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Categorizing diffuse parenchymal lung disease in children

Matthias Griese[1*], Armin Irnstetter[1], Meike Hengst[1], Helen Burmester[1], Felicitas Nagel[1], Jan Ripper[1], Maria Feilcke[1], Ingo Pawlita[1], Florian Gothe[1], Matthias Kappler[1], Andrea Schams[1], Traudl Wesselak[1], Daniela Rauch[1], Thomas Wittmann[1], Peter Lohse[2], Frank Brasch[3] and Carolin Kröner[1]

Abstract

Background: Aim of this study was to verify a systematic and practical categorization system that allows dynamic classification of pediatric DPLD irrespective of completeness of patient data.

Methods: The study was based on 2322 children submitted to the kids-lung-register between 1997 and 2012. Of these children 791 were assigned to 12 DPLD categories, more than 2/3 belonged to categories manifesting primarily in infancy. The work-flow of the pediatric DPLD categorization system included (i) the generation of a final working diagnosis, decision on the presence or absence of (ii) DPLD and (iii) a systemic or lung only condition, and (iv) the allocation to a category and subcategory. The validity and inter-observer dependency of this workflow was re-tested using a systematic sample of 100 cases.

Results: Two blinded raters allocated more than 80 % of the re-categorized cases identically. Non-identical allocation was due to lack of appreciation of all available details, insufficient knowledge of the classification rules by the raters, incomplete patient data, and shortcomings of the classification system itself.

Conclusions: This study provides a suitable workflow and hand-on rules for the categorization of pediatric DPLD. Potential pitfalls were identified and a foundation was laid for the development of consensus-based, international categorization guidelines.

Keywords: Childhood interstitial lung disease, chILD, Diffuse parenchymal lung disease, Rare pediatric lung disease, Categorization, Register, Registry

Background

Childhood interstitial lung diseases (ILD) represent a large spectrum of individually rare diffuse parenchymal lung diseases (DPLD), prevalent in children of all ages [1–3]. They comprise more than 200 different disease entities which are treated by pediatricians and general practitioners in general and specialized (children´s) hospitals. Due to the similarity of symptoms it is often difficult to differentiate these rare patients from children with more common respiratory diseases [4]. Clinical presentation of the disease may further be blurred by recurrent infections or allergies. Childhood DPLD may thus easily be underdiagnosed. Correct classification of all patients is however indispensable for the appropriate treatment, for a better understanding of the underlying pathophysiology, for the identification of biomarkers and for long-term studies and cohort investigations.

Several categorization systems of childhood DPLD have been proposed over time [1, 5–7]. The majority of the recent systems are based on lung histology, related to the study by Deutsch et al. [1], which classifies the broad spectrum of patients into eight disease categories containing various diagnoses [1]. The categorization system has in the meantime been expanded to the entire pediatric age range [6] and has been shown useful for pathological studies [7]. In a single center study the system was also used for cases not diagnosed by biopsy [8].

Aim of this study was to verify a systematic and practical categorization system that allows dynamic classification of pediatric DPLD irrespective of completeness of patient data.

* Correspondence: matthias.griese@med.uni-muenchen.de
[1]Department of Pediatric Pneumology, Dr. von Haunersches Kinderspital, University of Munich, German Center for Lung Research, Lindwurmstraße 4, 80337, Munich, Germany
Full list of author information is available at the end of the article

The work-flow and validity of the categorization system was tested, basis were all cases submitted to the kids-lung-register (KLR) between 1997 and 2012 [2]. The kids-lung-register is, an open, non-profit register for rare lung diseases in childhood and adolescence (www.kids-lung-register.eu). On average 147 children with lung diseases per year are referred to the kids-lung-register for consultation and laboratory services from diverse European centers. Based on the kids-lung-register a European management platform was established in 2013 for childhood interstitial lung diseases (http://www.klinikum.uni-muenchen.de/Child-EU/en/index.html) comprising 10 academic partners from 5 European countries.

Methods

DPLD are entities originating from abnormalities of lung interstitial tissue components. These structures in the periphery of the lungs include the alveolar epithelium, the vessel endothelium and the tissues between these structures. More centrally they include peribronchiolar and peribronchial tissues [9]. Airways may be involved secondary in the disease process. DPLD disorders more prevalent in infancy (A) and disorders occurring at all ages (B) are differentiated. Diseases which affect the parenchymal tissue, but are localized gross structural abnormalities of the lungs, either congenital (C1) or acquired (C2) are not classified as DPLD. Further separated are disorders which primarily affect the airways (airway disorders (D)), the pleural tissues (pleural diseases (E)), diseases caused by lung infections (F) or neoplasms (G), which may also involve the parenchyma.

Workflow for patient categorization during routine operation of the KLR

For the cases referred to the KLR the categorization system for DPLD suggested by Deutsch et al. [1] was further developed; three additional categories were introduced (Additional file 1: Table S1) to accommodate cases with "unclear respiratory distress syndrome" in the mature neonate (Ax) and in the almost mature neonate (Ay) and "unclear respiratory distress syndrome" in the non-neonate (By). These categories allow the future analysis of unclear cases. In addition, the rather wide category "disorders masquerading as ILD" was dissolved into two more specific categories: "DPLD related to lung vessels structural processes" (B4) and "DPLD related to reactive lymphoid lesions" (B5) (Fig. 1).

Practical categorization rules were initially set up by the KLR (Table 1) to assure consistent categorization. 2322 children were referred to the KLR between 1997 and 2012. DPLD was suspected in a child with (1) respiratory symptoms and signs such as cough, tachy-/dyspnea at rest or with exercise, crackles, retractions, digital clubbing, failure to thrive, or respiratory failure, and (2) hypoxemia, and (3) diffuse radiological abnormalities and (4) if feasible

