ORIGINAL ARTICLE

International management platform for children's interstitial lung disease (chILD-EU)

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ABSTRACT

Background Children's interstitial lung diseases (chILD) cover many rare entities, frequently not diagnosed or studied in detail. There is a great need for specialised advice and for internationally agreed subclassification of entities collected in a register. Our objective was to implement an international management platform with independent multidisciplinary review of cases at presentation for long-term follow-up and to test if this would allow for more accurate diagnosis. Also, quality and reproducibility of a diagnostic subclassification system were assessed using a collection of 25 complex chILD cases.

Methods A web-based chILD management platform with a registry and biobank was successfully designed and implemented.

Results Over a 3-year period, 575 patients were included for observation spanning a wide spectrum of chILD. In 346 patients, multidisciplinary reviews were completed by teams at five international sites (Munich 51%, London 12%, Hannover 31%, Ankara 1% and Paris 5%). In 13%, the diagnosis reached by the referring team was not confirmed by peer review. Among these, the diagnosis initially given was wrong (27%), imprecise (50%) or significant information was added (23%). The ability of nine expert clinicians to subcategorise the final diagnosis into the chILD-EU register classification had an overall exact inter-rater agreement of 59% on first assessment and after training, 64%. Only 10% of the 'wrong' answers resulted in allocation to an incorrect category. Subcategorisation proved useful but training is needed for optimal implementation.

Conclusions We have shown that chILD-EU has generated a platform to help the clinical assessment of chILD.

Trial registration number Results, NCT02852928.

Key messages

What is the key question?
Can an international management platform for children's interstitial lung disease (chILD) with independent multidisciplinary review be implemented and is the diagnostic subclassification reproducible?

What is the bottom line?
Well-functioning, web-based multidisciplinary teams were successfully set up and significantly changed 13% of the diagnoses submitted by paediatric pneumologists. Subclassification by review-teams proved useful although training in implementation is needed.

Why read on?
So you can learn how the system works and use it in the future.

INTRODUCTION

Children's interstitial lung diseases (chILD) is an umbrella term covering many rare conditions, frequently not diagnosed because the presentation is non-specific; and many entities which are ill-defined or poorly studied. Chest imaging shows diffuse abnormalities and age-appropriate lung function tests are abnormal. The incidence of these rare diseases in Europe is 0.5 to 1 cases in 100.000. In the UK and Ireland, prevalence was estimated as 3.6 per million children[1] and in Germany at 1.32 new cases per 1 million children/year.[2] Prevalence and incidence is likely greatly underestimated due to misdiagnosis, lack of an ICD code allowing hospital based estimates of cases and the absence of a common register. Extrapolation to Europe (about 500 million people, 80 million children<14 years) suggests there are about 2000 known cases and an incident case rate of more than 100 per year. The overall mortality in childhood is around 15%.[2] There are no evidence-based treatments for any of the diseases.[3]

The experiences of physicians, as well as the relatives and the patients, who often have been through a real diagnostic odyssey, show that these patients often do not receive optimal care.[4] Progress is also
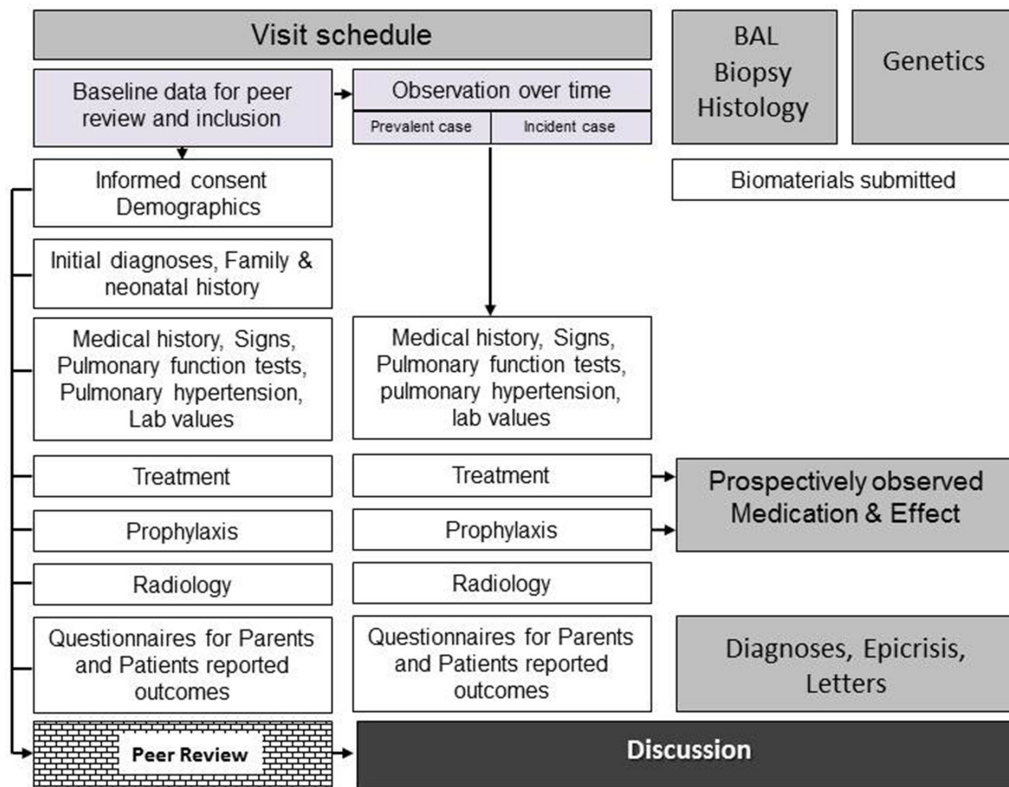
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Figure 1 Management platform. BAL, bronchoalveolar lavage.

very slow because of lack of technical resources for obtaining second opinions in complex individual cases and the absence of the sort of large, well-characterised cohorts which are essential for the conduct of randomised clinical trials. In paediatric oncology similar problems were solved decades ago as registries for diagnosis, systematic treatment plans and sufficient financial support were established.[5] In paediatric respiratory medicine, cystic fibrosis has led the way from simple registries to the establishment of clinical trial networks.[6] Networks have also been established for primary ciliary dyskinesia.[7]

In chILD, there is a pressing need for both specialised diagnostic advice from international experts because of the rareness of individual diagnoses and services to provide local care and therapy. Our objective was to implement an international management platform with independent multidisciplinary review of cases at presentation for long-term follow-up, to test if this would allow for more accurate diagnosis and thus provide structures for randomised controlled trials of treatment and translational studies. We here describe how we made such a platform and the chILD cases accumulated over a 3-year period. The outcomes from an expert review process are reported, together with assessment of the intraobserver consistency of expert reviewers, to help identify training requirements for clinical experts. We intend that this report will serve as a model for others setting up registries and biobanks across Europe in other diseases and disciplines.

METHODS
Rationale and need for the chILD register
The international registry for chILD was established to fill the previously unmet need of an international platform to systematically collect data from paediatric patients and allows all groups of professional and private stakeholders to participate in the care of patients with chILD. The registry governance fulfils the widely varying legal, data protection and ethical requirements across Europe, without compromising access to the data.

Eligibility criteria, consent and ethical approval
Patients are identified by their local physicians, who can register as participants in a referring centre. Any referring centre needs to ensure compliance with all necessary contractual legal and ethical requirements. The central register support team assists throughout this process. Each patient and/or caregiver gave respectively age-appropriate assent and written informed consent before any data were entered. The register and biobank study was approved by the responsible external lead ethics board, the Ethical Review Committee of the Ludwig-Maximilians University Munich, Germany (EK 111–13). The data safety protection processes of the register and biobank was approved by the Telematic Platform, an organisation for networked medical research. chILD was defined as entities originating from abnormalities of components of the lung parenchyma, which include the alveolar epithelium, vascular endothelium, interposed connective tissues and more centrally, the peribronchiolar and peribronchial tissues; airways may be involved as a secondary process.[8] chILD was suspected if there were (1) respiratory symptoms/signs such as cough, tachypnoea or dyspnoea at rest or with exercise, crackles, retractions, clubbing, failure to thrive, respiratory failure, (2) systemic arterial hypoxemia, (3) diffuse radiological abnormalities and if both feasible and available (4) abnormalities in pulmonary function testing, usually for a minimum duration of 4 weeks, but shorter in cases of acute severe chILD (usually neonatal onset), in accord with standard practice.[9 10] We included all suspected chILD.[11] A case not confirmed as chILD after peer review could be followed as a disease control. All patients included were prospectively and longitudinally followed. Baseline was the time of inclusion into the register; both prevalent cases which were already under
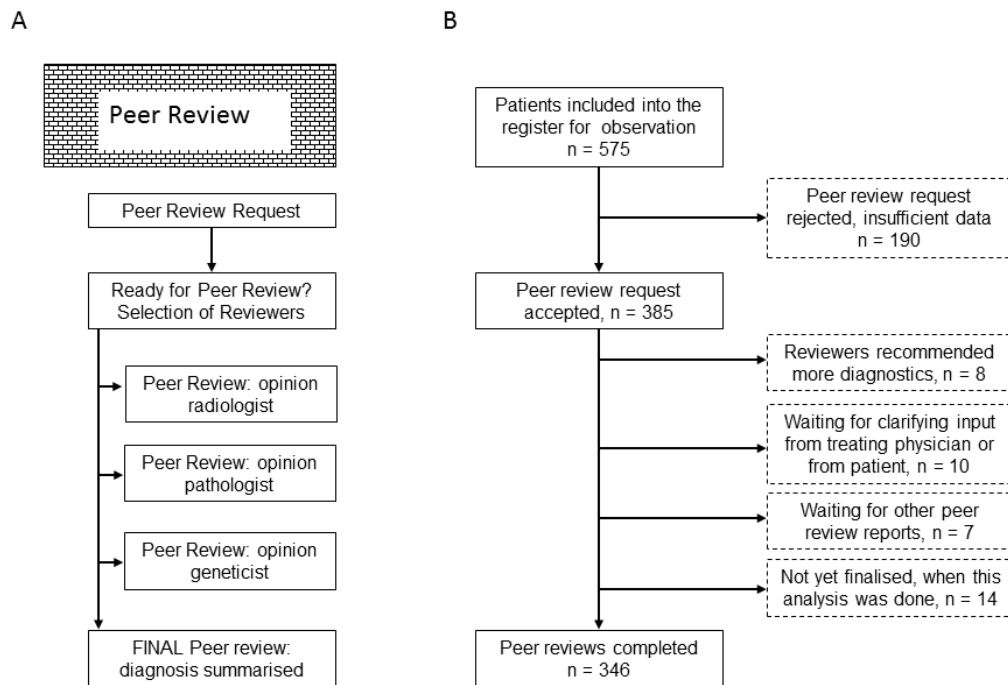
Figure 2 Peer review process in the chILD-EU register. (A) On peer review request by the local site physician, completeness of data is checked and if so, peer reviewers are selected and asked via emails from the system to start reviewing. The clinician peer reviewer prepares and presents the case in a common meeting, either in person or web-based with shared screen in internationally composed multidisciplinary teams. After completion, the clinician peer reviewer generates a final peer reviewer (working) diagnosis and subcategorises the diagnosis. The local site physician is informed via a mailing from the system about the conclusion of the review. (B) Consort diagram detailing patient flow during peer review process.

review at the inception of the platform and incident, newly diagnosed cases were followed. During follow-up, suitable patients with chILD in the register study were eligible to enter randomised controlled trials set up in the Secutrial database, if consent was given.

