of sarcoidosis treatment is based on watchfull waiting or immuno suppression, and is mainly symptomatic and not curative.
- Approximately 50% of patients recover spontaneously or using first-line immuno-suppressive therapy.

- IPF is always fatal and current therapies are at the most able to delay disease progression slightly.

References

[1] Feiten en cijfers chronische Longziekten, LAN 2013
[2] Feiten en cijfers chronische Longziekten, LAN 2010

4. Summary of SWOT analysis

Results of the web based SWOT

Strengths	*Weaknesses*
1. Biological mechanisms 2. Diagnosis and monitoring 3. Medical therapy	1. Environment and lifestyle 2. Prevention *3.* Datamanagement clinical studies
Opportunities	*Threats*
1. Biological mechanisms 2. Biobanking 3. Diagnosis and monitoring/medical therapy/ data management clinical studies	1. Medical therapy 2. Biobanking 3. Data management clinical studies

Relevance of research judged by 3 international experts (order of importance):
See Table *Relevance of research judged by international experts* in appendix

	Mean
Phenotyping and Severity	2.66
Biological mechanisms	2.66
Environment and lifestyle	3.00
Development and ageing	1.66
Prevention	2.33
Diagnosis monitoring	3.66
Therapy medical	3.33
Therapy non-medical	1.33
Biobanking	2.33
Data management clinical studies	1.00
Implementation and care	4.00

5. Description of the interface of ILD with other Roadmap teams

The SWOT analysis of Asthma and COPD show high scores for disease phenotyping-severity in the categories strength and opportunities. Scores of other SWOT analyses are too low for comparison. However we do see possibilities for synergy between research interest and approach of biological processes between ILD and other diseases. One of the most important will

be auto-immune diseases (AID). Systemic (collagen vascular) diseases are generally of auto-immune origin and are a main aetiology in ILD. All categories apply therefore reciprocally.
Furthermore, overlap (i.e. possible synergy) is seen in:

- Biological mechanism: immunology with Asthma, AID and COPD
- Biological mechanism: destruction and disturbed repair: COPD, Cancer, AID
- Environmental and lifestyle: smoking, COPD, Cancer
- Development and aging: COPD, Cancer, AID
- Medical therapy: last resort: LTX
- Medical therapy: drug targeting: COPD, AID
- Biobanking: Cancer, COPD, LTX, PH, CF
- Data management clinical studies: all
- Implementation and Care: Cancer, COPD

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

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

- biological mechanisms
- biobanking/registry
- phenotyping/severity
- therapy/interventions
- diagnosis monitoring

Provide the reasons for these choices
Past research success is built on medical expertise in ILD care and phenotyping. This has been combined with research interests in disease monitoring, e.g. therapy, fatigue, biomarkers, and genetic predisposition in sarcoidosis. Just recently focus has been turned to pulmonary fibrosis, the influence of therapy and genes has been studied with success.
Research needs of the patient organisations are focused on diagnostics and therapy and they support research on biological mechanisms.
This is congruent with the strength reported by the roadmap team. Altogether this results in our top research priorities listed above.
The list also includes biobanking, because ILD is a heterogeneous group of rare diseases. To bring the field further a coordinated effort building a registry with data of uniformly phenotyped patients and biobanking samples for research purposes
A final common pathway of many forms of ILD is the development of pulmonary fibrosis. As many attempts to more general forms of therapy until now are not successful, study of system biology (incl. genomics and mechanisms) is necessary and can provide (and should be aimed at) finding new drug targets.
Often high morbidity and lack of curative therapy warrants not only focussing on disease centered research but also research to improve care/palliation.

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

- biological mechanisms: focus on pulmonary fibrosis, disease cause and response to therapy
- biobanking/registry: focus on specific phenotypes
- phenotyping/severity: medical expertise, multidisciplinarity
- therapy/intervention: pharmaceutical trials and investigator initiated; national and international collaboration
- diagnosis monitoring: medical expertise, biomarker development, care.

The requirements for realization of these research priorities are: funding, national and international collaboration and multi-disciplinary expertise.

Funding: ILD are amongst the worst funded respiratory diseases.

- government funding is low and highly competitive, but ILD could well fit in specific research programs, perhaps in combination with other diseases like AID, or aging disorders. Indirect funding is extremely low. Public awareness should be created on both the often chronic and invalidating disease course of sarcoidosis in relatively young adults, and on the fatality of the diagnosis IPF to raise interest for funding.