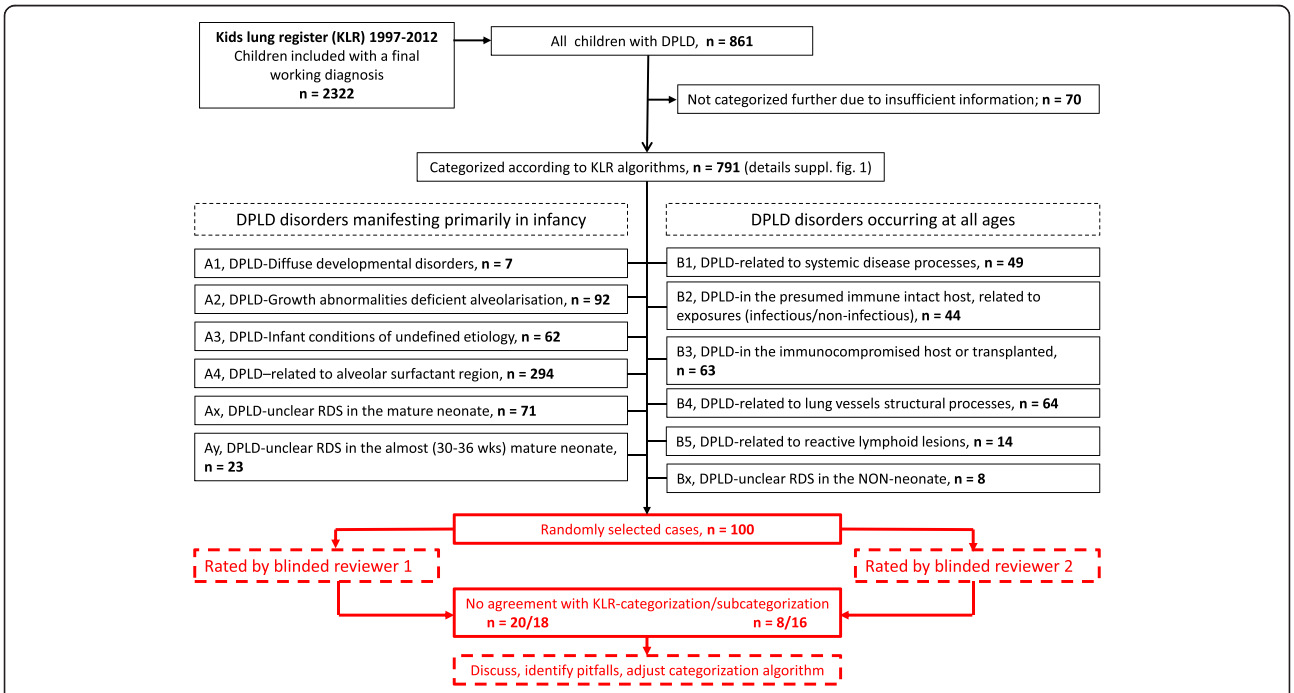

Fig. 1 Overview on study design. The upper part (black) of the figure shows the patients collected in the kids lung register (KLR) and categorized according to the KLR algorithm between 1997 and 2012. Patients received a working diagnosis and were categorized into DPLD categories and subcategories; the latter process is described in more detail in Addditional file 2: Figure S1. The lower part of the figure (red) describes the workflow used for the re-categorization of 100 cases selected randomly and in proportion of their occurrence in the KLR. Two reviewers (AI, MG) re-assessed those cases blinded and independently and obtained a working diagnosis, categorization and sub-categorization according to the workflow in the lower part of Addditional file 2: Figure S1 (red)

Table 1 Rules for allocating a "final working diagnosis" to the disease categories and subcategories

General rules	Examples
1. A final working diagnosis is established based on the available information	
The final working diagnosis is the diagnosis with the highest likelihood. Even if some diagnostic tests are missing or the information level is low, a final working diagnosis is defined and used for categorization. Clinical symptoms (cough, dyspnea, etc.) are only considered informative for categorization if typical for the diagnosis	- Sarcoidosis is diagnosed based on chronic dyspnea, interstitial fine nodules, granulomatous skin lesions in biopsy, and increased angiotensin converting enzyme levels. - Respiratory distress in the mature neonate as DPLD is diagnosed after the exclusion of infectious, cardiac, metabolic, neurologic and localized pulmonary causes. - Tachypnoe in infants with NEHI
2. DPLD or not? Are any aspects of the final working diagnosis related to DPLD?	
(a) Yes: the case should be categorized in the DPLD system (b) No: no categorization in the DPLD system	- Child with juvenile myelomonocytic leukemia and dyspnea, cough and reversible airway obstruction. On CT scan no evidence for obliterative bronchiolitis and bronchiectasis. ⇨ Airway disease, no DPLD - Same history with same findings, but on CT scan septal thickening and centrilobular nodules ⇨ DPLD-in the immunocompromised host or transplanted (B3) - Pneumonia in a patient with chronic granulomatous disease, no evidence of an interstitial lung disease ⇨ systemic disease, no DPLD
3. Systemic or lung-only condition? Is the lung disease part of a systemic disease process or is it a lung-only condition?	
a) Allocation of a lung disease as part of a systemic disease process is preferred over classifying as lung-only DPLD, if there is any evidence for the involvement of systemic structures *Reason*: it is more likely that the systemic disease causes a lung problem, than that an independent rare lung disease emerges in addition to a DPLD related to a systemic disease. *Consequences*: (i) same histological pattern may be present in different categories (ii) carefully re-evaluate for potential lung disease only	- Clinical, BAL or histological evidence for pulmonary hemorrhage without any evidence for systemic involvement, diagnosis of idiopathic pulmonary hemosiderosis ⇨ DPLD - related to lung vessels structural processes (B4) - Pulmonary hemorrhage and a disease-causing mutation for Osler's disease ⇨ DPLD - related to systemic disease processes (B1) - Pulmonary hemorrhage and celiac disease ⇨ DPLD - related to systemic disease processes (B1)
b) Allocation of a disease as a lung-only DPLD in the presence of hints for the involvement of systemic structures should only be done if convincing evidence supports a lung-only DPLD	- Acute lymphatic leukemia treated with chemotherapy and stem cell transplant, development of pulmonary pathology, histologically NSIP ⇨ DPLD – related to systemic disease processes (B1): lung injury as a complication or therapy more likely than independent lung disease - Same history, but detection of two disease causing ABCA3 mutations in the patient ⇨ DPLD – related to alveolar surfactant region (A4): lung-only DPLD in addition to oncologic disease
4. Select a category and a subcategory which best accommodates the final working diagnosis	
Prefer the category/subcategory with	
(a) a better causal link/explanation for the lung disease: cause of pulmonary disease is for example ranked higher than the histological pattern alone, since the same histological result can be allocated to several categories. If the cause is not determinable, the most likely association of the histological pattern with a disease is selected.	- a patient with a drug-induced hypersensitivity reaction of the lung and the histological pattern of NSIP ⇨ DPLD - in the presumed immune intact host, related to exposures (B2) - A patient with NSIP and no further clinical information ⇨ DPLD - related to the alveolar surfactant region (A4) is selected and awaits further molecular characterization, as NSIP can be associated with SFTPC, ABCA3, or TTF1/Nkx2.1 mutations

Table 1 Rules for allocating a "final working diagnosis" to the disease categories and subcategories *(Continued)*

(b) the overall better proof, even if less specific	- BPD-cLDI is preferred over pulmonary hypoplasia as the latter can reliably only be assessed by radial counting of pathology specimens or experimentally by using novel imaging techniques not routinely available

Abbreviations: ABCA3, ATP-binding cassette sub-family A member 3, *BAL* bronchoalveolar lavage, *BPD-cLDI* bronchopulmonary dysplasia - chronic lung disease of infancy, *DPLD* diffuse parenchymal lung disease, *NEHI* Neuroendocrine cell hyperplasia of infancy, *NSIP* non-specific interstitial pneumonitis, *SFTPC* surfactant protein C, *TTF1* thyroid transcription factor 1

and available, abnormalities in pulmonary function testing. Minimum duration of symptoms was 4 weeks.

During capture of the cases with suspected DPLD the referring physician mostly specialized in pediatric pulmonology on the level of a tertiary or university hospital diagnosed the patients in cooperation with the radiologist and in cases with biopsy the pathologist. Available material included a clinical history, biochemical, radiological, histological and genetic data of varying level of detail. A diagnosis was independently also established by each of the KLR experts: F. B., a pathologist; P. L. a geneticist; M. G., a pediatric clinician and pulmonologist (Additional file 2: Figure S1).