Minimal dataset and workflows of operation

Cases were entered into the register using minimal dataset (generation and database dictionary (see online supplementary file 1 and table s1), peer-reviewed, categorised[12] and followed over time. Automatic reminders were sent if follow-up was due. Communication on cases was strictly within the database using a discussion tool automatically embedding the local physician, the peer reviewers and additional experts if wished, in order to pool information without compromising security.
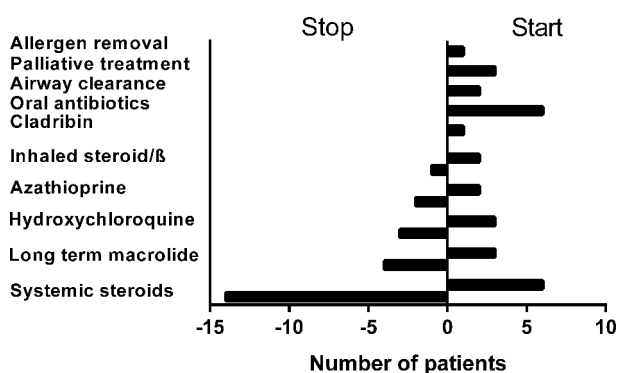

Figure 3 Changes in therapy observed after peer review in those 44 patients in whom the diagnosis was altered by peer review.

Data safety concept, database and biobank

In accord with best practice data protection (http://www.tmf-ev.de/EnglishSite/Home.aspx), there is an institutionally and

Table 1 Number of subjects included with country indicated and peer reviews done (status: 31 November 2016)

Country	Number of subjects included with country indicated	Country (%)	Final peer review done (n)	Peer reviews done (%)
Germany	243	42.3	158	65.0
Italy	22	3.8	10	45.5
Turkey	55	9.6	47	85.5
UK	103	17.9	65	63.1
France	41	7.1	19	46.3
Belgium	4	0.7	1	25.0
Brazil	2	0.3	1	50.0
Croatia	1	0.2	1	100
Denmark	9	1.6	8	88.9
Netherlands	2	0.3	1	50.0
Poland	28	4.9	23	82.1
South Africa	3	0.5	1	33.3
Spain	4	0.7	2	50.0
Switzerland	7	1.2	6	85.7
Austria	5	0.9	1	20.0
Serbia/Montenegro	1	0.2	0	0.0
Not indicated	45	7.8	2	4.4
All	575	100.0	346	60.2

Table 2 Results from the peer reviewing activities

	Number of cases	Percentage
No change from initial diagnosis to peer review diagnosis	302	87%
Change from initial diagnosis to peer review diagnosis	44	13%
Initial diagnosis was wrong=>corrected*	12	27%
Initial diagnosis was too general=>specified final diagnosis given†	22	50%
Initial diagnosis was incomplete=>relevant information added‡	10	23%
Time from peer review request until acceptance (days)	Median, mean (range)	1;30.5 (0–746)
Time from peer review acceptance until completion (days)	Median, mean (range)	37;67.5 (0–803)

Complete changes from peer-review are listed in Tab S3; typical examples are:
*'Postinfectious bronchitis obliterans' was changed to 'Neuroendocrine cell hyperplasia of infancy'.
†'Interstitial lung disease 'was specified as 'Cellular non-specific interstitial pneumonitis due to SFTPC mutation'.
‡'Alveolar capillary dysplasia without misalignment of the pulmonary veins' was changed to 'Alveolar capillary dysplasia without misalignment of the pulmonary veins and associated pulmonary interstitial glycogenosis PIG'.

organisationally separated storage of identifying (IDAT) and medical data (MDAT) (see online supplementary figure s1). The processing of the pseudonymised medical data is using Secu-Trial, which is US Food and Drug Administration (FDA)-compliant and is concordant with good clinical practice rules. An additional SecuTrial-database for managing biomaterials is the central biobank at Munich University Hospital (see online supplementary figure s2).

Quality control

The register manager and register physicians carefully audit data completeness and score the quality of imaging and histological studies. Early in the project, the standards working group generated consensus-agreed diagnostic and management clinical guidelines.[13] Due to shortage of resources, no source data verification is currently in place. In addition to immediate individual feedback to the centres via the national coordinator, annual reports are generated for each centre and the register.

Peer review

A central novel element of the register was the involvement of a multidisciplinary team review board. Although this is routine in adult ILD,[14] until now this has not been routine in Europe in chILD. The goal of peer review was to give advice on diagnosis and differential diagnosis, to ensure adherence to diagnostic standards set previously,[13] to have a case review independent of the submitting centre, to use a harmonised categorisation system[12] and to come up with a final working diagnosis. Peer review teams were composed of a respiratory paediatrician, a paediatric radiologist and pathologist; if necessary, a geneticist was also consulted. The teams were constituted first on a national basis to establish the workflow within the management platform and then rolled out as an international resource. For online training, Skype conferences with shared screen features were organised. Peer review was started as soon as all relevant clinical data, imaging (see online supplementary file 1) and histology glass slides were available for the reviewers.

To assess the skills of categorisation of the final working diagnosis by clinicians, we randomly selected 25 chILD cases (from the first 312 cases peer-reviewed) with a pulmonary and non-pulmonary diagnosis to be allocated to one of five given subcategories (see online supplementary table s2). The correct selection was determined by a group of three paediatric pneumologists who were very familiar with the categorisation system and strictly adhered to the previously set up categorisation rules.[12] The test took about 30–45 min. Nine paediatric pneumologists with long-standing experience and interests in chILD were asked to subcategorise, and this test was repeated after 3 months. In between, a video and interactive training 'How to categorise chILD' was used for teaching.

RESULTS

Register design—how the chILD-EU management platform works

After registration of the local physician, an educational and interactive training session is undertaken. When familiar with the system, the physician or coordinator enters the web-based site to set up a new patient and enter the minimal dataset necessary for peer review. This includes a structured referral letter and imaging. Individual support for data entry by the central registry is offered. Great care is taken to pseudonymise uploaded letters and reports, and radiological images are automatically pseudonymised during upload (see online supplementary figure s1).

Baseline data include the entire past clinical course of the patient until entry into the database (figure 1, left column). chILD-specific patient reported outcomes were developed and validated and together with developmentally adapted versions for different age groups now available on the chILD platform in different languages (for details, see online supplementary file 1) as is information on health-economic status. Data obtained on a single occasion, such as biopsy, lavage and genetics, and prospective observations of specific treatments are entered separately (figure 1, right column). Information is exchanged and saved between local physician, data manager and peer reviewer via emails dispatched from the system and a discussion panel. Following review, diagnosis and categorisation (see below), the patient is observed prospectively over time with entry of a limited dataset (figure 1, middle column).

Material sent for central biobanking is indicated in the patient dataset with a collection number, so that local physician can track material associated with each subject. Site staff at central biobank record what has been sent with a collection identifier, so they can track materials. Biomaterials are entered into the separately run biobank. The material remains the property of the patient and/or family all the time.

Enrolment and demography

From January 2014 to November 2016, 575 patients (53% male) from 82 centres in 16 countries were enrolled in the database (table 1). The median age of the children at inclusion was 5.5 years (range 0–25; mean 7.0, SD 6.3) with an almost even distribution over time.

Peer review of cases to establish final working diagnosis, disease category and subcategory

When a peer review has been requested, the national coordinating team receives a message with an embedded link to the case, checks for completeness of data and materials and decides if the review process can be started or not (figure 2A). During the review meeting, the clinician presents the case using the referral letter; the images are demonstrated by the radiologists and the pathological review when relevant material is available is also presented. When

Table 3 Distribution of 346 subjects in the disease categories and subcategories of the chILD-EU register after peer review

Category	Subcategory/Diagnosis	Total	Percentage
A1—DPLD-diffuse developmental disorders		9	2.6%
	Alveolar capillary dysplasia with misalignment pulmonary vein	7	
	Congenital alveolar dysplasia	2	
A2—DPLD-growth abnormalities deficient alveolarisation		22	6.4%
	Related to preterm birth	11	
	Related to chromosomal disorders	8	
	Others	3	
A3—DPLD-infant conditions of undefined aetiology		64	18.5%
	Chronic tachypnoea of infancy (usual or aberrant)	30	
	Neuroendocrine cell hyperplasia of infancy	27	
	Pulmonary interstitial glycogenosis	5	
	Others	2	
A4—DPLD-related to alveolar surfactant region		77	22.3%
	ABCA3 mutations	18	
	SFTPC mutation	10	
	NKX2.1 mutations	3	
	NSIP	19	
	Pulmonary alveolar proteinosis	9	
	Others	18	
Ax—DPLD-unclear RDS in the mature neonate		5	1.4%
Ay—DPLD-unclear RDS in the almost (30–36 weeks) mature neonate		9	2.6%
B1—DPLD-related to systemic disease processes		54	15.6%
	Sarcoidosis	12	
	Idiopathic pulmonary haemosiderosis	6	
	Storage diseases	4	
	Immune-mediated/collagen vascular disorders	4	
	Familial dysautonomia	3	
	Filamin A mutation	3	
	Langerhans cell histiocytosis	3	
	GPA—Granulomatosis with polyangiitis (Wegener)	3	
	Others	16	
B2—DPLD-in the presumed immune intact host, related to exposures (infectious/non-infectious)		46	13.3%

Continued

Table 3 Continued

Category	Subcategory/Diagnosis	Total	Percentage
	Infectious/postinfectious processes	17	
	BO	14	
	Exogen allergic alveolitis/hypersensitivity pneumonitis	7	
	Others	8	
B3—DPLD-in the immunocompromised host or transplanted		15	4.3%
	NSIP	4	
	BO	3	
	Related to transplantation and rejection	3	
	Others	5	
B4—DPLD-related to lung vessels structural processes		16	4.6%
	Pulmonary haemorrhage	8	
	Pulmonary hypertension	5	
	Others	3	
B5—DPLD-related to reactive lymphoid lesions		4	1.2%
	Lymphocytic interstitial pneumonia	3	
	Others	1	
Bx—DPLD-unclear RDS in the NON-neonate		1	0.3%
By—DPLD-unclear NON-neonate		5	1.4%
Bz—DPLD		1	0.3%
C1—localised, congenital gross structural abnormalities of the lungs		6	1.7%
C2—localised, acquired gross structural abnormalities of the lungs		0	0%
D—Airway disorders		12	3.5%
	Chronic bronchitis	7	
	Others	5	

Cases of chronic tachypnoea of infancy (usual or aberrant) had no biopsy and were defined as described previously;[16] cases were only labelled 'Neuroendocrine cell hyperplasia of infancy' if there was proof by biopsy and concordant clinical symptoms. Details on the classification system and definitions used are given in the supplement of Griese *et al*.[12]

BO, bronchiolitis obliterans; DPLD, diffuse parenchymal lung diseases; NSIP, non-specific interstitial pneumonitis; RDS, respiratory distress syndrome.

needed, genetic advice is also taken. After discussion, the lead clinician summarises the diagnosis, categorises the case and concludes the peer review. An automatic message informs the site physician about the result and further recommendations.