National and international cooperation: Internationally research on ILD is performed by a small group of people, efforts in the last two decades have resulted in international recognition of the Netherlands as a country with high standard medical care for patients with ILD and a strong research interest.

- National and international collaboration might increase changes for funding and are always opportune because they are often efficiently run by primary investigators.
- Our international position has also been recognized by pharmaceutical companies, who are now regarding The Netherlands as an interesting partner for possible ILD contract research.

Multi-disciplinary expertise: ILD-research is dependent on a cross-collaborative chain of experts for diagnosis, phenotyping, and study of biological mechanisms.
There is sufficient etiological/pathogenic overlap with other AID-like diseases, that expertise in this field is often applied to research in sarcoidosis.
Other ILD require registering and biobanking, national or even international collaboration for research purposes to successfully study the disease. In this regard The Netherlands can be an attractive partner in EU research if we have a registry, biobanks and adequate phenotyping of patients. Experience shows that patient willingness to participate in registering and biobanking is extremely high.
Drug studies for ILD, however, should in most cases probably be conducted in international settings to be able to include sufficient patients in the short period of time generally available.

8. What do patients want?

Four patient organizations were requested to describe their research needs: patient organizations for sarcoidosis, pulmonary fibrosis, Sjögren syndrome and lymphangioleiomyomatosis.
All patient organizations regard research in the field of diagnostics and medical (interventions) and non-medical therapy most essential and opportune. From a patient's perspective, fundamental research on disease phenotypes and biological mechanisms is strong and holds promises for translational impact: putting science into practise. To be (internationally) successful biobanking is required and registration might enable patients and centers to participate in therapeutic trials. Although patients are most restricted by the pulmonary aspect of the disease, co-morbidities deserve attention in research and care.

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

Theme	Article	Citations	
		Total	Mean/ yr
Intraepidemal	Bakkers, M, Merkies, I. S. J.; Lauria, G.; Devigili, G.; Penza, P, Lombardi, R, Hermans, M.C.E, van Nes, S.I, De Baets, M, Faber, C.G. Intraepidermal nerve fiber density and its application in sarcoidosis. Neurology. 2009; 73(14):1142-1148	37	7.4
Antioxidant	Boots, A.W, Drent, M, Swennen, E.L.R, Moonen, H.J.J Bast, A, Haenen, G.R. M. M. Antioxidant status associated with inflammation in sarcoidosis: A potential role for antioxidants Respiratory Medicine. 2009; 103(3):364-372	27	5.4
Chronic Fatigue	Korenromp, I. H.E.; Heijnen, C.J.; Vogels, O.J. M, van den Bosch, J.M.M, Grutters,J.C. Characterization of Chronic Fatigue in Patients With Sarcoidosis in Clinical Remission. Chest. 2011; 140(2):441-447	10	3.3
Genetics	Keijsers, R.G, Verzijlbergen, F.J, Oyen, W. J.; van den Bosch, J.M, Ruven, H.J, van Velzen-Blad, H, Grutters, J.C. F-18-FDG PET, genotype-corrected ACE and sIL-2R in newly diagnosed sarcoidosis. Eur. J. Nucl. Med. Mol. Imaging. 2009; 36(7):1131-1137	16	3.2
Fatigue	de Kleijn, W.P.E, Elfferich, M.D.P, De Vries, J, Jonker, G.J, Lower, E.E, Baughman, R.P, King, T.E, Jr, Drent, M. Fatigue In Sarcoidosis: American Versus Dutch Patients. Sarc. Vasc. Diff. Lung Diseases. 2009; 26(2):92-97	15	3.0

Table 1b . Top 10 most cited basic research initiated by a Dutch group – Interstitial lung disease:

Theme	Article	Citations	
		Total	Mean/ yr
Genetics	van Moorsel, C.H. M, van Oosterhout, M.F.M, Barlo, N. P, de Jong, P.A, van der Vis, J.J, Ruven, H.J.T, van Es, H.W. van den Bosch, J. M. M, Grutters, J.C. Surfactant Protein C Mutations Are the Basis of a Significant Portion of Adult Familial Pulmonary Fibrosis in a Dutch Cohort Am J. Resp. Crit Care. 2010; 182(11):1419	31	7.8
Genetics	Wijnen, P.A.H.M, Drent, M, Nelemans, P.J, Kuijpers, P.M.J.C, Koek, G.H, Neef, C, Haenen, G.R.M.M, Bekers, O. Role of Cytochrome P450 Polymorphisms in the Development of Pulmonary Drug Toxicity A Case-Control Study in the Netherlands Druf Safety 2008; 31(12):1125-1134	14	2.3
Myofibroblast Differentiation	Borensztajn, K, Bresser, P, van der Loos, C, Bot, I, van den Blink, B, den Bakker, M. A, Daalhuisen, J, Groot, A. P, Peppelenbosch, M. P, von der Thusen, J.H, Spek, C.A. Protease-Activated Receptor-2 Induces Myofibroblast Differentiation and Tissue Factor Up-Regulation during Bleomycin-Induced Lung Injury Potential Role in Pulmonary Fibrosis AM. J. Pathology. 2010; 177(6):2753-2764	7	1.8
Immunoglobulin Free Light Chains	Kormelink, T, Groot; P, Knipping, K, Buendia-Roldan, I, Garcia-de-Alba, C, Blokhuis, B.R, Selman, Moises, Redegeld, F.A. Immunoglobulin Free Light Chains Are Increased in Hypersensitivity Pneumonitis and Idiopathic Pulmonary Fibrosis. Plos One. 2011; 6(9)e25392	5	1.7
Genetics	Korthagen, N. M, van Moorsel, C.H.M, Barlo, N. P, Kazemier, K. M, Ruven, H.J.T, Grutters, J. C. Association between Variations in Cell Cycle Genes and Idiopathic Pulmonary Fibrosis Plos One. 2012; 7(1) e30442	7	1.4

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

Theme	Article	Citations	
		Total	Mean/ yr
PET	Keijsers, R.G.M, Verzijlbergen, J.F, van Diepen, D. M, van den Bosch, J.M.M, Grutters, J.C. F-18-FDG Pet In Sarcoidosis: An Obseevational Study In 12 patients treated with Inflixlmab. Sarc. Vasc. Diff. Lung Diseases. 2008; 25(2):143-149	22	3.7
Cognitive Failure	Elfferich, M.D, Nelemans, P.J, Ponds, R.W, De Vries, J, Wijnen, Petal A, Drent, M. Everyday Cognitive Failure in Sarcoidosis: The Prevalence and the Effect of Anti-TNF-alpha Treatment. Respiration 2010; 80(3):212-219	17	4.3
Treatment Adalimumab	Erckens, R.J, Mostard, R.L.M, Wijnen, P.A.H. M, Schouten, J.S, Drent, M. Adalimumab successful in sarcoidosis patients with refractory chronic non-infectious uveitis. Graefes Arch. Clin. Exp. Ophthalmology. 2012; 250(5):713-720	11	5.5
Ultrasound biopsy	Bartheld, M.B, Veselic-Charvat, M, Rabe, K.F, Annema, J. T. Endoscopic ultrasound-guided fine-needle aspiration for the diagnosis of sarcoidosis. Endoscopy. 2010; 42(3):213-217	9	2.3
Imaging	Keijsers, R.G, Grutters, J.C, Thomeer, M, Du Bois, R.M, Van Buul, M. M, Lavalaye, J, Van Den Bosch, J.M, Verzijlbergen, F.J. Imaging the inflammatory activity of sarcoidosis: sensitivity and inter observer agreement of Ga-67 imaging and F-18-FDG PET. Q J Nucl Med Mol Imaging. 2011; 55(1):66-71	7	2.3

Table 2b. Top 10 most cited clinical research initiated by a Dutch group - Interstitial lung disease:

Theme	Article	Citations	
		Total	Mean/ yr
Treatment trastuzumab	Pepels, M.J, Boomars, K.A, van Kimmenade, R, Hupperets, P.S. Life-threatening interstitial lung disease associated with trastuzumab: case report Breast Cancer Research and Treatment. 2009; 113(3):609-612	7	1.4
CT Imaging	Arzhaeva, Y, Prokop, M, Murphy, K, van Rikxoort, E.M, de Jong, P.A, Gietema, H.A, Viergever, M.A, van Ginneken, B. Automated estimation of progression of interstitial lung disease in CT images. Medical Physics. 2010; 37(1):63-73	5	1.3
Imaging	Lavalaye, J, Grutters, J.C, van de Garde, E.M. W, van Buul, M. M.C, van den Bosch, J.M.M, Windhorst, A.D, Verzijlbergen, F.J. Imaging of Fibrogenesis in Patients with Idiopathic Pulmonary Fibrosis with cis-4-[F-18]-Fluoro-L-Proline PET Molecular Imaging and Biology. 2009; 11(2):123-127	6	1.2
Diffusion	Peelen, L, Wells, A.U, Prijs, M, Blumenthal, J.P, van Steenwijk, R.P, Jonkers, R.E, Peek,N, Bresser, P. Fibrotic idiopathic interstitial pneumonias: Mortality is linked to a decline in gas transfer. Respirology. 2010; 15(8):1233-1243	4	1.0
Treatment bortezomib	Wondergem, M.J, Grunberg, K, Wittgen, B.P.H, Sonneveld, P, Zweegman, S. Interstitial pneumonitis caused by Pneumocystis jirovecii pneumonia (PCP) during bortezomib treatment Histopathology. 2009; 54(5):631-633	3	0.6

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

Theme	Article	Citations	
		Total	Mean/ yr
Genetics H4A	Saltini, C, Pallante, M, Puxeddu, E, Contini, S, Voorter, C.E, Drent, M, Amicosante, M M. Avium binding to hla-dr expressed alleles in silico: a model of Phenotypic susceptibility to Sarcoidosis Sarcoidosis Vasculitis and Diffuse Lung Diseases. 2008; 25(2):100-116	15	2.5
Genetics H4A	Sato, H, Woodhead, F.A, Ahmad, T, Grutters, J.C, Spagnolo, P, van den Bosch, J.M.M, Maier, L.A, Newman, L.S, Nagai, S, Izumi, T, Wells, A.U, du Bois, R. M, Welsh, K. I. Sarcoidosis HLA class II genotyping distinguishes differences of clinical phenotype across ethnic groups. Human Molecular Genetics. 2010; 19(20):4100-4111	7	1.8
Treatment anti-TNF	Loza, M.J, Brodmerkel, C, Du Bois, R.M, Judson, M. A, Costabel, U, Drent, M, Kavuru, M. Flavin, S.; Lo, K.H, Barnathan, E.S, Baughman, R.P. Inflammatory Profile and Response to Anti-Tumor Necrosis Factor Therapy in Patients with Chronic Pulmonary Sarcoidosis. Clinical and Vaccine Immunology. 2011; 18(6):931-939	4	1.3
Genetics C1	Mrazek, F, Kvezereli, M, Garr, E, Kubistova, Z, Kriegova, E, Fillerova, R, Arakelyan, A, Ruven, H.J.T, Drabek, J, van den Bosch, J.M.M, Kolek, V Welsh, K. I, Grutters, J. C, du Bois, R.M., Petrek, M. Complement receptor 1 single nucleotide polymorphisms in Czech and Dutch patients with sarcoidosis. Tissue Antigens. 2008; 71(1):77-80	6	1.0

Table 3b. Top 10 most cited collaborative international basic research (excl. reviews, guidelines) - Interstitial lung disease:

Theme	Article	Citations	
		Total	Mean/ yr
Amyloid	P Murray, L. A, Chen, Q, Kramer, M. S, Hesson, D. P, Argentieri, R. L, Peng, X, Gulati, M, Homer, R. J, Russell, T, van Rooijen, N, Elias, J.A, Hogaboam, C. M.; Herzog, E. L. TGF-beta driven lung fibrosis is macrophage dependent and blocked by Serum amyloid. International Journal of Biochemistry & Cell Biology. 2011; 43(1):154-162	22	7.3
Macrophage	Gibbons, M.A, MacKinnon, A. C, Ramachandran, P, Dhaliwal, K, Duffin, R, Phythian-Adams, Alexander T, van Rooijen, N, Haslett, C, Howie, S.E, Simpson, A. J, Hirani, N, Gauldie, J, Iredale, J .P, Sethi, T, Forbes, S.J. Ly6C(hi) Monocytes Direct Alternatively Activated Profibrotic Macrophage Regulation of Lung Fibrosis. American Journal of Respiratory and Critical Care Medicine 2011; 12(2):127-130	19	6.3