A four-step algorithm was used for categorization (Table **1**): in a first step, a "final working diagnosis" was defined by consensus discussion, entered into the data-base and used for categorization and sub-categorization. In a second step it was analyzed if the final working diagnosis was related to DPLD. In a third step it was decided whether the patient suffered from a lung only condition or if the lung disease was part of a systemic disease. Of note, the latter are not restricted to the diagnosis of category B1. Other organ systems than the lungs may also be involved in diseases of categories B3, B4, B5, A1 and in particular A2 (Fig. 1, Additional file 1: Table S1). In a fourth step, the appropriate category and subcategory were selected, preferring the strongest causal explanation of the condition and the most conclusive supporting evidence taking into account the categorization rules shown in Table 1. A total of 791 children of 2322 children in the KLR qualified for childhood DPLD and were further categorized into one of the 12 DPLD categories (Fig. 1, Additional file 1: Table S1) and the respective subcategories.

Workflow for re-rating of selected DPLD cases retrieved from the KLR

The validity and observer-dependency was tested in 2012 using a systematic sample of 100 DPLD cases from the cohort of 791 children previously categorized according to the KLR algorithm. 100 cases were selected randomly and in proportion to their frequency in the KLR categories. All 100 cases were pseudonymized for blinded and independent re-categorization by two pediatric pneumologists, familiar with the KLR categorization system (Fig. 1, red lowever part, Additional file 3: Tables S2, Additional file 4: Table S3). One of the physicians involved in re-rating was already involved in the initial categorization, the other was an independent physician. A final working diagnosis was newly established by each re-rater and allocated in the KLR categorization system, again according to the rules indicated in Table 1 and the workflow detailed in Additional file 2: Figure S1, red part. As re-rating of the categorization was the goal of the study the initial categorization obtained during routine work-flow was set as the correct one. The overall frequencies of diagnostics available for the establishment of the final working diagnosis, categorization and subcategorization are indicated in Additional file 5: Table S4.

Ethics Statement

All participants gave their written informed consent to participate in the KLR consultation and diagnosis program. The retrospective analysis of the data was approved by the institutional review board (EK 026–06). Prospective collection and analysis of data was approved in the GOLD.net project (EK 257–10), and analysis was performed under the project FP7-305653-chILD-EU (EK 111–13).

Results

Of 2322 children referred to the KLR between 1997 and 2012, 861 were related to DPLD and included into this cohort. Subjects with insufficient information were excluded. 791 remaining subjects were assigned to the 12 DPLD categories (Fig. 1). Of these subjects 55 % were male; their age at presentation was 4.2 ± 5.5 years (median 1.0 years, range 0 to 20). 549 subjects had a lung disease manifesting primarily in infancy, of which the largest number (294) was assigned to the category A4 (DPLD–related to alveolar surfactant region) (Fig. 1).

Re-categorization of 100 cases was in agreement with the first allocation in more than 80 % (Table 2). Analysis of deviation in allocation showed that four kinds of allocation mistakes were made (Table 2): (1) one source for error was a lack of appreciation of all details available in the medical records; most of these mistakes were associated with wrong allocation of subcategories. (2) a second rater-related source of error was too little knowledge of and erroneous application of the categorization rules. For example, chromosomal abnormalities are listed as an independent category in A2 because they are present at birth and mainly manifest in infancy, and not in B1, i.e. related to systemic disease processes. (3) For some cases previously categorized, the re-rater decided that data was insufficient. In one case for instance, clinical and radiological data was available, however no genetic or histologic information. Information on low levels of

Table 2 Results of blinded re-rating of 100 subjects with pediatric DPLD by two independent raters and reasons for incorrect rating (see individual values in Additional file 3: Table S2)

	Blinded rater 1		Blinded rater 2	
	Category	Subcategory	Category	Subcategory
Correct categorization	80	82	92	84
Non-correct categorization	20	18	8	16
1 Reports not appreciated/read in detail (= true mistake of rater)	5	8	2	6
2 Poor knowledge of the classification rules	3	4	2	4
3 Insufficient data on case	8	0	2	2
4 Deficit of the classification system	4	6	2	4

Data are absolute numbers (total $n = 100$) or %

hydrophobic surfactant protein content of BAL was not judged to be helpful (4).

Lastly, shortcomings of the categorization system itself lead to non-correct categorization: main deficits of the categorization system were observed for the differentiation of chronic tachypnea of infancy (A3), and for diseases involving the parenchyma but also or primarily the peripheral airways. The latter, such as post-infectious obliterative bronchiolitis and Mac-Leod-Swyer-James-Syndrome, both for immune-competent and immune-compromised hosts, were frequently categorized as airway disorders and not as DPLD. The former, i.e. infants with tachypnea were identified as neuroendocrine cell hyperplasia, even if there was no biopsy available. A comprehensive list of erroneous classification is displayed in Additional files 3 and 4: Tables S2, S3.

Discussion

Here we describe an algorithm to categorize children with DPLD; we defined and assessed rules for categorization and suggest a tool for establishing large cohorts of consistently categorized subjects with rare pulmonary diseases. We thus provide an important basis for the development of consensus-based, international guidelines for categorization and management of pediatric DPLD. Consistent categorization is indispensable for handling individual cases in registries and biobanks appropriately. It allows to combine or split diagnosis groups and to compare subcategories and categories. A consistent categorization system is the basis for future adjustments, such as the inclusion of new molecular disease entities or of novel diagnostic methods. A specific working diagnosis may change over time or knowledge may evolve on a particular subject, however, the allocation rules should not change, representing an important constant term.

In this study, several important barriers to a consistent categorization of rare lung diseases were identified. It was shown that consistent categorization needs to be repeatedly practiced especially for the use in large registers. Continuous evaluation of the categorization process within a register will be an important element of quality control.

Lack of sufficient data in a case is a common problem in clinical practice, hindering the establishment of a correct diagnosis. Data may be insufficient for many reasons, such as high costs for diagnostic testing, invasiveness of tests (e.g. lung biopsy), missing data or poor quality of the data (e.g. incomplete history, CT scans performed in infants with improper technique). The problem of insufficient data should not distract from making a diagnosis. Appreciating all information and details available will yield a final working diagnosis, which should be clearly indicated. Even if the diagnosis leaves open questions e.g. "unclear RDS in the mature neonate", these cases must nevertheless be categorized. For this purpose the categories Ax, Ay, Bx were created (Fig. 1, Additional file 1: Table S1). The cases in these categories can (and must) be systematically revisited and if more information becomes available, should be allocated into more specific categories. These patients can furthermore be included into non-hypothesis based screening projects, like exome sequencing or disease marker identification projects, with the aim to identify previously unknown disease causes or to determine disease activity.

Any classification system is continuously evolving. Increasing knowledge on molecular disease mechanisms allows the definition of new entities, which must be easily accommodated in the categorization system, as is the case for the current system.

It is furthermore essential to continuously take note of potential areas of uncertainty within the system and to clarify these: there are for example entities for which no precise diagnostic criteria are available, such as the differentiation of infants with chronic tachypnea in the absence of a lung biopsy (See examples in Additional file 3: Table S2). Another area which needs clarification is the categorization of diffuse parenchymal diseases which also involve the distal airways. These patients overlap with those presenting primarily as obstructive airway diseases, but cannot merely be classified as such, because the remodeling of the lung tissue component is dominant. A precise definition of all subcategories is not yet available but will be significant to be developed as "gold-standard".