Results from peer reviewing by multidisciplinary review teams

Of the 575 patients included into the register for observation, 190 patients had insufficient data precluding the start of the peer review. In 385 patients, peer review requests were accepted, 39 could not be finalised due to information for which the reviewers
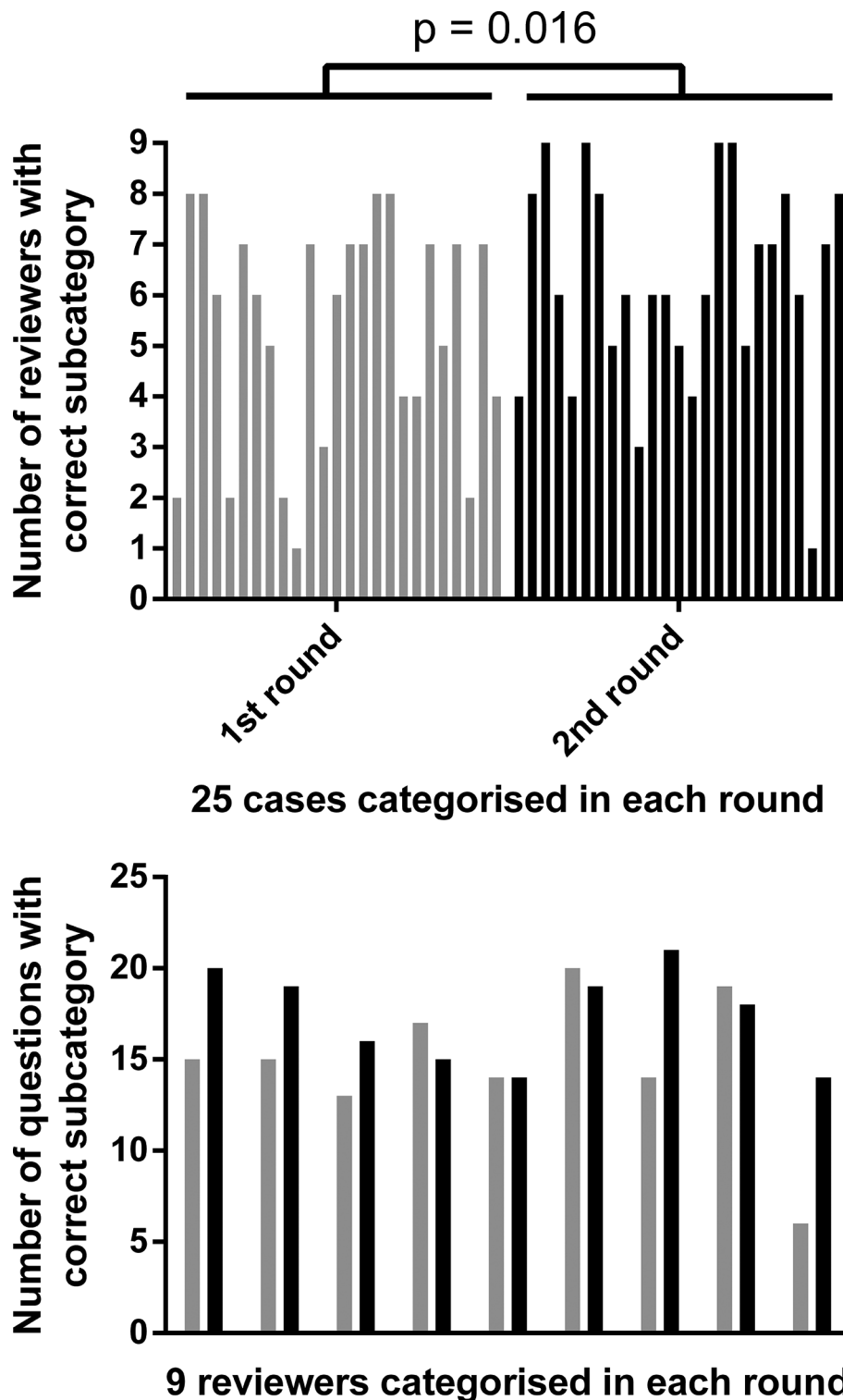
Figure 4 Selection of the correct subcategory from a panel of five suggestions each for 25 final working diagnoses by nine experienced paediatric clinical peer reviewers (see also online supplementary table s2). The upper panel shows the correct reviewers by question 1 to 25 in the first and second rounds. The latter was done after training using a video tutorial, web-based email-discussion of open issues and a personal meeting. The lower panel shows the responses of the individual peer reviewers before and after training. Responses of first and second round were compared by 2-sided paired t-test. The lower panel shows the responses of the individual peer reviewers before and after training.

asked but was not forthcoming (figure 2B) and a total of 346 peer reviews completed. These were done by teams in Munich (n=176; 51%), London (n=43, 12%), Hannover (n=107, 31%), Ankara (n=2; 1%) and Paris (n=18; 5%). Forty-six per cent of the cases had genetic testing (in 13%, a final genetic diagnosis was made) and 43% a histopathology sample at the time of peer review. Both were not required for review, but may be recommended by the reviewers. In 87%, the initial diagnosis given by the submitting paediatric pneumologist was confirmed by peer review (table 2). Among the 44 cases with their diagnosis altered by peer review, the diagnosis was wrong in 27%, in 50% it was too general and in 23% significant information

Box 1 Practical advice from lessons learnt during work with the management platform

All participants
- ► Do not start peer review until all necessary information and materials on a case are collected
- ► Do not expect even after training that ability to work with the database is sustained without participants using it regularly
- ► Strictly keep communication on cases within the management platform
- ► Training in relatively complex procedures like uploading imaging should only be done in central/national sites, as technical details to be solved (eg, hospital firewalls) may otherwise be too time-consuming.
- ► Plan extensive time for local ethics applications and other local centre processes if a randomised controlled trial is contemplated
- ► Practical support to enter data should be supplied centrally including upload of imaging, digitising of letters, cutting of wax blocks, staining slides, upload of scans, shared screen guided support lessons, double entry of quality of life and other questionnaires and so on.

Peer reviewer/national coordinator
- ► Organisation of regular local conference sessions using active cases
- ► Explanation and exercises using the categorisation system
- ► Data manager and auditing staff
- ► Build a personal relation with site staff
- ► Always offer training and help regarding all aspects of the register
- ► Constantly collect, document and optimise (screenshot, explanation, suggested solutions) problems faced when working with the database

was added (table 2) (for detailed cases, see online supplementary table 2). The respecification of the diagnosis from peer review in conditions categorised as chILD occurring primarily in infancy ('A' groups in online supplementary table s3) was mainly due to knowledge from pathology review (20 of 44 cases) and genetics (seven cases), whereas in chILD conditions occurring at all ages ('B' groups in online supplementary table s3) radiological imaging and clinical review had the biggest impact. The age distribution of the children peer-reviewed had an initial peak in the first 2 years of life and an almost even distribution towards early adulthood (see online supplementary figure s3). Although changes in therapy were usually not recommended by peer review, we observed changes made in the majority of cases with an altered diagnosis (figure 3 and online supplementary table s3).

Overall, the spectrum of chILD categories and subcategories observed was broad, the majority of the patients coming from conditions more prevalent in infancy, that is, categories A3 and A4 and DPLD-related to systemic disease processes (table 3). The times to peer review acceptance and to peer review completion was very variable, which was mainly due to the need to retrieve missing information and communication delays (table 2). Some of the cases peer-reviewed entered the randomised controlled trial on hydroxychloroquine run by this platform (see online supplementary file 1).

Ability of clinicians to subcategorise the final working diagnosis in the classification system used by the chILD-EU register

This was tested in a collection of 25 complex chILD cases. In the first round, none of the cases was subcategorised correctly by any of the nine experts, whereas in the second round and after training there was a significant improvement of correct categorisation (figure 4, upper panel). The overall exact agreement of the nine experts in the first round was 59% (free marginal kappa 0.19) and in the second round 64%. This seems to be a relatively low inter-rater agreement; however, it must be considered that of the 225 (25×9) answers received, for example, in first round, a total of 54 were incorrect of which 23 (10% of all answers) resulted in allocation to a false category and 31 merely in a wrong subcategory.

The many other important lessons which we have learnt during the project are listed in box 1.

DISCUSSION

Here, we report details on the successful design and implementation of a web-based chILD management platform. We showed that it was feasible and practical to develop a European registry and biobank based for independent and multidisciplinary review of chILD, leading to protocolised follow-up and the setting up of randomised controlled trials. Our experiences may be a useful model for those setting up registries and biobanks across Europe in other fields. Specifically, we also detail the results on the subclassification of chILD diagnoses, the consequences of peer reviewing and the spectrum of the cases accumulated over a 3-year period.

The chILD-EU project has linked national, European and international respiratory and general paediatricians, patients and parents groups, radiologists, pathologists, geneticists, translational and clinical scientists. The platform is an open resource for interested individuals and institutions. We have proposed diagnostic pathways of chILD[13] which were implemented here, and we have established and harmonised peer review to actively help participating physicians with the diagnosis and treatment of their cases. In 44 cases, the diagnosis was altered by peer review and substantial changes in treatment were observed. Making a correct and independently peer–reviewed final working diagnosis in rare diseases is of importance for several reasons. First, the treating local physician may receive help or guidance during the diagnostic work-up, which may translate into more appropriate treatment. Second, both the physician and the family are reassured; these conditions are so rare that even big centres will not see enough always to be confident, and sharing cases can increase expertise across Europe. This may have important psychosocial and prognostic consequences. Third, for the register and biobank, it is of great importance to have a reliable diagnosis and categorisation, to allow specific long-term follow-up and ensure only children with an appropriate diagnosis are entered into randomised controlled trials. Here, we have organised for the first time an easily accessed system tapping in to international expertise and described the activities since inception. The biggest hurdle for peer review is the local site physician who frequently lacks the time and resources to complete cases which were partially submitted, as indicated by the 190 patients with insufficient data precluding the start of the peer review. Although for the majority of cases the initial working diagnosis was confirmed by peer reviewers, there were significant changes of the final working diagnosis in nearly one in seven cases (see online Supplementary table s3), underpinning

the pivotal role of peer review in paediatrics, as for adults with diffuse parenchymal lung disease.[14] Future studies will address the reproducibility and precision of making the working diagnosis in chILD by multidisciplinary paediatric teams.

Categorisation and subcategorisation of a diagnosis is of great importance for any systematic register. Based on our previous local assessment of the reliability in chILD diffuse parenchymal disease and an average correct rate of 87%,[2] we were not surprised by the relatively low rate of correct categorisation (72%) obtained from a large group of nine untrained experts. The number of cases put by individual reviewer into a wrong category was low (10%). Nevertheless, in subcategorisation, a diagnosis is sometimes difficult and this needs to be further harmonised and practiced by the teams.

We are now studying the natural history of patients with chILD and will describe frequencies and variability of end-points such as clinical scoring, pulmonary exacerbations,[15] medication usage, hospitalisation rates, costs of care and quality of life; this would be impossible without this sort of platform. Importantly, we have commenced the first ever randomised, placebo-controlled interventions in chILD after overcoming all administrative hurdles in Germany and started to recruit peer-reviewed cases (www.childeu.net, see online supplementary file 1). We have a unique collective experience and have learnt many lessons in the day-to-day practicalities of running a register and biobank (see box 1).

chILD are difficult to study because nomenclature varies in a group of more than 200 entities, all of which are rare. Although diffuse parenchymal disease may more correctly describe the entities included, we adopted the acronym chILD in line with the statement of the American Thoracic Society in 2013.[9] The chILD-EU project introduced the term in Europe and increased the awareness of chILD. The interaction between professionals and family groups across Europe has perhaps been the most important result of this initiative. Also of importance is the support of the growing chILD-EU group by the European Respiratory Society establishing a Clinical Research Collaboration and the European Union by the COST Action CA16125. Long-term follow-up of a large cohort of patients with chILD to learn about the natural history will be a major challenge in the future. Hurdles include access to funding to support clinicians faced with a big daily workload to ensure high-quality data continue to be entered into the register. Furthermore, the large administrative hurdles are a major barrier to investigator-initiated studies in rare diseases in Europe (see online supplementary discussion).

Taken together, the FP7 project chILD-EU has generated a solid basis for the comprehensive study of paediatric interstitial lung diseases. The platform is a stepping stone for future work. Many new tools were made available to improve the care of individual cases. Collectively, data are generated to describe simple and complex end-points, medication usage, and some centres were opened to perform randomised placebo-controlled interventions in chILD. In the future, much more diverse activities are envisioned including basic and translational mechanistic studies, epidemiological investigations and teaching activities, all of which would be impossible without a central registry.