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

Theme	Article	Citations	
		Total	Mean/ yr
Treatment of infliximab	Judson, M. A, Baughman, R. P, Costabel, U, Flavin, S, Lo, K.H, Kavuru, M.S, Drent, M. Efficacy of infliximab in extrapulmonary sarcoidosis: results from a randomised trial. European Respiratory Journal. 2008; 31(6):1189-1196	67	11.2
Endoscopic ultrasound	Tournoy, K. G, Bolly, A, Aerts, J.G, Pierard, P, De Pauw, R, Leduc, D, Leloup, A, Pieters, T, Slabbynck, H, Janssens, A, Carron, K, Schrevens, L, Pat, K, De Keukeleire, T, Dooms, C. The value of endoscopic ultrasound after bronchoscopy to diagnose thoracic sarcoidosis. European Respiratory Journal. 2010; 35(6):1329-1335	16	4.0
Imaging	Baughman, R.P, Shipley, R, Desai, S, Drent, M, Judson, M.A, Costabel, U, du Bois, R. M, Kovuru, M, Schlenker-Herceg, R, Flavin, S, Lo, K.H, Barnathan, E.S. Changes in Chest Roentgenogram of Sarcoidosis Patients During a Clinical Trial of Infliximab Therapy Comparison of Different Methods of Evaluation. Chest. 2009; 136(2):526-535	18	3.6
Diffusion	Boros, P.W, Enright, P. L, Quanjer, P.H, Borsboom, G.J.J.M, Wesolowski, S.P, Hyatt, R. E. Impaired lung compliance and DL, CO but no restrictive ventilatory defect in sarcoidosis. European Respiratory Journal. 2010; 36(6):1315-1322	6	1.5
Epidemiology	K. Goossens, J.H.M, van Tilborg, T.C, Kunavisarut, P, Choovuthayakorn, J, Rothova, A. Ocular sarcoidosis in Thailand Pathanapitoon. Eye. 2010' 24(11):1669-1674	1	0.3

Table 4b. Top 10 Most cited collaborative international clinical research (excl, reviews, guidelines) - Interstitial lung disease:

Theme	Article	Citations	
		Total	Mean/ yr
Lung function	Behr, J, Demedts, M, Buhl, R, Costabel, U, Dekhuijzen, R.P.N, Jansen, H.M, MacNee, W, Thomeer, M, Wallaert, B, Laurent, F, Nicholson, A. G, Verbeken, E.K, Verschakelen, J, Flower, C.D.R, Petruzzelli, S, De Vuyst, P, van den Bosch, J.M.M, Rodriguez-Becerra, E, Lankhorst, I, Sardina, M, Boissard, G. Lung function in idiopathic pulmonary fibrosis - extended analyses of the IFIGENIA trial. Respiratory Research. 2009;10(1):101.	19	3.8
Treatment Rituximab	Vandenbroucke E, Grutters, J.C, Altenburg, J, Boersma, W.G, ter Borg, E.J, van den Bosch, J.M.M. Rituximab in life threatening Antisynthetase Syndrome Vandenbroucke. Rheumatology International. 2009; 29(12):1499 1502	15	3.0
Vasculature	Corte, T.J, Wort, S. J, MacDonald, P.S, Edey, A, Hansell, D. M, Renzoni, E, Maher, T.M, Nicholson, A.G, Bandula, S, Bresser, P, Wells, A. U. Pulmonary function vascular index predicts prognosis in idiopathic interstitial pneumonia. Respirology. 2012; 17(4):674-680	3	1.5