Lastly, a rating of the confidence level of the quality of the data used for establishing the working diagnosis for the individual cases would be a valuable additional indicator and is desirable to be established in the future.

Using a clinically oriented categorization system such as the one presented here has the advantage that different registries or studies using the same definitions and rules may be compared or combined for analysis. Consistent application of a clinically oriented categorization system is prerequisite for the establishment of urgently needed larger cohorts of patients with rare pediatric lung diseases.

Conclusions

We present hands-on rules for the categorization of all pediatric DPLD, independent of the presence or absence of a lung biopsy or the quality of diagnostic data. We empirically identify pitfalls of categorization and suggest solutions for improvement with the aim to provide the basis for the development of consensus-based, international guidelines for the categorization and management of pediatric DPLD.

Additional files

Additional file 1: Table S1. Definitions of diffuse parenchymal lung diseases (DPLD) - disease categories and subcategories. (DOCX 26 kb)

Additional file 2: Figure S1. Routine work-flow used in the Kids lung register (KLR) to obtain a final working diagnosis and to categorize and subcategorize cases with suspected DPLD (black and red). The work-flow used for re-rating is depicted in red. *reference pathologist was Frank Brasch, **genetical diagnosis was made by Peter Lohse and ***lavage report on surfactant protein analysis, as well as the establishment of the final working diagnosis during routine KLR workflow were done by Matthias Griese. (PDF 176 kb)

Additional file 3: Table S2. Blinded and independent re-rating of a random sample of 100 DPLD cases from the kids-lung register. Only differences to the original categorization are indicated; empty cells indicate correct categorization. (DOCX 35 kb)

Additional file 4: Table S3. Summary of reasons for incorrect categorization. (DOCX 15 kb)

Additional file 5: Table S4. Overall frequencies of diagnostics available for the establishment of the final working diagnosis, categorization and sub-categorization. Note that not all tests were performed in all patients. (DOCX 15 kb)

Additional file 6: Table S5. Centers and physicians contributing cases to the kids-lung-register. (DOCX 34 kb)

Abbreviations

DPLD: Diffuse parenchymal lung disease; KLR: Kids-lung-register; RDS: Respiratory distress syndrome.

Competing interests

The authors declare to have no competing interests.

Authors' contributions

MG designed the study, organized long term collection of subjects, patient recruitment and evaluation, data analysis, and drafted the manuscript. He is the guarantee of the work. AI was involved in patient evaluation; re-review of patients sample, chart review, data analysis, and revisions of the manuscript. MH, HB, FN, JR, MF, IP, FG, MK evaluated patients, made chart reviews, and revised the manuscript. AS, TW, DR, TW organized the study logistics, did laboratory analysis, sample and patient organization, and made critical revisions of the manuscript. PL did chart review, the genetic analyses and revised the manuscript. FB evaluated patients with biopsies, performed histo-pathological analyses and revised the manuscript. CK did patient evaluations, chart review, data analysis, and revised the manuscript. All authors read and approved the final manuscript.

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We thank all institutions and physicians contributing cases to this project. A complete listing is indicated in Additional file 6: Table S5.

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Author details

[1]Department of Pediatric Pneumology, Dr. von Haunersches Kinderspital, University of Munich, German Center for Lung Research, Lindwurmstraße 4, 80337, Munich, Germany. [2]Praxis für Humangenetik, CeGaT GmbH, Tübingen, Germany. [3]Department of Pathology, Academic Teaching Hospital Bielefeld, Bielefeld, Germany.

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Supplemental Table 1 Definitions of diffuse parenchymal lung diseases (DPLD) - disease categories and subcategories

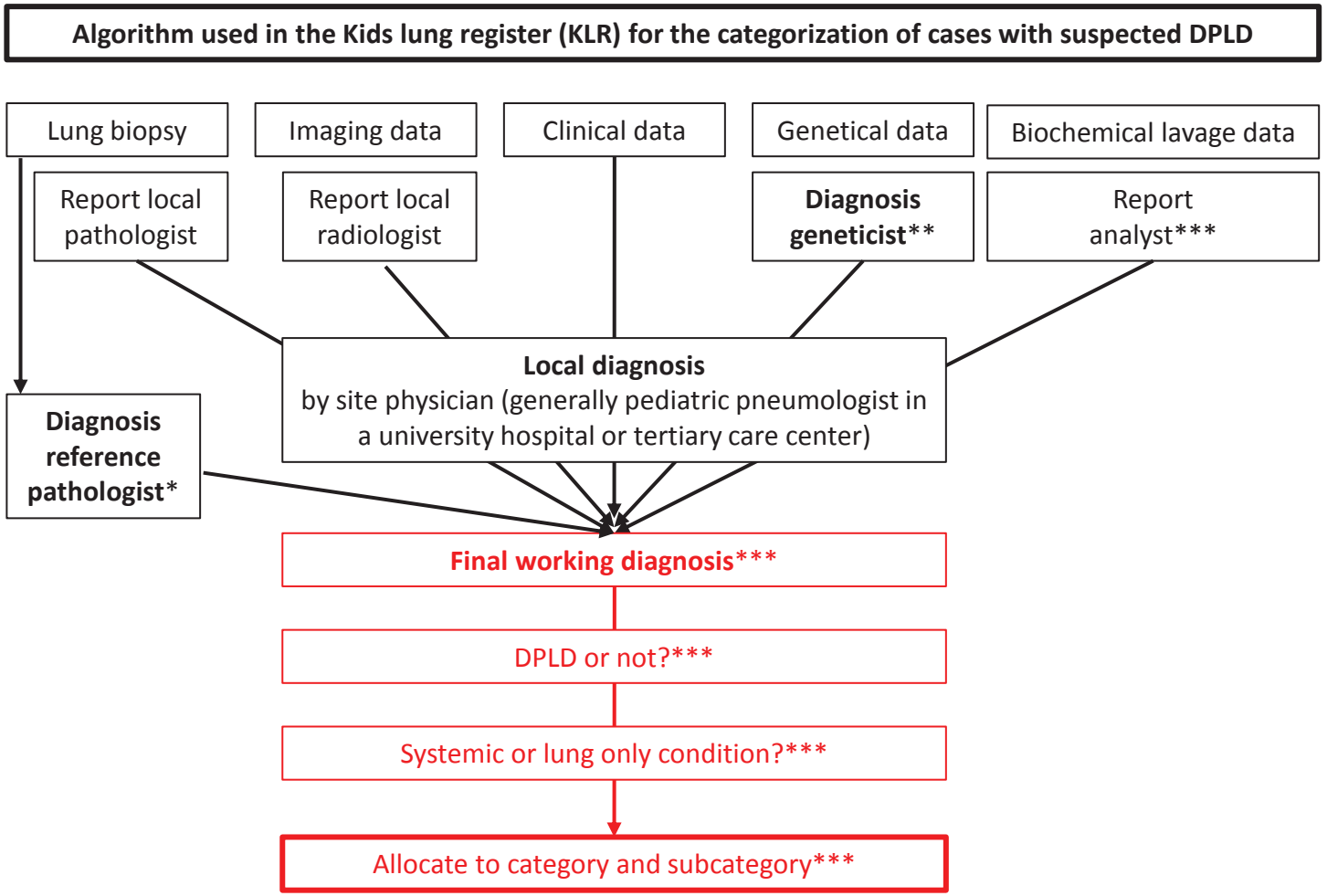
Category		Definition	Subcategories
A	**DPLD disorders manifesting primarily in infancy**		
A1	Diffuse developmental disorders	Disorders of lung development leading to bilateral structurally abnormal lung parenchyma	- Acinar dysplasia - Congenital alveolar dysplasia - Alveolar-capillary dysplasia with pulmonary vein misalignment - Alveolar-capillary dysplasia without misalignment of the vessels
A2	Alveolarisation deficiencies	Disorders with deficient alveolarisation due to pre- or postnatal abnormal lung growth	- Pulmonary hypoplasia, primary (idiopathic) - Pulmonary hypoplasia, secondary (e.g. diaphragmatic hernia) - Related to chromosomal disorders - Related to congenital heart disease (without chromosomal disorder) - Bronchopulmonary dysplasia - chronic lung disease of prematurity (BPD-cLDI) -Wilson Mikity syndrome
A3	Specific conditions of undefined etiology	Disorders in infants with chronic tachypnea without a yet recognized genetic disorder, with a clear histological and/or radiological pattern	- Chronic tachypnea of infancy (CTI) - Neuroendocrine cell hyperplasia of infancy (NEHI) - Pulmonary interstitial glycogenosis
A4	Surfactant dysfunction disorders	Disorders related to the alveolar surfactant region, with a proven genetic defect or with a defined histological pattern	- ABCA3 mutations - SFTPC mutations - SFTPB mutations - NKX2-1 mutations - GMCSF-RA mutations - GMCSF-RB mutations - Chronic pneumonitis of infancy (CPI) - Usual interstitial pneumonia (UIP) - Nonspecific interstitial pneumonia (NSIP) - Desquamative interstitial pneumonia (DIP) - Pulmonary alveolar proteinosis (PAP) with GMCSF autoantibodies - Pulmonary alveolar proteinosis (PAP) without GMCSF autoantibodies - Pulmonary alveolar proteinosis (PAP) juvenile - Pulmonary alveolar proteinosis (PAP) neonatal