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Online supplement

An International Management Platform for Children´s Interstitial Lung Disease (chILD-EU)

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Methods

<u>Brief history</u>

The nucleus for this project was a long-standing scientific cooperation of the participants in the European Respiratory Society chILD-working group, which works in close cooperation with the US and Australasian chILD working groups. The award of the chILD-EU (FP7-305653) project (December 2012 to November 2016) stimulated the initiation of this international platform, starting with 10 academic partners from 5 European countries and now including more than 80 clinical sites.

<u>Generation of items of the minimal data set and workflows of operation</u>

Consensus about the minimal data set necessary for a sufficiently in-depth description of chILD cases was obtained on the basis of the experience with the GOLDnet pediatric database of the kids lung register, the French Respirare system and the US-chILD database, which were all in a state of development around 2012. For each variable compromises were generated by the chILD experts and support groups during two 2-day face-to-face meetings and many web-based conferences, balancing the workload needed to enter data and the need for comprehensive information. A concise minimal data set was established and is appended as Supplemental Table S1. The structure of the registry was organized to reflect the workflow of baseline data collection, peer review, data collected only once and that collected repeatedly during the observation of the course of the disease, as newly diagnosed (incident, 4, 8, 12 weeks, 6 months, annually) or cases already known to the center (prevalent, 6 months, annually). Peer review was started, when necessary clinical data, imaging and (where relevant) histology slides were available for the reviewers. Cases were then followed over time; the newly diagnosed incident cases at 4, 8, 12 weeks, 6 months, then annually; cases

already known to the center, i.e. prevalent cases were re-studied after 6 months and then annually.

Data safety concept, data base and biobank

The data protection concept of the European management platform for children´s interstitial lung disease register (chILD-EU) is based on the generic data protection concepts of the Technologie- und Methodenplattform für die vernetzte medizinische Forschung e.V. (TMF) for the provision of treatment and research data in clinically focused research centers (http://www.tmf-ev.de/EnglishSite/Home.aspx). The Kids Lung Register (KLR) e.V. is responsible for processing and storing data and biomaterials. An internationally agreed patient information and consent form was translated into different European languages. Signed consent and age-appropriate assent when relevant for each patient and/or their legal parental representatives is obtained by the attending physician, and is a prerequisite for inclusion. Patients may at any time withdraw access rights to his or data or deletion of the data or biomaterials. The Philipps-University Marburg (PUM) and a separate institution, the University of Giessen Institut für medizinische Biometrie, Epidemiologie und Informatik are respectively responsible for medical data storage (MDAT) and processing and for storage of the central list of patients for identifying data (IDAT). This institutionally and organizationally separated storage of identifying (IDAT) and medical data (MDAT)(Fig. S1) is achieved using independent system administrators. The MDAT is hosted under the responsibility of PUM in the high security center of T-Systems in Nürnberg, Germany, administered and monitored by IMotion, Fürth on behalf of PUM. The collaboration between the PMU and the University of Giessen is contractual with a written agreement that specifies the complete independence of University of Giessen from any authority.

The processing of MDAT is based on the portal solution SecuTrial®, already proven in many other medical research projects and provided to the participants at their local sites via usage over the internet within a web browser. It is Food and Drug Administration (FDA)-compliant and is compliant with basic good clinical practice (GCP). The platform is provided and licensed by the Central Information Office at Philipps-Universität Marburg. For pseudonymization the study database has an interface to a central list of patients that holds the identifying data and the corresponding patient ID (PID) which is returned to the study database when a new request for patient entry is made. All CT images were available as during upload automatically pseudonomized DICOM files which were downloaded in zipped format from the SecuTrial® web-based system and viewed on local work stations with the help of Syngo fastview (Siemens, Munich, Germany). An additional secuTrial®-database for managing the biomaterials collected by and sent from participating centers is provided for the central biobank at Munich University Hospital (Fig. S2). The biomaterial management database is neither connected to the central patient list nor to the medical study database and does not contain data to track back to an individual patient. It holds information about the storage location and condition of biological samples identified by its own unique biomaterial collection-ID for each sample. It cannot track back to the individual patient. The study and biomaterial management databases are implemented with the technical core components of secuTrial® based on the following components: LINUX as the operating system for database and web server, ORACLE as database server, WebObjects Application Server Java as a server-side programming language, HTML and JavaScript within the web browser on the client computers, and fully encrypted data transfer protocol using SSL. Access to all MDAT and all biomaterial management data are completely logged within a system-integrated audit-trail. Meticulous attention to data handling ensuring compliance with EU regulation was an important, albeit very time-consuming, part of the project.

<u>Outcome parameters</u>

The clinical and biological relevance and feasibility of outcomes commonly used in clinical practice were discussed with clinicians, pathologists, radiologists, individual patients and representatives of patient organizations. Those items judged to be of clear relevance for chILD were included in the data dictionary of the register (Table S1) and requested at baseline and during visits. A family of measures assessing generic and chILD-specific health-related quality of life (HrQoL), and developmentally adapted versions for infants and toddlers, pre-school children, school children and adolescents is now available on the chILD platform in different languages. Proxy ratings of HrQoL can be obtained from the parents, and self-reports can be provided from children and adolescents 7 years and older. We implemented the generic HRQoL scales of the PedsQL^{TM} [15], which has good psychometric properties and is available in different European languages. Additionally we developed chILD specific QoL scales for each age group. The combination of generic and chILD specific dimensions and items allows both comparisons with reference data of other clinical groups or healthy patients and the description of chILD specific issues. Additionally, parental quality of life is evaluated with the EQ-5D^{TM}. Thus, HrQoL serves not only as indicator of the individual patient's health status and assists in determining the need for medical and psychosocial interventions, but also changes in QoL outcomes will be an important part of observational and interventional studies.

For health-economic evaluation a questionnaire was selected based on the validated FIMA- Questionnaire for Health-Related Resource Use in an Elderly Population [16]. Following direct medical costs (inpatient and outpatient treatment, medical aids and devices, informal and formal care) and indirect costs (work absenteeism of the parents and the patient due to ILD, if appropriate) will be calculated based on reported utilization volumes by applying specific actual unit costs for the distinct services. Additionally travelling costs,

operationalized via distance between the healthcare institution and the patient's place of residence will also be included. All questions refer to the previous 3 months. Cost analysis enables characterization of high utilizers on patient and subgroup level.

Reviewer teams

Experts identified were those senior specialists of the five participating centers who were specialized in pediatric lung pathology, pediatric radiology and pediatric pneumology. Each of the countries was initially involved with a team. Due to availability and volunteering experts participated in the peer review process. After set up and training of the teams members can be mixed internationally as needed.

Collection and analysis of materials

Collection of initial samples of biomaterials in the central biobank was successful in most cases including from Germany, UK and Turkey. As shipping of BAL and frozen tissue had to be on dry ice, this was a hindrance, and only a minority of subjects had lavages in their collections in the biobank. Follow-up samples were supplied by a few centers only.

Data output and sharing

An overview of the individual patient´s data and biomaterials entered can be obtained by the treating center. Coordinators can produce lists of patients with a specific diagnosis or based on other features. There is a separate export tool available, allowing output of any data into several different formats for further statistical analysis. For clinical research investigators are invited to produce short proposals and submit them to the project steering committee for discussion of feasibility and scientific merit. Common rules regarding the participation in the research and the publication of results obtained in projects are described in detail on the

website of the kids-lung register foundation (www.kids-lung-register.eu). For statistical analysis output into SAS, SPSS or other formats is used.

<u>Investigator initiated randomized controlled trials selection, set up and administration</u>

A major goal of the chILD-platform was the identification of areas of greatest need for randomized trials by a consensus process and to initiate first pilot trials. In a Delphi-process involving all groups included in the initial chILD-EU project, as well as many other experts in pediatric pneumology from European countries and the US, the surfactant dysfunction disorders were identified as the most important group of molecularly and histologically defined entities to be addressed. Mutations in genes encoding for surfactant protein C, the lipid transporter ABCA3, thyroid transcription factor 1 and others, cause chILD with high morbidity and early mortality [17]. Unfortunately there is no treatment available. Hydroxychloroquine (HCQ) has been used empirically for these disorders [18] and is a potential lead compound for this group of diseases. The highest priority for further study in clinical trials was thus assigned to HCQ as being the greatest patient needs, there being wide off-label usage, and from the results of a worldwide Delphi process and recommendations from members of the Committee for Orphan Medicinal Products (COMP). A randomized phase 2b double blind clinical study, which allows either the initiation or the withdrawal of HCQ was commenced and patients were included after peer-review. The primary objective is to investigate if HCQ improves oxygenation compared to placebo. Secondary objectives of the project are to generate important knowledge on other parameters, as indicated above. Further details on the study were deposited at clinicaltrials.gov (NCT02615938).

The other area of unmet need identified is the treatment of extrinsic allergic alveolitis (EAA) or hypersensitivity pneumonitis [19]. Treatment primarily is based on removal of the patient from the suspected etiologic exposure. However, allergen exposure may remain high

despite these efforts. Glucocorticoid treatment is given routinely to accelerate recovery and because complete removal from allergen exposure is difficult to achieve. The study is parallel group (NCT02631603) with the primary endpoint being change in forced vital capacity (FVC) with prednisolone after 6 months, compared to change from placebo.

The investigator initiated trials on the platform separately underwent ethics review, approval by competent authorities and administrative contracts; again, this was no small task across Europe.

Discussion

Local hurdles to include subjects into registers

A major obstacle for a local site physician caring for a subject with a rare disease and willing to enter a patient into the register is the discrepancy between the wish and the work load to accomplish this. An estimated time of 120 min is necessary to collect the clinical data, fill them into forms, either electronically or on paper, an additional 30 min to have radiology imagines burnt on CD, shipped to central site or upload into the system if trained appropriately, an additional 60 to 120 min to organize and ship pathology materials and other biomaterials and 30 min to write a brief case description. Thus about 5h have to be spent before the discussion and peer review of a case can start. Man-power for this and resources necessary for shipping are usually not available in busy hospitals. This immediately explains that 190 of 575 patients included into the register had insufficient data precluding the start of the peer review. These patients were mainly from centers outside the consortium and lacking any support, except the one given by the register, to enter their cases. Beyond automatic reminders by the SecuTrial® system briefly before and 4 weeks after a regularly scheduled visit, in case of missing data all centers were reminded individually at least twice from within

the electronic system and also by direct emailing. A major conclusion from this data is the need for local financial site support when cases are included into the register, and importantly during long term follow up.

<u>Administrative hurdles within Europe for investigator-initiated studies in rare pediatric respiratory diseases</u>

Among the largest obstacles faced for the development of novel treatments of rare and ultra-rare pediatric respiratory conditions is the lack of a functioning international clinical trial network. It is extremely difficult to find significant numbers of subjects and families willing to participate in clinical trials, as cohorts to observe the natural history are not available for all entities. Close collaboration with patient organizations will help, but many countries do not have such organizations. Established cohorts of subjects with rare entities are prerequisites for successful winning of research awards; however funding bodies frequently do not appreciate the rarity of these diseases. Novel funding strategies, e.g. stretching relatively low budgets over 6 to 10 years for many institutions, are necessary to collect sufficient rare cases.