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

Theme	Article	Citations	
		Total	Mean/ yr
Treatment anti-INF	Baughman, R. P,Lower, E.E, Drent, M. Inhibitors of tumor necrosis factor (tnf) in sarcoidosis: who, what, and how to use them. Sarcoidosis Vasculitis and Diffuse Lung Diseases. 2008; 25(2):76-89	31	5.2
Fatigue	de Kleijn, W.P.E, De Vries, J,Lower, E.E, Elfferich, M.D.P, Baughman, R.P, Drent, M. Fatigue in sarcoidosis: a systematic review. Current opinion in Pulmonary Medicine. 2009; 15(5):499-506	19	3.8
Clinical outcome	Baughman, R. P, Nagai, S, Balter, M, Costabel, U,Drent, M, du Bois, R, Grutters, J.C, Judson, M. A,Lambiri, I, Lower, E.E, Muller-Quernheim, J, Prasse, A,Rizzato, G, Rottoli, P, Spagnolo, P, Teirstein, A. Defining the clinical outcome status (cos) in sarcoidosis: results of wasog task force. Sarcoidosis Vasculitis and Diffuse Lung Diseases. 2011; 28(1):56-64	9	3.0
Fatigue	Drent, M, Lower, E.E, De Vries, J. Sarcoidosis-associated fatigue. European Respiratory Journal. 2012; 40(1):255-263	4	2.0
Neuro - sarcoidosis	Hoitsma, E, Drent, M, Sharma, O.P. A pragmatic approach to diagnosing and treating neurosarcoidosis in the 21st century. Current opinion in Pulmonary Medicine. 2010; 16(5):472-479	5	1.3

Table 5b: Top 10 best cited review and guideline papers with Dutch collaborators – Interstitial lung disease:

Theme	Article	Citations	
		Total	Mean/ yr
Integrin-TGF-beta crosstalk	Margadant, C, Sonnenberg, A. Integrin-TGF-beta crosstalk in fibrosis, cancer and wound healing. Embo Reports 2010;11(2):97-105	86	21.5
Rehabilitation	Spruit, M.A, Janssen, D.J. A, Franssen, F.M.E, Wouters, E.F.M. Rehabilitation and palliative care in lung fibrosis Respirology. 2009; 14(6):781-787	15	3.0
Oxidative stress	Bast, A,Weseler, A.R, Haenen, G.R.M.M, den Hartog, G.J.M. Oxidative stress and antioxidants in interstitial lung disease. Current opinion in Pulmonary Medicine . 2010;16(5):516-520	8	2.0
Biomarkers	van den Blink, B, Wijsenbeek, M. S, Hoogsteden, H.C. Serum biomarkers in idiopathic pulmonary fibrosis Pulmonary Pharmacology & Therapeutics. 2010; 23(6):515-520	7	1.8
Biomarkers	Thomeer, M, Grutters, C, Wuyts, W.A, Willems, S, Demedts, M.G. Clinical use of biomarkers of survival in pulmonary fibrosis. Respiratory Research. 2010; 11(1):89	5	1.3

APPENDIX

Opinions of international key opinion leaders

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

Expert 1

To my eye there are only three groups in the Netherlands that have outside visibility in the field of ILD:

1. Grutters' group. His group has the widest range of research interests, especially in sarcoidosis and the idiopathic interstitial pneumonias. Strikingly, he has outside impact/leadership in the clinical, clinical science and basic science (especially genotyping/phenotyping) of these diseases that are visible and impact outside the Netherlands. A fully translational programme so I would rank his group #1.

2. Drent group. She has focused predominantly on quality of life and health related issues particularly in sarcoidosis. She also leads in the use of bronchoalveolar lavage in ILD. Both of these areas are visible and impact outside the Netherlands.

3. Hoogsteden/v.d. Blink at Erasmus. This group has a broader range of lung interests than just ILD so ILD output is less than the above two groups. V.d.Blink is a younger guy finding his way and his impact is yet to be fully made outside the Netherlands but he is worthy keeping in the frame.

Expert 2

These are
- Sarcoidosis in Maastricht (M. Drent) relevance grade 5
- ILD in general in Utrecht (J. Grutters) relevance grade 5
- Sarcoidosis in Rotterdam (Van de Blink/Hoogsteeden) relevance grade 3

Expert 3

The primary topics focus on genetics, imaging, and sarcoidosis.

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

Expert 1

Not sure what “less visible” meant so took a yes/no approach to those topics that are less visible than those I have highlighted above.

Expert 2

Expert 3

Minimal contributions have been made disease mechanisms/pathogenesis and IPF.

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

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

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

	1	2	3	Mean
Phenotyping and Severity	3	3	2	2.66
Biological mechanisms	4	4	0	4.00
Environment and lifestyle	3	3	3	3.00
Development and ageing	2	2	1	1.66
Prevention	2	2	3	2.33
Diagnosis monitoring	4	4	3	3.66
Therapy medical	4	4	2	3.33
Therapy non-medical	1	1	2	1.33
Biobanking	4	3	0	3.50
Data management clinical studies	1	1	1	1.00
Implementation and care	5	4	3	4.00