			- Pulmonary alveolar proteinosis (PAP) secondary to associated disease - Pulmonary alveolar proteinosis (PAP) with GATA2 mutation - Other surfactant-associated disorders without a yet defined genetic defect - Alveolar microlithiasis - Lipoid pneumonitis, Cholesterol pneumonia
Ax	Unclear Respiratory Distress Syndrome in the mature neonate	DPLD disorders in neonates of gestational age $\geq$ 37 weeks, after the exclusion of neonatal infection, congenital heart disease, inborn metabolic diseases, central or peripheral nervous system disorders	- Familial - Pulmonary hypertension - No or very low surfactant proteins SP-B or SP-C biochemically
Ay	Unclear Respiratory Distress Syndrome in the almost (30-36 weeks) mature neonate	DPLD disorders in neonates of gestational age 30 to 36 weeks, unlikely due to immaturity alone, after the exclusion of neonatal infection, congenital heart disease, inborn metabolic diseases, central or peripheral nervous system disorders	- Familial - Pulmonary hypertension - No or very low surfactant proteins SP-B or SP-C biochemically
B	**DPLD disorders occurring at all ages**		
B1	DPLD related to systemic disease processes	DPLD due to systemic disorders with pulmonary manifestation	- Achondroplasia, e.g. cartilage-hair hypoplasia - Alagille syndrome - Goodpasture's disease - Antisynthetase syndrome - Behcet's disease - Birt-Hogg-Dubé syndrome - Blau syndrome - Congenital central hypoventilation syndrome (CCHS) - Churg-Strauss syndrome (CSS) - Congenital muscle disease - Diffuse alveolar hemorrhage due to vasculitis disorder - Disseminated Visceral Giant Cell Angiitis - Erdheim-Chester disease

			- Familial dysautonomia (FD) - Giant cell arteritis - Hermansky-Pudlak syndrome (HPS) - Hoyeraal-Hreidarsson syndrome - Hypercalcuric hypercalcemia - Immune-mediated/collagen vascular disorders - Lymphangioleiomyomatosis (LAM) - Langerhans cell histiocytosis - Osler's disease - Malignant infiltrates - Microscopic polyangiitis - Necrotizing sarcoid granulomatosis - Neurofibromatosis, von Recklingshausen's disease - Other rare causes of granulomatous arteritis - Polyarteritis nodosa - Rubinstein-Taybi-syndrome - Sarcoidosis - Sickle cell disease - Sinus histiocytosis with massive lymphadenopathy - Stevens-Johnson syndrome - drug induced, with or without obliterative bronchiolitis - Stevens-Johnson syndrome – idiopathic, with or without obliterative bronchiolitis - Stevens-Johnson syndrome - infection related, with or without obliterative bronchiolitis - Storage diseases - Systemic lupus erythematosus - Takayasu's arteritis - Wegener's granulomatosis
B2	DPLD in the presumed immune-intact host, related to exposures (infectious/non-infectious)	DPLD as consequence of exposure to substances or infectious agents in the lungs in the immune-intact host	- Acute fibrinous and organizing pneumonia - Aspiration syndromes, with or without obliterative bronchiolitis - Diffuse alveolar damage and acute interstitial pneumonia - Drug reactions - Eosinophilic pneumonia - Exogen allergic alveolitis, hypersensitivity pneumonitis - Infectious/post-infectious processes, with or without bronchiolitis obliterans

			- Occupational lung diseases and pneumoconioses - Organizing pneumonia, cryptogenic (COP, former idiopathic BOOP) or secondary (OP) - Radiation lung injury - Respiratory bronchiolitis interstitial lung disease (RB-ILD) - Swyer-James-syndrome - Toxic inhalation, with or without obliterative bronchiolitis
B3	DPLD in the immunocompro-mised or transplanted host	DPLD characteristic for and developing only in the presence of specific immune dysfunctions or transplantation-related immune processes	- Diffuse lung damage of unknown etiology - Infections, due to antibody deficiencies - Infections, due to phagocyte defects - Infections, due to T cell deficiencies - Infections, miscellaneous - Nonspecific interstitial pneumonia (NSIP) - Related to therapeutic intervention, with or without obliterative bronchiolitis - Related to transplantation and rejection, with or without obliterative bronchiolitis
B4	DPLD related to lung vessels structural processes	DPLD disorders due to dysfunctional structural components of the pulmonary veins, arteries, capillaries or lymphatics. Involvement of systemic or other organ vessels is absent or marginal.	- Pulmonary hypertension, primary or secondary - Congestive changes related to cardiac dysfunction - Idiopathic pulmonary hemosiderosis (IPH) - Lymphatic disorders - Pulmonary capillary hemangiomatosis - Pulmonary hemorrhage, idiopathic or due to infection - Veno-occlusive disease
B5	DPLD related to reactive lymphoid lesions	DPLD due to non-malignant disorders affecting lymphocyte numbers and functions in the lungs	- Follicular bronchitis/bronchiolits - Giant lymph node hyperplasia (Castleman´s disease) - Intrapulmonary lymph nodes - Lymphocytic interstitial pneumonia (LIP) - Nodular lymphoid hyperplasia of the lung
Bx	Unclear Respiratory Distress Syndrome in the non-neonate	DPLD disorders in children older than 30 days, after the exclusion of infection, heart disease or circulatory disorders, metabolic diseases, central or peripheral nervous system disorders	- familial

Suppl Fig 2



Routine work-flow used in the Kids lung register (KLR) to obtain a final working diagnosis and to categorize and subcategorize cases with suspected DPLD (black and red). The work-flow used for re-rating is depicted in red.
*reference pathologist was Frank Brasch, **genetical diagnosis was made by Peter Lohse and ***lavage report on surfactant protein analysis, as well as the establishment of the final working diagnosis during routine KLR workflow were done by Matthias Griese

Suppl. Table 2. Blinded and independent re-rating of a random sample of 100 DPLD cases from the kids-lung register. Only differences to the original categorization are indicated; empty cells indicate correct categorization.