Additional problems are generated by current regulatory rules, established previously for diseases with a higher prevalence. Such rules are unnecessarily burdensome and obstructive for investigator initiated studies in rare diseases. Many "low hanging, but extremely important fruits" cannot be harvested. These encompass a multitude of off-label treatments which are given to the patients anyway in an uncontrolled and heterogeneous fashion, as well as diagnostic procedures which were never assessed and are only done because they have always been done by clinicians in a certain way. Patients with the same disease are treated differently in different centers and outcomes are never compared. However due to current legislation it is legally not possible to enroll such subjects into simple randomized investigations. Administrative hurdles are so high that they cannot reasonably be overcome and studies will never be done.

An additional level of complexity is added by the fact that all the different European countries need different competent authority applications and different insurance policies. Nothing can be done efficiently, using a single approach. All authorities come up with similar, but somewhat different suggestions, which do not improve, but merely delay the process. All this is extremely costly and cumbersome to organize for non-commercial interest groups, such as clinicians caring for patients. Ethics applications are sometimes even more fragmented. For example in Germany all local ethics board give their valuable comments for approval.

Lastly, contracts between administrations, contracts with hospital pharmacies, and contracts with local research organizations are needed before a subject can be studied. Site staff needs not only to be trained but also to demonstrate conformity with GCP with regularly updated re-certification. The recently established ERIC (European Research Infrastructure Consortium) and earlier ECRIN (European Research Infrastructure Consortium) networks may be of substantial help. The EMA is aware of some of these problems however solutions which work have not been achieved [21]. The chILD community is currently ill-served by all these national and EU regulations.

Supplemental Figures

Fig S1
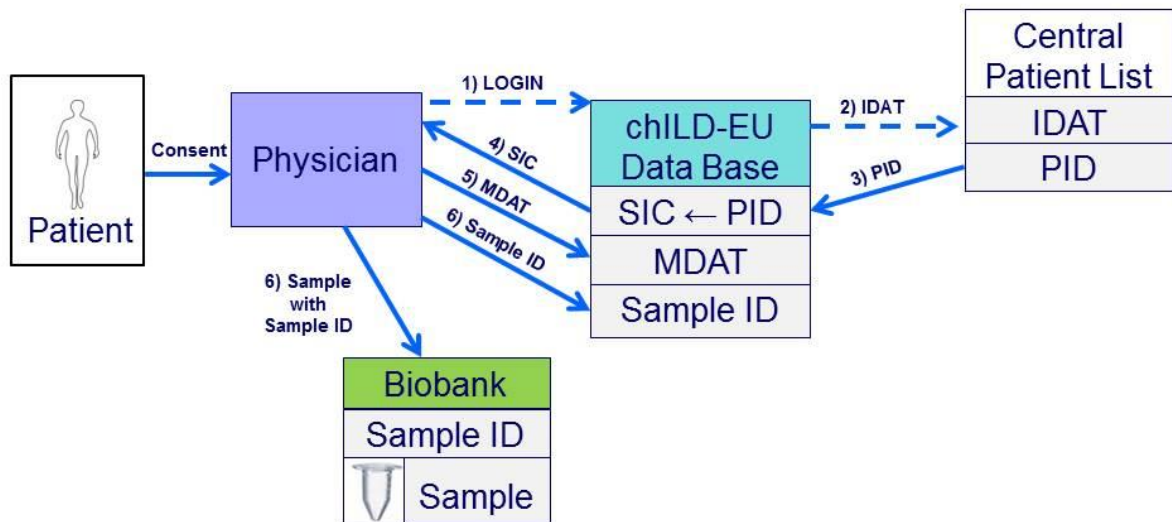
Organizational and data safety concept of chILD-EU register and biobank. After patient

consent and completion of the paperwork to register as a center, the local site physician logs

into the data base and deposits patient identification data (IDAT) on a separate server

administering the central patient list and generating a patient identification number (PID). A

project specific subject identification code (SIC) is returned and the local site physician enters

the medical data, which are stored on a different server and linked to the SIC. An

identification number for biomaterials is also entered into the data base. This sample ID is

used for shipping of bio-samples to the biobank for storage. The biobank is completely

separated from the medical data base.

Fig S2
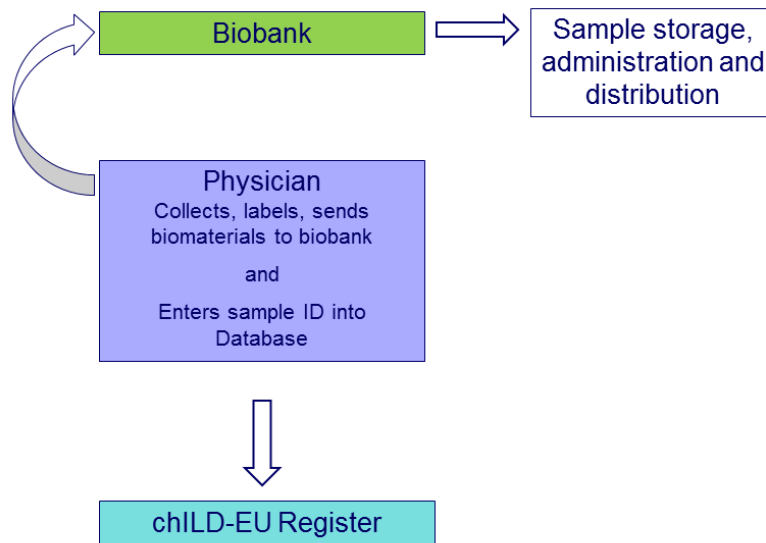
Organizational concept of chILD-EU biobank. The biobank administers and stores biomaterial independent of medical data in order to avoid identification of subjects via their biomaterials. The local site physician links biomaterials to medical data by entering the sample identification under the subject identification code (SIC) into the register.

Fig S3
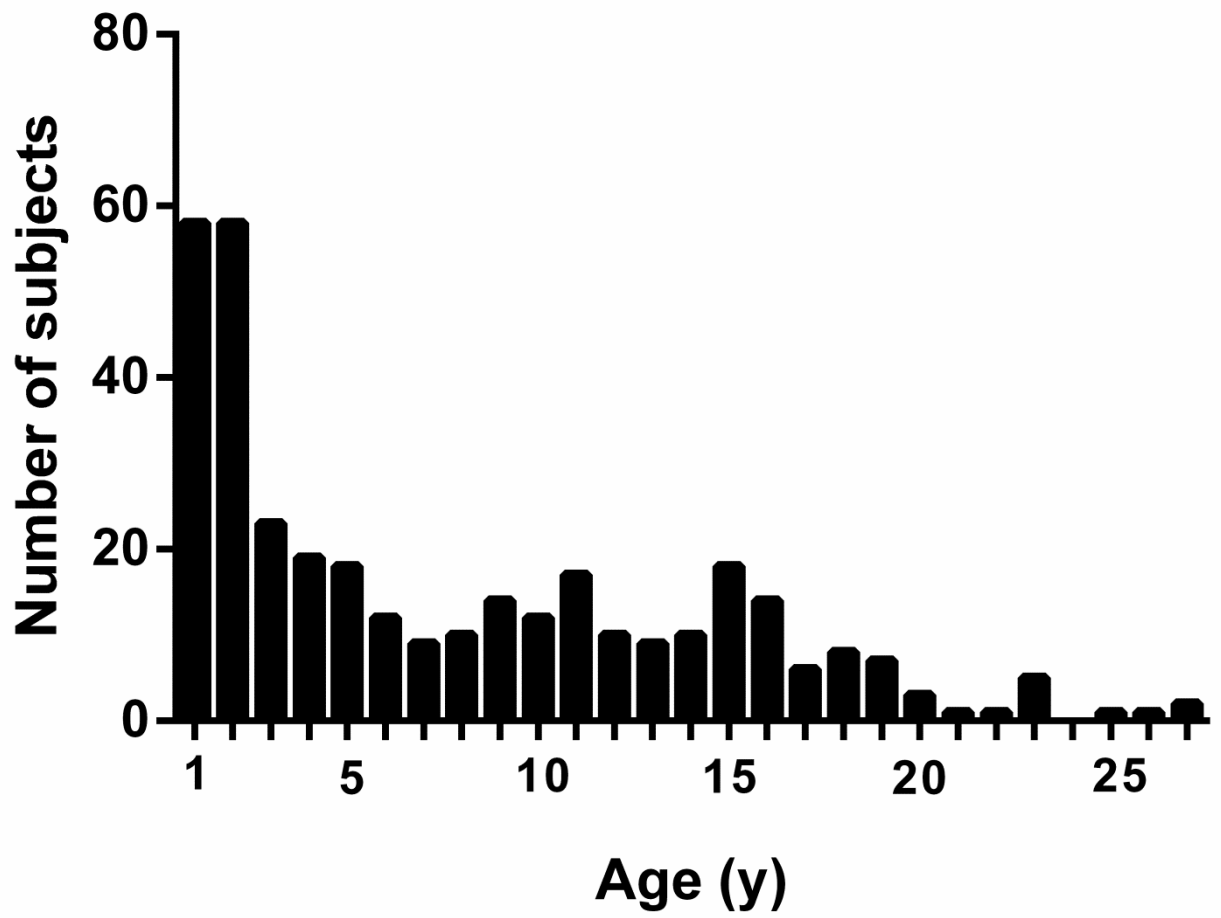
Distribution of the age at inclusion of the 346 patients with peer-review

Form	Parameter
Demographics	Consent
Demographics	Birthdate
Demographics	Gender
Demographics	Country name
Demographics	Age at database inclusion (in years)
Family and Neonatal history	Death/sick from interstitial lung disease
Family and Neonatal history	Death/sick from other disease (under age 60 year)
Family and Neonatal history	Race/Ethnics of MOTHER
Family and Neonatal history	Race/Ethnics of FATHER
Family and Neonatal history	Consanguinity
Family and Neonatal history	Chronic illness or death of relatives
Family and Neonatal history	Gestational age
Family and Neonatal history	Birth weight
Family and Neonatal history	Any respiratory problems
Family and Neonatal history	Neonatal oxygen supplementation
Family and Neonatal history	Neonatal ventilation
Vital Signs, lung function and pulmonary hypertension	Respiratory rate
Vital Signs, lung function and pulmonary hypertension	Height
Vital Signs, lung function and pulmonary hypertension	Weight
Vital Signs, lung function and pulmonary hypertension	Body-Mass-Index (BMI)
Vital Signs, lung function and pulmonary hypertension	Heart rate
Vital Signs, lung function and pulmonary hypertension	O2 saturation
Vital Signs, lung function and pulmonary hypertension	O2-flow
Vital Signs, lung function and pulmonary hypertension	O2-saturation with room air challenge
Vital Signs, lung function and pulmonary hypertension	Flow air
Vital Signs, lung function and pulmonary hypertension	Flow O2
Vital Signs, lung function and pulmonary hypertension	FiO2
Vital Signs, lung function and pulmonary hypertension	PEEP
Vital Signs, lung function and pulmonary hypertension	PIP
Vital Signs, lung function and pulmonary hypertension	Respiratory rate
Vital Signs, lung function and pulmonary hypertension	FiO2
Vital Signs, lung function and pulmonary hypertension	Ti (inspiration time)
Vital Signs, lung function and pulmonary hypertension	MPAW (Mean airway pressure)
Vital Signs, lung function and pulmonary hypertension	PaO2 (Partial pressure of oxygen in arterial blood)
Vital Signs, lung function and pulmonary hypertension	PcapO2 (Partial pressure of oxygen in capillary blood)
Vital Signs, lung function and pulmonary hypertension	FEV1
Vital Signs, lung function and pulmonary hypertension	FVC
Vital Signs, lung function and pulmonary hypertension	MEF 25/75