		Kids-lung register (KLR) diagnoses and categorization		Blinded rater 1				Blinded rater 2			
ID	**KLR-ID**	**Category**	**Subcategory**	**Category**	**Reason for Error***	**Subcategory**	**Reason for Error***	**Category**	**Reason for Error***	**Subcategory**	**Reason for Error***
1	254	A1	Alveolo capillary dysplasia								
2	202	A1	Congenital alveolar dysplasia	A4	1	Diffuse Alveolar Damage and Acute Interstitial Pneumonia	1				
3	1863	A2	Pulmonary hypoplasia								
4	818	A2	Pulmonary hypoplasia	D	1	Congenital Bronchial Cartilage Deficiency	1				
5	422	A2	Pulmonary hypoplasia			Related to preterm birth (BPD-cLDI)	2b				
6	1400	A2	Related to chromosomal disorders	B1	2a						
7	491	A2	Related to preterm birth (BPD-cLDI)							Related to preterm birth (Wilson Mikity, new BPD)	4c
8	225	A2	Related to preterm								

			birth (BPD-cLDI)								
9	1448	A2	Related to preterm birth (BPD-cLDI)								
10	1891	A2	Related to preterm birth (BPD-cLDI)								
11	1404	A2	Related to preterm birth (Wilson Mikity, new BPD)	A4	2b	Diffuse Alveolar Damage and Acute Interstitial Pneumonia	2b			Related to preterm birth (BPD-cLDI)	4c
12	600	A2	Related to preterm birth (Wilson Mikity, new BPD)		4a	Related to preterm birth (BPD-cLDI)	4c				
13	544	A3	Chronic tachypnoe of infancy (CTI)	D	4a	Bronchiolitis obliterans	4a				
14	697	A3	Chronic tachypnoe of infancy (CTI)	B2		Infectious/post-infectious processes	4a				
15	1735	A3	Chronic tachypnoe of infancy (CTI)					D	4a	Bronchitis, chron. neutrophil (BAL)	4a
16	2469	A3	Chronic tachypnoe of infancy (CTI)			Neuroendocrine cell hyperplasia of infancy	1				
17	1641	A3	Chronic tachypnoe of infancy (CTI)								
18	2231	A3	Chronic tachypnoe of infancy (CTI)								
19	1610	A3	Chronic tachypnoe of								

			infancy (CTI)								
20	1909	A3	Chronic tachypnoe of infancy (CTI)								
21	2163	A3	Neuroendocrine cell hyperplasia of infancy			Chronic tachypnoe of infancy (CTI)	1				
22	1344	A3	Neuroendocrine cell hyperplasia of infancy								
23	687	A3	Neuroendocrine cell hyperplasia of infancy								
24	1703	A3	Neuroendocrine cell hyperplasia of infancy								
25	2152	A3	Neuroendocrine cell hyperplasia of infancy								
26	2316	A3	Neuroendocrine cell hyperplasia of infancy								
27	1831	A3	Pulmonary interstitial glycogenosis (PIG)								
28	627	A4	ABCA3 mutations 1							NSIP, cellular	2d
29	208	A4	ABCA3 mutations 2								
30	458	A4	ABCA3 mutations 2								
31	2202	A4	ABCA3 mutations 2								
32	1616	A4	Alveolar microlithiasis								
33	1900	A4	Chronic pneumonitis of infancy (CPI)			PAP, neonatal	1				
34	1916	A4	DIP	Insuff. data	3			Insuff. data	3		
35	251	A4	DIP					B1	2c	Drug reaction	2b
36	68	A4	DIP			PAP, sec. to	1				

						associated disease					
37	1859	A4	Lipoidpneumonitis, Cholesterol pneumonia								
38	227	A4	Lipoidpneumonitis, Cholesterol pneumonia								
39	1399	A4	Nkx21 gene defect								
40	507	A4	Nonspecific interstitial pneumonia (NSIP)							NSIP, cellular	1
41	2229	A4	Nonspecific interstitial pneumonia (NSIP)								
42	2066	A4	Nonspecific interstitial pneumonia (NSIP)								
43	2173	A4	Nonspecific interstitial pneumonia (NSIP)								
44	173	A4	PAP, adult NO GMCSF autoantibodies								
45	143	A4	PAP, adult with GMCSF autoantibodies								
46	163	A4	PAP, GATA2 mutation								
47	195	A4	PAP, GM-CSF-RA Mutation								

48	1787	A4	PAP, GM-CSF-RA Mutation								
49	629	A4	Surfactant protein B mutations								
50	336	A4	Surfactant protein C mutations								
51	240	A4	Surfactant protein C mutations								
52	1446	A4	Surfactant protein C mutations								
53	2064	A4	Surfactant protein C mutations								
54	599	Ax	Insuff. data								
55	717	Ax	No or very low SP-C biochemically	Insuff. data	3					Insuff. data	3
56	713	Ax	Pulmonary hypertension							Insuff. data	3
57	471	Ay	Insuff. data	Insuff. data	3						
58	468	Ay	No or very low SP-C biochemically	Insuff. data	3						
59	551	Ay	No or very low SP-C biochemically	A2	1	Related to preterm birth (BPD-cLDI)	1				
60	2073	B1	Hermansky-Pudlak Syndrome								
61	1509	B1	Immune-mediated/collagen vascular disorders			Diffuse alveolar hemorrhage due to vasculitic disorders	4c	B2	1	Related to therapeutic intervention	1

62	1795	B1	Langerhans cell histiocytosis								
63	2479	B1	M. Osler								
64	1649	B1	Rubinstein-Taybi-syndrome					A1	2a	Related to chromosomal disorders	2a
65	1343	B1	Sarcoidosis	Insuff. data	3						
66	1934	B1	Sarcoidosis								
67	1983	B1	Storage diseases	A4	2c	PAP, neonatal	2c				
68	284	B1	Storage diseases								
69	1579	B1	Wegener Granulomatosis								
70	692	B2	Aspiration syndromes	Insuff. data	3						
71	1688	B2	Eosinophilic pneumonitis					B1	1	Churg-Strauss Syndrome	1
72	233	B2	Eosinophilic pneumonitis								
73	264	B2	Exogen allergic alveolitis								
74	644	B2	Exogen allergic alveolitis								
75	1453	B2	Exogen allergic alveolitis								
76	1638	B2	Exogen allergic alveolitis								
77	1627	B2	Mac-Leod-Swyer-	D	4b	Bronchiolitis	4b				