Vital Signs, lung function and pulmonary hypertension	DLCO
Vital Signs, lung function and pulmonary hypertension	6 min. walk distance
Vital Signs, lung function and pulmonary hypertension	Borg Scale
Vital Signs, lung function and pulmonary hypertension	Pulmonary hypertension
Vital Signs, lung function and pulmonary hypertension	Fan 5 point severity scale
Radiology Images and Findings	CT/X-Ray
Genetics	Gene mutation
Genetics	Chromosomal Abnormality or Array Comparative Genomic Hybridization (array CGH) Abnormality
Histology, EMI - images	Histology, EMI - images
Laboratory tests	LDH
Laboratory tests	ANA [Autoantibody screen]
Laboratory tests	c-ANCA [Proteinase 3 ANCA, i.e. Wegener]
Laboratory tests	p-ANCA [Myeloperoxidase ANCA, i.e. Churg-Strauss Syndrome]
Laboratory tests	GMCSF-autoantibodies [Autoimmune alveolar proteinosis]
Laboratory tests	Bird IgG antibodies [bird precipitines]
Laboratory tests	Fungus IgG antibodies [fungi precipitines]
Laboratory tests	Aspergillus IgE
Laboratory tests	Immunoglobulines - IgG
Laboratory tests	Immunoglobulines - IgM
Laboratory tests	Immunoglobulines - IgA
Laboratory tests	Immunoglobulines - IgE
Laboratory tests	Hb
Laboratory tests	Eosinophils
Laboratory tests	White cell count (absolute)
Radiology images and findings	Imaging
Lung biopsy - report	Lung biopsy - report
Lung biopsy - additional Pathology - report	Lung biopsy - additional Pathology - report
Bronchoalveolar lavage (BAL)	Recovery
Bronchoalveolar lavage (BAL)	Viability
Bronchoalveolar lavage (BAL)	Total number of cells
Bronchoalveolar lavage (BAL)	Macrophages
Bronchoalveolar lavage (BAL)	Lymphocytes
Bronchoalveolar lavage (BAL)	PMN
Bronchoalveolar lavage (BAL)	EOS
Bronchoalveolar lavage (BAL)	Plasma cells
Bronchoalveolar lavage (BAL)	PAS stain
Bronchoalveolar lavage (BAL)	Iron + Mac
Bronchoalveolar lavage (BAL)	Fat + Mac
Medical history	Date interstitial lung disease (ILD) first suspected

Medical history	Start of chronic lung disease symptoms
Medical history	Primary ciliary dyskinesia
Medical history	Cystic fibrosis comment
Medical history	Clinical course of lung disease
Medical history	Pulmonary exacerbation
Medical history	Cough
Medical history	Dyspnea
Medical history	Tachypnoe
Medical history	Fine crackles
Medical history	Wheezing
Medical history	Gastro-esophageal reflux, clinically relevant
Medical history	Hemoptysis
Medical history	Recurrent asprations
Medical history	Recurrent otitis
Medical history	Recurrent lower airway infections/pneumonia
Medical history	Failure to thrive / Weight loss
Medical history	Autoimmune disease
Medical history	Immunodeficiency / HIV/Aids
Medical history	Blood disease
Medical history	Heart disease
Medical history	Intestine disease
Medical history	Kidney disease
Medical history	Liver disease
Medical history	Lymphatic system disease
Medical history	Musculoskeletal system disease
Medical history	Nervous system disease
Medical history	Skin disease
Medical history	Thyroid gland disease
Medical history	Other disease
Medical history	Exposure to bird/fungal antigens
Prophylaxis	Recommended basic immunisations
Prophylaxis	Influenza, annual shot
Prophylaxis	RSV, monthly shots during season
Prophylaxis	Immunoglobulins i.v./s.c.
Treatment	Anticoagulants
Treatment	Azathioprine
Treatment	Calcium channel blocker
Treatment	Cyclophosphamide
Treatment	ECMO / other support

Treatment	Endothelin receptor antagonist
Treatment	Hydroxychloroquine
Treatment	Lung transplant listing
Treatment	Macrolide, long term
Treatment	Mycophenolate
Treatment	NO (inhaled)
Treatment	Non invasive ventilation
Treatment	Oxygen supplementation
Treatment	Phosphodiesterase inhibitor
Treatment	Pirfenidon
Treatment	Prostaglandines
Treatment	Steroids, systemic
Treatment	Surgery of the airways, lung, thorax
Treatment	Surgery of the intestine (PEG, Fundoplicatio)
Treatment	Ventilation (invasive, except neonatal ventilation)

Table S2: For each of the 25 cases information on a pulmonary and a non-pulmonary diagnosis was given (two columns on the left). Each of the nine reviewers tested had to select the best fitting answer out of five. The case numbers correspond to those given in figure 4a.

Nr	Pulmonary diagnosis	Non pulmonary diagnosis		Check correct	Category and Subcategory
1	Interstital lung disease with mixed type of NSIP-Pattern, DIP-Pattern with focal intraalveolar Cholesterin granulomas (Cholesterinpneumonitis) and focal discrete PAP-Pattern No Mutation in the ABCA3- and SPC-gene detected	Adrenoleucodystrophy		x	B1 - DPLD-related to systemic disease processes - Storage diseases
					B1 - DPLD-related to systemic disease processes - Immune-mediated/collagen vascular disorders
					B2 - DPLD-in the presumed immune intact host, related to exposures (infectious/non-infectious) - Drug Reactions
					A4 - DPLD–related to alveolar surfactant region - Nonspecific interstitial pneumonia (NSIP)
					A2 - DPLD-Growth abnormalities deficient alveolarisation - Related to chromosomal disorders
2	DPLD from 2 ABCA3 mutations			x	A4 - DPLD–related to alveolar surfactant region - ABCA3 mutations 2
					A2 - DPLD-Growth abnormalities deficient alveolarisation - Related to chromosomal disorders
					A4 - DPLD–related to alveolar surfactant region - ABCA3 mutations 1
					A4 - DPLD–related to alveolar surfactant region - Chronic pneumonitis of infancy (CPI)
					A4 - DPLD–related to alveolar surfactant region - Usual interstitial pneumonitis
3	DPLD probabely related to surfactant metabolism disorder Bronchopulmonary dysplasia	Prematurity		x	A2 - DPLD-Growth abnormalities deficient alveolarisation - Related to preterm birth (BPD-cLDI)
					A2 - DPLD-Growth abnormalities deficient alveolarisation - Pulmonary hypoplasia
					A2 - DPLD-Growth abnormalities deficient alveolarisation - Related to preterm birth (Wilson Mikity, new BPD)
					A2 - DPLD-Growth abnormalities deficient alveolarisation - Related to chromosomal disorders
					A1 - DPLD-Diffuse developmental disorders - Congenital alveolar dysplasia
4	Persistent tachypnea of infancy; aberrant; Neuroendocrine cell hyperplasia of infancy				A3 - DPLD-Infant conditions of undefined etiology - Chronic tachypnoe of infancy (CTI)
					A3 - DPLD-Infant conditions of undefined etiology - Chronic tachypnoe of infancy (CTI), aberrant
				x	A3 - DPLD-Infant conditions of undefined etiology - Neuroendocrine cell hyperplasia of infancy (NEHI)
					A3 - DPLD-Infant conditions of undefined etiology - Chronic tachypnoe of infancy (CTI), usual
					Ax - DPLD-unclear RDS in the mature neonate - Familial
5	Alveolar proteinosis of unknown origin DD postinfectious DD GMCSF-Ab mediated DD related to GMCSF-beta mutation On lung biopsy alveolar proteinosis, yet of unknown origin	Battered child			A4 - DPLD–related to alveolar surfactant region - PAP, juvenile
				x	A4 - DPLD–related to alveolar surfactant region - PAP histopattern +
					A4 - DPLD–related to alveolar surfactant region - PAP, secondary to associated disease
					A4 - DPLD–related to alveolar surfactant region - NSIP, PAP pattern
					A3 - DPLD-Infant conditions of undefined etiology - Pulmonary interstitial glycogenosis (PIG) primary
6	Wilson Mikity Snydrome Chronic lung disease of prematurity (29+2) Status after neonatal infection Centroacinar emphysema				A2 - DPLD-Growth abnormalities deficient alveolarisation - Related to preterm birth (BPD-cLDI)
				x	A2 - DPLD-Growth abnormalities deficient alveolarisation - Related to preterm birth (Wilson Mikity, new BPD)
					B1 - DPLD-related to systemic disease processes - Alagille Syndrome (arteriohepatic dysplasia)
					B1 - DPLD-related to systemic disease processes - Diffuse alveolar hemorrhage due to vasculitic disorders
					A4 - DPLD–related to alveolar surfactant region - Nkx21 gene defect
7	DPLD related to infections - Bronchiolitis (maybe obliterans) with prebronchiectasis Asthma				D - Airway disorders - Bronchitis
					B2 - DPLD-in the presumed immune intact host, related to exposures (infectious/non-infectious) - Mac-Leod-Swyer-James-Syndrom
					B1 - DPLD-related to systemic disease processes - Storage diseases
				x	B2 - DPLD-in the presumed immune intact host, related to exposures (infectious/non-infectious) - Infectious/post-infectious processes
					B3 - DPLD-in the immunocompromised host or transplanted - Infections–Miscellaneous
8	NSIP, cellular pattern Atelectasis right UL Hyperplasia of neuroendocrine cells (sign of immaturity) IRDS, familial. Overinflated lungs with prominent bronchovascular structures.	Dystrophy, 11 ribs			A4 - DPLD–related to alveolar surfactant region - NSIP, DIP pattern
					A4 - DPLD–related to alveolar surfactant region - NSIP, fibrotic
					A4 - DPLD–related to alveolar surfactant region - Nonspecific interstitial pneumonia (NSIP)
					A4 - DPLD–related to alveolar surfactant region - NSIP +/- DIP +/- PAP pattern
				x	A4 - DPLD–related to alveolar surfactant region - NSIP, cellular
9	Chronic suprative lung disease with bronchiolitis, atelectasis and ground glas attenuation; biochemical Surfactant Protein C - (SP-C)-Deficiency; DD secundary to infection, or recurrent pneumonia. Sepsis with pneumococcus 05/2013	Failure to thrive			Ax - DPLD-unclear RDS in the mature neonate - Familial
					B1 - DPLD-related to systemic disease processes - Stevens-Johnson Syndrome-idiopathic+BO
				x	By - DPLD-unclear NON-neonate - Unclear DPLD/ILD
					Bx - DPLD-unclear RDS in the NON-neonate - Familial
					B2 - DPLD-in the presumed immune intact host, related to exposures (infectious/non-infectious) - Infectious/post-infectious processes
10	1. Suppurative lung disease with secondary involvement of the lungs from infections, DD aspirations, DD ILD (acc.	1. Psychomotoric retardation, 2. Muscular hypotonia, 3. Diabetes insipidus centralis, 4. Growth			B2 - DPLD-in the presumed immune intact host, related to exposures (infectious/non-infectious) - Aspiration syndromes+BO
					B2 - DPLD-in the presumed immune intact host, related to exposures (infectious/non-infectious) - Bronchiolitis without Transplantation
					D - Airway disorders - Aspirations, recurrent