			James-Syndrome			obliterans					
78	1920	B3	Diffuse lung damage of unknown etiology	Insuff. data	1			Insuff. data	1		
79	535	B3	Infections–Antibody deficiencies	D	4d	Infectious Bronchiolitis and Postinfectious Constrictive Bronchiolitis	4d				
80	1696	B3	Infections–Antibody deficiencies					D	4d	chronic Bronchitis	4d
81	721	B3	Infections–Antibody deficiencies								
82	1329	B3	Infections–T cell deficiencies							Infections–Miscellaneous	1
83	678	B3	Related to therapeutic intervention								
84	218	B3	Related to transplantation and rejection	Insuff. data	3						
85	1276	B3	Related to transplantation and rejection								
86	1577	B3	Related to transplantation and rejection								
87	1620	B3	Related to transplantation and								

			rejection								
88	1960	B4	Idiopathic pulmonary hemosiderosis			Pulmonary hemorrhage	2c				
89	1551	B4	Idiopathic pulmonary hemosiderosis								
90	1816	B4	Idiopathic pulmonary hemosiderosis								
91	1988	B4	Primary pulmonary hypertension due to Chr 2q33							Pulmonary hypertension	2d
92	1894	B4	Pulmonary capillary hemangiomatosis								
93	1419	B4	Pulmonary capillary hemangiomatosis								
94	306	B4	Pulmonary capillary hemangiomatosis								
95	1665	B4	Pulmonary hypertension								
96	541	B5	Lymphocytic interstitial pneumonia (LIP)	B1	1	Immune-mediated/collagen vascular disorders	1				
97	346	B5	Lymphocytic interstitial pneumonia (LIP)							Follicular bronchiolitis	1
98	1679	B5	Lymphocytic interstitial pneumonia (LIP)								
99	732	D	cardiac cause	Ay	1					Bronchiolitis	1

										obliterans	
100	1494	F	Pneumonia from Pneumocystis								

*Reason for Error:

1 Reports not appreciated/read in detail (= true mistake of physician), 2 Poor knowledge of the classification rules, 3 Insufficient data on case, 4 Deficit of the classification system

Supplemental Table 3. Summary of reasons for incorrect categorization

	Blinded rater 1		Blinded rater 2	
	Category	**Subcategory**	**Category**	**Subcategory**
% non-correct categorizations	**20**	**18**	**8**	**16**
1 Reports not appreciated/read in detail (= true mistake of physician)	5	8	2	6
2 Poor knowledge of classification rules	3	4	2	4
Correct application of rules				
2a Related to chromosomal abnormality is A2, not B1	*1*	*0*	*1*	*1*
2b Choose more likely, although less specific classification	*1*	*2*	*0*	*1*
2c Select systemic disorder if there is any involvement of systemic structures instead of local pulmonary alone	*1*	*2*	*1*	*0*
2d Molecular result to be rated higher than histologic result	*0*	*0*	*0*	*2*
3 Insufficient data on case	8	0	2	2
4 Deficit of the classification	4	6	2	4
4a Differentiation of NEHI	*2*	*2*	*1*	*1*
4b Post infectious BO can also be classified as airway disease and if one-sided as Mac-Leod-Swyer-James-Syndrome	*1*	*1*	*0*	*0*
4c No precise diagnostic criteria for an entity available	*0*	*2*	*0*	*2*
4d DPLD in the immunocompromised host/transplanted needs differentiation from airway disease or obstructive bronchiolitis or bronchitis	*1*	*1*	*1*	*1*

Supplemental Table 4. Overall frequencies of diagnostics available for the establishment of the final working diagnosis, categorization and sub-categorization. Note that not all tests were performed in all patients.

	Category	N	Molecular genetics done	Chest CT done	Lung biopsy done	Lavage surfactant analysis done
A1	Diffuse developmental disorders	2	2	1	2	2
A2	Alveolarisation deficiencies	10	7	6	4	7
A3	Specific conditions of undefined etiology	15	9	14	10	7
A4	Surfactant dysfunction disorders	26	21	20	16	16
Ax	Unclear Respiratory Distress Syndrome in the mature neonate	3	2	0	1	1
Ay	Unclear Respiratory Distress Syndrome in the almost (30-36 weeks) mature neonate	3	2	1	2	2
B1	DPLD related to systemic disease processes	10	3	6	4	3
B2	DPLD in the presumed immune-intact host, related to exposures (infectious/non-infectious)	8	2	6	6	3
B3	DPLD in the immunocompro-mised or transplanted host	10	1	4	1	2
B4	DPLD related to lung vessels structural processes	8	3	3	5	2
B5	DPLD related to reactive lymphoid lesions	3	3	4	3	2
D	Airway disorders	1	0	1	0	1
F	Lung infections	1	0	1	0	1
	Sum	100	55	67	54	49

Supplemental Table 5. Centers and physicians contributing cases to the kids-lung-register

Adler	Fribourg	Switzerland
Ahrens	Hamburg	
Ahrens	Lübeck	
Ahrens	Darmstadt	
Albrecht	Essen	
Alfaré	Uster	Switzerland
Anani	Nürnberg	
Andree	Krefeld	
Ankermann	Kiel	
Armbruster	München	
Aschmann	Dresden	
Baden	Tübingen	
Barbato	Padova	Italy
Baretton	Dresden	
Barikbin	Berlin	
Barker	Berlin	
Bauer	Essen	
Bendstrup	Aarhus	Denmark
Berger	Luzern	Switzerland
Bernet-Büttiker	Zürich	Switzerland
Bewig	Kiel	
Boelke	Villingen-Schwenningen	
Bohnhorst	Hannover	
Borie	Paris	France
Bosch	Karlsruhe	
Bösing	Bielefeld	
Boske	Tuebingen	
Bouikidis	Essen	
Brand	Frankfurt	
Brasch	Bielefeld	
Braun	Erfurt	
Brcic	Zagreb	Croatia
Briassoulis	Heraklion	
Brodt	Frankfurt	
Buchenroth	Bonn	
Buchvald	Kopenhagen	Denmark
Campo	Pavia	Italy
Casaulta	Bern	Switzerland
Chevret	Le Kremlin Bicetre	France
Corbelli	Geneve	Switzerland
Costabel	Essen	
De Blic	Paris	France
Delbeck	Krefeld	
Deppermann	Erfurt	
Di Rocco	Genoa	Italy
Dick	Rendsburg	
Donato	Strassbourg	France
Dötsch	Köln	
Ebbecke	Lingen	
Eberle	Zürich	Switzerland
Egermann	München	
Elnazir	Dublin	Ireland
Enaud	St. Pierre	La Réunion
Engelhardt	Landshut	
Erler	Dortmund	
Escribano	Valencia	Spain
Faas	Giessen	
Fanconi	Zürich	Switzerland
Felgentreff	Freiburg	
Firnhaber	Hamburg	
Förster	Hannover	
Freihorst	Aalen	
Freisinger	Reutlingen	
Frommhold	Heidelberg	
Fuchs	Ulm	
Gappa	Hannover	
Gappa	Wesel	
Garhammer	München	
Gascon	Frankfurt	
Gerein	Frankfurt	
Gerstlauer	Augsburg	
Gesierich	Gauting	
Giese	Berlin	
Glöckler	Erlangen	
Goelz	Tübingen	
Gortner	Homburg	
Griese	München	
Gröbner	Linz	Austria
Groebel	Detmold	
Grolle	Hamburg	
Große-Onnebrink	Essen	