#	Clinical	Additional		x	Classification
	to radiologist peer review), 2. Central and obstruive apnoe-CPAP	hormone deficiency, 5.Chronic sinusitis maxillaris+surgery of adenoids 2x, 6. Excision papilloma uvula, 7. Enlarged lymph nodes mediastinum		x	D - Airway disorders - Chronic Bronchitis
					D - Airway disorders - Bronchitis
11	Bronchiolitis obliterns, post Mycoplasma (2009) DD Stevens-Johnson-Syndrom, DD Erythema exsudative major	Recurrent Stomatitis, sometimes with conjunctivitis and exanthema			B2 - DPLD-in the presumed immune intact host, related to exposures (infectious/non-infectious) - Infectious/post-infectious processes
				x	B2 - DPLD-in the presumed immune intact host, related to exposures (infectious/non-infectious) - Bronchiolitis obliterans
					B1 - DPLD-related to systemic disease processes - Stevens-Johnson Syndrome-infection related+BO
					F - Lung infections- Mycoplasma Pneumoniae
					B3 - DPLD-in the immunocompromised host or transplanted - Infections–Miscellaneous
12	Likely genetically caused disorder, e.g.IPEX related; histo lymphocytic alveolits, interstitial lung disease LIP pattern) Partial respiratory insufficiency Recurrent pneumonia	NYHA III-IV, chronic Inflammation disease of the intestine with chronic diarhoe, exocrine pancreatic insufficienc, dystrophi, chronic recurrent arthralgia, severe GERD			B3 - DPLD-in the immunocompromised host or transplanted - Interferonopathy
					B1 - DPLD-related to systemic disease processes - Immune-mediated/collagen vascular disorders
					B2 - DPLD-in the presumed immune intact host, related to exposures (infectious/non-infectious) - Infectious/post-infectious processes
					B3 - DPLD-in the immunocompromised host or transplanted - Diffuse lung damage of unknown etiology
				x	B3 - DPLD-in the immunocompromised host or transplanted - LIP
13	Bronchiolitis obliterans following haematopoietic stem cell transplantatio, respiratory failure, chronic Pseudomonas aeruginosa lung infection (since 02/2011), recurrent infective exacerbations, recurrent pneumothoraces (06/2011, 03/2012, 05/2012, 01/2013, 02/2013), unilateral pleurodesis (left), wedge resection apical left	Haematopoietic stem cell transplantation (11/2009) Busulfan conditioning prior to transplantation Acute myeloid leukemia (AML), relapsed Chronic GvHD Failure to Thrive			B3 - DPLD-in the immunocompromised host or transplanted - Follicular bronchitis/bronchiolitis
					B3 - DPLD-in the immunocompromised host or transplanted - Diffuse lung damage of unknown etiology
				x	B3 - DPLD-in the immunocompromised host or transplanted - Related to Tx or rejection+BO
					B3 - DPLD-in the immunocompromised host or transplanted - BO
					B3 - DPLD-in the immunocompromised host or transplanted - Related to transplantation and rejection
14	chILD in a patient with rheumatologic disease (MCTD) No radiological signs for LIP. Pulmonary arterial hypertension Respiratory Failure	Mixed connective tissue disease with oligoarthritis, uveitis, pancreatitis, hepatitis			B1 - DPLD-related to systemic disease processes - Microscopic Polyangiitis
					B3 - DPLD-in the immunocompromised host or transplanted - Related to therapeutic intervention
					B1 - DPLD-related to systemic disease processes - Undifferentiated connective tissue disease
					B2 - DPLD-in the presumed immune intact host, related to exposures (infectious/non-infectious) - Acute Fibrinous and Organizing Pneumonia
				x	B1 - DPLD-related to systemic disease processes - Immune-mediated/collagen vascular disorders
15	Persistent tachypnea of infancy				A3 - DPLD-Infant conditions of undefined etiology - Neuroendocrine cell hyperplasia of infancy (NEHI)
				x	A3 - DPLD-Infant conditions of undefined etiology - Chronic tachypnoe of infancy (CTI)
					By - DPLD-unclear NON-neonate - Unclear DPLD/ILD
					A4 - DPLD–related to alveolar surfactant region - Chronic pneumonitis of infancy (CPI)
					A3 - DPLD-Infant conditions of undefined etiology - Chronic tachypnoe of infancy (CTI), aberrant
16	Premature (36+2, SGA), recurrent lower respiratory tract infection, pulmonary hypertension Consistent with TTF1 defect	Trisomy 22 (cat eyes syndrome) hypothroidy, hypotonia, agenesis of corpus callosum			A2 - DPLD-Growth abnormalities deficient alveolarisation - Pulmonary hypoplasia
					A2 - DPLD-Growth abnormalities deficient alveolarisation - Related to preterm birth (BPD-cLDI)
				x	A2 - DPLD-Growth abnormalities deficient alveolarisation - Related to chromosomal disorders
					A2 - DPLD-Growth abnormalities deficient alveolarisation - Related to preterm birth (Wilson Mikity, new BPD)
					Ay - DPLD-unclear RDS in the almost (30-36 wks) mature neonate - Familial
17	Congenital lobar emphysema Residuals from infection (CMV, other bugs)			x	C1 - Localized, congenital gross structural abnormalities of the lungs - Infantile Lobar Emphysema/Polyalveolar Lobe
					A1 - DPLD-Diffuse developmental disorders - Congenital alveolar dysplasia
					A1 - DPLD-Diffuse developmental disorders - Alveolar Dysgenesis/Primary Pulmonary Hypoplasia
					A2 - DPLD-Growth abnormalities deficient alveolarisation - Pulmonary hypoplasia
					D - Airway disorders - Emphysema
18	Suspected pulmonary hemosiderosis	Thrombosis of sinus venosus Death after blood Transfusion in other hospital			B1 - DPLD-related to systemic disease processes - Diffuse alveolar hemorrhage due to vasculitic disorders
					B1 - DPLD-related to systemic disease processes - Idiopathic pulmonary capillaritis
					B1 - DPLD-related to systemic disease processes - Immune-mediated/collagen vascular disorders
					B4 - DPLD-related to lung vessels structural processes - Pulmonary hemorrhage due to coagulopathy
				x	B4 - DPLD-related to lung vessels structural processes - Pulmonary hemorrhage
19	Hypersensitive pneumonitis, but it is atypical				A4 - DPLD–related to alveolar surfactant region - Nonspecific interstitial pneumonia (NSIP)
					B2 - DPLD-in the presumed immune intact host, related to exposures (infectious/non-infectious) - Infectious/post-infectious processes
				x	B2 - DPLD-in the presumed immune intact host, related to exposures (infectious/non-infectious) - Exogen allergic alveolitis/hypersensitivity pneumonitis
					B2 - DPLD-in the presumed immune intact host, related to exposures (infectious/non-infectious) - Drug Reactions+BO
					B2 - DPLD-in the presumed immune intact host, related to exposures (infectious/non-infectious) - Bronchiolitis without Transplantation
20	NSIP - cellular, follicular bronchiolitis	Atrial septal defect, Pneumocystis infection			A4 - DPLD–related to alveolar surfactant region - Nonspecific interstitial pneumonia (NSIP)

#	Clinical description	History/comorbidities		x	Classification
		Pneumocystis infection, hypoglycemia at birth, hypogammaglobulinemia		x	B3 - DPLD-in the immunocompromised host or transplanted - NSIP
					B3 - DPLD-in the immunocompromised host or transplanted - NSIP and BO
					B3 - DPLD-in the immunocompromised host or transplanted - Diffuse lung damage of unknown etiology
					Bx - DPLD-unclear RDS in the NON-neonate - Familial
21	Chronic tachypnea of infancy (CTI)				A3 - DPLD-Infant conditions of undefined etiology - Neuroendocrine cell hyperplasia of infancy (NEHI)
					A4 - DPLD–related to alveolar surfactant region - Usual interstitial pneumonitis
				x	A3 - DPLD-Infant conditions of undefined etiology - Chronic tachypnoe of infancy (CTI), aberrant
					B2 - DPLD-in the presumed immune intact host, related to exposures (infectious/non-infectious) - Infectious/post-infectious processes
					A4 - DPLD–related to alveolar surfactant region - Chronic pneumonitis of infancy (CPI)
22	Severe diffuse lung disease, radiologicaly consistent with pleuroparenchymal fibroelastosis after high dose chemotherapy and bone marrow transplant	Neuroblastoma, tumor lysis syndrome, recurrent severe infections, poor nutrition			B3 - DPLD-in the immunocompromised host or transplanted - Lymphoid hyperplasia
				x	B3 - DPLD-in the immunocompromised host or transplanted - Related to therapeutic intervention
					B3 - DPLD-in the immunocompromised host or transplanted - Infections–Miscellaneous
					B3 - DPLD-in the immunocompromised host or transplanted - Related to transplantation and rejection
					B2 - DPLD-in the presumed immune intact host, related to exposures (infectious/non-infectious) - Drug Reactions
23	Undefined interstitial lung disease with neonatal onset (In an older child you would be looking at diffuse pulmonary haemorrhage, extremely rare in neonates) As per radiology discussion there appears to be non-specific ground glass, with some elements of aspiration.	Similar case in a previous sibling, died from as mature infant from neonatal respiratory distress		x	Ax - DPLD-unclear RDS in the mature neonate- Familial
					A4 - DPLD–related to alveolar surfactant region - Chronic pneumonitis of infancy (CPI)
					Ax - DPLD-unclear RDS in the mature neonate - Pulmonary hypertension
					By - DPLD-unclear NON-neonate - Unclear DPLD/ILD
					A2 - DPLD-Growth abnormalities deficient alveolarisation - Pulmonary hypoplasia
24	The HRCT and the biopsy are both compatible with distal airway disease (chronic bronchiolitis) which we have not infrequently encountered			x	B2 - DPLD-in the presumed immune intact host, related to exposures (infectious/non-infectious) - Bronchiolitis obliterans
					B2 - DPLD-in the presumed immune intact host, related to exposures (infectious/non-infectious) - Respiratory Bronchiolitis-Interstitial Lung Disease (RB-ILD)
					B1 - DPLD-related to systemic disease processes - Stevens-Johnson Syndrome-idiopathic+BO
					B1 - DPLD-related to systemic disease processes - Stevens-Johnson Syndrome-infection related+BO
					D - Airway disorders - Chronic Bronchitis
25	Pulmonary hemosiderosis of unknown origin, diffuse lung disease with emphysematous lesions as well as signs for growth anomalies with multiple interfissural blebs	Pectus deformity			B4 - DPLD-related to lung vessels structural processes - Pulmonary capillary hemangiomatosis
					B4 - DPLD-related to lung vessels structural processes - Pulmonary hemorrhage due to vascular disorder
					B4 - DPLD-related to lung vessels structural processes - Pulmonary hemorrhage due to infection
					B1 - DPLD-related to systemic disease processes - Immune-mediated/collagen vascular disorders
				x	B1 - DPLD-related to systemic disease processes - Idiopathic pulmonary hemosiderosis

Tab S3 Diagnoses altered by peer review

Nr	Initial pulmonary diagnosis	Peer review pulmonary diagnosis	Cate-gory	Specification (primarily due to)*	Therapy change observed**
1	Alveolar proteinosis, DD alveolar capillary dysplasia with misalignement of the pulmonary veins	Diffuse developmental disorder. ACD with or without (both status observed in same tissue) misalignment, likely with, as patient died soon. Of interest is the radiological diagnosis of PAP; may be due to surfactant applied previously	A1	specified diagnosis by adding relevant info (pathology)	Y Palliative treatment
2	Severe Respiratory failure, ECMO, Suggested chILD developmental disorder or growth anomaly, Chylothorax, Pulmonal arterial hypertension with suprasystemic pressure and persistent fetal circulation	Alveolar dysplasia, chylothorax and lymphangiectasia of the lungs with severe respiratory failure, ECMO. Pulmonary arterial hypertension (suprasystemic), persistent fetal circulation. Pulmonary interstitial glycogenosis (PIG)	A1	specified diagnosis by adding relevant info (pathology)	N Palliative treatment
3	Interstitial lung disease with obstructive and (pseudo)restrictive ventilatory dysfunction with emphysema and fibrosis on chest CT. Severe RDS in an almost term-born child (36+5 weeks gestations) with mechanical ventilation over 10 days. Continuous oxygen dependency in the first months of life. Persistent hypoxemia with frequent exacerbations and oxygen requirement in viral infections 2009-2012 and 2015. Intermittent hypoxemia with home oxygen supply	Pulmonary hypertension in association with small patella Syndrome, possibly due to TBX4 mutations. Histology: in parts alveolar-capillary dysplasia without misalignment	A1	specified diagnosis was made (genetics)	Y Stop hydroxy-chloroquine
4	Interstitial lung disease	Wilson Mikity syndrome, chronic lung disease of prematurity (29+2), status after neonatal infection, centro-acinar emphysema	A2	specified diagnosis was made (clinical, imaging)	Y Stop systemic steroids
5	Alveolar capillary dysplasia without misalignement of the pulmonary veins, chronic oxygen dependency, ventilator dependent respiratory failure since June 2015, pulmonary hypertension	Trisomy 21 with abnormal alveolarization and associated PIG	A2	specified diagnosis by adding relevant info (pathology)	Y Start systemic steroids