Grychtol	Freiburg	
H.Vier	Leipzig	
Hammer	Basel	Switzerland
Hampel	Regensburg	
Hansen	Hannover	
Hanssler	Essen	
Härtling	Freiburg	
Hartmann	Erlangen	
Hecht	Frankfurt	
Hermon	Wien	Austria
Herren	Bern	Switzerland
Herrmann	Sankt Augustin	
Hinrichs- alt	Hamburg	
Hofer	Winterthur	Switzerland
Höhn	Düsseldorf	
Holbe	Berlin	
Holzinger	München	
Hoppe	Köln	
Huber	Zürich	Switzerland
Hülskamp	Münster	
Hünseler	Köln	
Huttegger	Salzburg	Austria
Hutten	Amsterdam	Netherlands
Illing	Stuttgart	
Irani	Aarau	Switzerland
Irnstetter	München	
Jong de	Amsterdam	Netherlands
Jung	Kiel	
Junghänel	Köln	
Kaiser-Labusch	Bremen	
Karen	Tuebingen	
Kehm	Hemer	
Kemen	Hamburg	
Kitz	Frankfurt am Main	
Klaer Hlawetsch	Mainz	
Kleinert	Berlin	
Knol	Amsterdam	Netherlands
Köhler	Schmallenberg	
Kopp	Freiburg	
Körner-Rettberg	Bochum	
Korsch	Köln	
Köster	Oldenburg	
Kramer	Maastricht	Netherlands
Krause	Kiel	
Kremers	Aalen	
Kriebel	Göttingen	
Kristensen	Kopenhagen	Denmark
Krüger	Freiburg	
Kühr	Karlsruhe	
Kumpf	Tübingen	
Kunde	Osnabrück	
Kunzmann	Würzburg	
Lange	Göttingen	
Lange	Bonn	
Langenhorst	Salzburg	Austria
Langlitz	Iserlohn	
Lasch	Bremen	
Latzin	Basel	Switzerland
Lau	Berlin	
Laux	Hamburg	
Lebecque	Brussels	Belgium
Leis	Erlangen	
Lemke	Hamburg	
Lenzana Fernandez	Mexico D.F.	Mexico
Lex	Halle	
Lieb	Frankfurt am Main	
Lingenbauer	Hamburg	
Littek-Rottmann	Lemgo	
Litterst	Hemer	
Lohse	Singen	
Luisetti	Pavia	Italy
Magdorf	Berlin	
Mahlert	Oldenburg	
Maier	Bern	Switzerland
Mannfeld	Augsburg	
Manzke	Neubrandenburg	
Matasova	Martin	Slovakia
Mayr	Memmingen	
Merz	Darmstadt	
Meyer	Homburg	
Miera	Berlin	

Mildenberger	Mainz	
Mornand	Genf	Switzerland
Mostafa	Wien	Austria
Muench	München	
Nachbaur	Wien	Austria
Nährlich	Giessen	
Nielsen	Arhus	Denmark
Niesytto	Greifswald	
Nöh	Worms	
Nüßlein	Bochum	
O'Brien	Long Beach, CA	USA
Ocker	Stuttgart	
Ollerieth	Wien	Austria
Omran	Münster	
Oppermann	Erlangen	
Ott	Münster	
Perez Gallofre	Escalades	Andorra
Peros-Golubicic	Zagreb	Croatia
Petri	Neunkirchen	
Pfleger	Graz	Austria
Pilgrim	Luzern	Switzerland
Pin	Grenoble	France
Pinheiro	Barga	Portugal
Poplawska	Mainz	
Pöschl	Heidelberg	
Prenzel	Leipzig	
Probst	Freiburg	
Stehling	Essen	
Steinhagen	Wuppertal	
Proesmans	Leuven	Belgium
Pross	Stuttgart	
Ramalho	Lisboa	Portugal
Rau	Hannover	
Reinhard	Mannheim	
Reitz	Berlin	
Renner	Neuburg/Donau	
Reverdin	Genf	Switzerland
Richter	Hannover	
Riedel	Hamburg	
Riedler	Schwarzach im Pongau	Austria
Rietschel	Köln	
Rigourd	Paris	France
Rochat-Guignard	Lausanne	Switzerland
Rodeck	Osnabrück	
Rodriguez Becerra	Sevilla	Spain
Rollow	Dresden	
Romano	Paris	France
Rose	Frankfurt	
Rosenthal	London	England
Roth	Köln	
Rücker	München	
Ruf	Mannheim	
Runge	Wuppertal	
Rupprecht	Zollikerberg	
Ruß	Köln	
Saadi	München	
Wiebe	Sankt Augustin	
Wiebel	Heidelberg	
Sanen	Leuven	Belgium
Sauerbrey	Erfurt	
Saur	Aalen	
Schäfer	Hamburg	
Schaible	Mannheim	
Schebeck	Kassel	
Schelstraete	Gent	Belgium
Schenk	Augsburg	
Schindera	Karlsruhe	
Schindler	Regensburg	
Schirmer-Zimmermann	Nürnberg	
Schmitt-Grohé	Bonn	
Schneider	Frankfurt	
Schoor van der	Amsterdam	Netherlands
Schröder	Lüneburg	
Schroten	Mannheim	
Schroth	Erlangen	
Schuerman	Amsterdam	Netherlands
Schulze	Frankfurt	
Schuster	Düsseldorf	
Schwerk	Hannover	
Seidenberg	Oldenburg	
Silwedel	Würzburg	
Singer	Hamburg	
Slot	Amsterdam	Netherlands
Sommerburg	Heidelberg	
Stanzel	Gauting	
Steiß	Giessen	
Stengel	Aalen	

Stocker	Luzern	Switzerland
Stöhring	Berlin	
Störmann	Osnabrück	
Stumpner	Eschwege	
Teig	Bochum	
Teschler	Essen	
Thomas	Würzburg	
Ueköter	Münster	
van de Loo	Amsterdam	Netherlands
van Dellen	Amsterdam	Netherlands
van Kaam	Amsterdam	Netherlands
Varnholt	Berlin	
Vierzig	Köln	
Vogelberg	Dresden	
Vollmann	Neuwied	
von der Hardt	Hannover	
von der Thüsen	Amsterdam	Netherlands
Weckelmann	Wuppertal	
Weis	Koblenz	
Weitzdoerfer	Wien	
Wellmann	Basel	Switzerland
Welzing	Köln	
Werner	Münster	
Welzing	Köln	
Werner	Münster	

Wildhaber	Zürich	Switzerland
Willasch	Frankfurt	
Wintgens	Moenchengladbach	
Wittekindt	Frankfurt	
Woitsch	München	
Wolff	Mannheim	
Yalcin	Ankara	Turkey
Zeidler	Bonn	
Zielen	Frankfurt	
Zimmer	Gießen	
Zimmermann	Erlangen	