6	Unclear lung disease	Recurrent chylothoraces, respiratory decompensation. Pulmonary hypertension. No evidence for interstitial lung disease. Recurrent atelectasis and lung infections. Possibly on the basis of alveolo-vascular abnormalities with Noonan-Syndrome	A2	wrong diagnosis (clinical, genetics)	Y Stop systemic steroids
7	suspected postinfectious BO (Rhinovirus infection)	Neuroendocrine cell hyperplasia	A3	wrong diagnosis (pathology)	Y Stop systemic steroids
8	Parenchymal lung disease. Suspected infection with Pneumocystis jirovecii (mild positive in PCR). Partial respiratory insufficiency	Chronic tachypnoea of infancy, aberrant type. Neuroendocrine cell hyperplasia	A3	wrong diagnosis (pathology)	Y Stop systemic steroids, stop long term macrolide
9	Airway inflammation with recurrent infections, suspicion of chILD	Chronic tachypnea of infancy, Neuroendocrine cell hyperplasia	A3	wrong diagnosis (pathology)	Y Start long term macrolide, stop inhaled salbutamol
10	Interstitial lung disease	Chronic pneumonitis of infancy; related recurrent pulmonary infections, related to immunodeficiency	A3	specified diagnosis was made (pathology)	N
11	Interstitial lung disease	Chronic tachypnoe of infancy; neuroendocrine cell hyperplasia by histology; CT Shows in addition some consolidation and linear markings. Aberrant neuroendocrine cell hyperplasia	A3	specified diagnosis was made (pathology)	Y Stop long term macrolide
12	Interstitial lung disease	Persistent tachypnea of infancy, neuroendocrine cell hyperplasia on biopsy; aberrant form	A3	specified diagnosis was made (pathology)	Y No medical treatments given
13	interstitial lung disease	Neuroendocrine cell hyperplasia	A3	specified diagnosis was made (pathology)	Y Stop systemic steroids

14	Interstitial Pneumonitis	Chronic tachypnea of infancy. Almost mature (35 wks), no postnatal respiratory distress. Since wk 2 chronic tachypnea. Since 8 mon O2 supplementation at night/or for sleeping	A3	wrong diagnosis (clinical, imaging)	Y Stop azathioprine, systemic steroids
15	Suspected ILD (steroid sensitive).Post-pneumonia. Acute respiratory decompensation. Lung edema	Diffuse parenchymal lung disease with the histological pattern of Neuroendocrine cell hyperplasia (Steroid sensitive). Chronic respiratory failure with continuous Oxygen/high flow dependency and hypercapnia. Recurrent severe lower respiratory infections with Deterioration of the underlying disease	A3	specified diagnosis by adding relevant info (pathology)	Y Stop systemic steroids
16	Surfactant metabolism or production disorder	Mild alveolar hypoplasia. PIG pattern. Post infectious lung disease with focal obliterative bronchiolitis in histology. Post inflammatory minimal residual intraalveolar fibrin, few interstitial inflammatory cells, interstitial edema, focal hyperplasia of type II pneumocytes. Bilateral pneumothoraces	A3	wrong diagnosis (pathology)	Y Stop macrolides and hydroxychloroqui ne
17	Interstitial pneumonitis of unknown etiology. Persistent nocturnal oxygen requirement (1 l/min). Asthma	Chronic tachypnea of infancy	A3	specified diagnosis by adding relevant info (clinical, imaging)	Y Stop systemic steroids
18	Pulmonary interstitial glycogenosis (PIG)	Persistent tachypnea of infancy, aberrant, lung biopsy not conclusive for PIG	A3	specified diagnosis by adding relevant info (pathology)	N
19	Suspected lung fibrosis, respiratory insufficiency, tachypnoea	Surfactant dysfunction syndrome due to ABCA3 mutations	A4	specified diagnosis was made (genetics)	Y Start hydroxy-chloroquine, azathioprine
20	Severe neonatal respiratory distress, respiratory failure, ventilator-dependent, presently HFO-Ventilation, minimum peep required 11 torr	chILD related to inherited Surfactant metabolism disorder (ABCA3 mutations)	A4	specified diagnosis was made (genetics)	Y Start systemic steroids, hydroxy-chloroquine

21	Suspected interstitial Lung disease, recurrent bronchitis, prolonged pneumonia 2004 with persistent cyanosis	NSIP, fibrosing	A4	specified diagnosis was made (pathology)	Y Stop systemic steroids
22	Suspected ILD, tachypnea	DPLD (NSIP cellular) related to SP-C deficiency	A4	specified diagnosis was made (pathology, genetics)	Y Stop systemic steroids
23	Suspected CVID, recurrent pulmonary infections, chronic interstitial lung disease, steroid-dependence, intermittent O2 need, secondary pulmonary hypertension, chronic atrophic bronchitis	TTF1 Deficiency with (a) pulmonary symptoms (Ureaplasma postnatal, prolongend ventilation, recurrent pneumonia/Bronchitis) (b) mild developmental retardation. (c) pulmonary hypertension (d) IgG deficiency	A4	wrong diagnosis (genetics)	Y Stop long term macrolides
24	Unexplained IRDS	Interstitial lung disease from compound heterozygous ABCA3 mutations	A4	specified diagnosis was made (genetics)	Y Palliative treatment
25	Interstitial lung disease - unknown cause	NSIP, follicular bronchiolitis, pneumocystis infection	A4	specified diagnosis was made (pathology)	y Stop systemic steroids
26	Respiratory distress Syndrome. Pneumonia, unknown lung disease	Diffuse lung disease related to surfactant dysfunction disorder	A4	specified diagnosis was made (genetics)	Y Stop systemic steroids
27	Interstitial lung disease	Desquamative interstitial pneumonia in a mature neonate with respiratory distress syndrome	A4	specified diagnosis by adding relevant info (pathology)	Y Start hydroxy-chloroquine, azathioprine, systemic steroids
28	Pulmonary fibrosis of unknown origin, respiratory failure type 1, hypoxemia since first year of life, pulmonary arterial hypertension, secondary Pseudomonas aerugionsa infection	Filamin-A Mutation with pulmonary arterial hypertension, secondary emphysema, fibrosis, respiratory failure	B1	specified diagnosis was made (genetics)	Y Stop hydroxy-chloroquine, azathioprine

29	Severe restrictive lung disease, pulmonary cysts and bullae. exercise induced dyspnea since October 2014	Langerhans cell histiocytosis	B1	specified diagnosis was made (pathology)	Y Start cladribin
30	Suspected Williams-Campbell-Syndrome. Status post resection right upper- and middle lobe	Diffuse lung disease probably related to Filamin A - mutation	B1	wrong diagnosis (imaging, pathology)	N
31	Interstitial lung disease	BO, likely post-infectious	B2	specified diagnosis was made (clinical, imaging)	Y Start long term macrolide
32	Interstitial lung disease	Hypersensitivity pneumonitis due to feathers	B2	specified diagnosis was made (clinical, imaging)	Y Stop systemic steroids
33	Interstitial lung disease	Post-infectious obliterative bronchiolitis	B2	specified diagnosis was made (clinical, imaging)	Y Inhaled steroids
34	Neuroendocrine hyperplasia of infancy, previous 34 weeks infant, parainfluenza bronchiolitis 2014	Post-infectious obliterative bronchiolitis	B2	specified diagnosis by adding relevant info (clinical, imaging)	Y Inhaled ß-adrenergics
35	Interstitial lung disease of unknown origin, maybe related to SP-C-dysfunction (father with severe ILD and same radiological pattern), may be hypersensitivity pneumonitis (positive precipitins against bird feather and positive exposition)	Chronic hypersensitivity pneumonitis	B2	specified diagnosis was made (clinical, imaging, pathology)	Y Improve allergen removal, reduce systemic steroids
36	Interstitial lung disease	Post infectious bronchiolitis (may be obliterans?) with mosaic perfusion peripheral air trapping and pseudo-restriction	B2	specified diagnosis by adding relevant info (clinical, imaging)	Y Start systemic steroids
37	Combined restrictive and obstructive lung disease	Progressive virus triggered and P ae entertained bronchiolitis obliterans syndrome (BOS) after SCT with pulmonary hemorrhages	B3	specified diagnosis was made (clinical, imaging)	Y Start long term macrolide

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38	Interstitial lung disease. RDS IV° with intubation and surfactant therapy twice after birth. Invasive ventilation (HFO, SIMV) for six days, noninvasive ventilation (CPAP, HighFlow) intermittently, persistent oxygen requirement and hypercapnia	Immune deficiency with A-gamma-globulinemia. Previous Pneumocystis infection. RDS IV° of the almost mature. Interstitial lung disease with pattern of DIP+PMN and CPI+CIP. Obstructive apnea, retrognathia	B3	specified diagnosis by adding relevant info (clinical, pathology)	Y Start Cotrimoxazol, Amoxicillin, systemic steroids
39	Recurrent infection of the respiratory tract. Interstitial lung disease	Lymphocytic Interstitial pneumonia. Protracted bacterial infection. Bronchiectasis. Recurrent otitis. Recurrent sinusitis	B3	specified diagnosis by adding relevant info (pathology)	Y Continue mycophenolate and start antibiotics
40	Interstitial lung disease	Lymphocytic interstitial pneumonia. Recurrent chest infections. Tracheo-bronchomegaly (Mounier-Kuhn-Syndrome)	B3	specified diagnosis was made (pathology)	Y Start systemic steroids
41	Interstitial lung disease (not defined)	Idiopathic pulmonary hypertension. No interstitial lung disease	B4	wrong diagnosis (clinical, imaging)	Y Start long term macrolide (infectious reason)
42	Suspected CTI/Neuroendocrine cell hyperplasia. Recurrent obstructive Bronchitis. Respiratory partial insufficiency. Status post protracted bacterial bronchitis	Protracted bacterial bronchitis with chronic wet cough responsive to antibiotic treatment. Multi-trigger wheeze, bronchial hyper-reactivity with response to ICS/LTRA's. Intermittent, not chronic tachypnea. CT: minimal, but not suggestive signs for neuroendocrine cell hyperplasia	D	wrong diagnosis (clinical, imaging)	N
43	Interstitial Inflammation. Interstitial Fibrosis. William-Campbell syndrome. Allergic asthma (house dust mite allergy)	Cystic fibrosis; non-classical form. Interstitial inflammation and fibrosis. Allergic asthma (house dust mite allergy)	D	wrong diagnosis (clinical, imaging)	Y Airway clearance, antibiotics
44	Interstitial inflammation. Interstitial Fibrosis. William-Campbell syndrome. Sibling of previous case.	Postinfectious Bronchiolitis. Bronchiectasis based on cystic fibrosis; non-classical form.	D	wrong diagnosis (clinical, imaging)	Y Airway clearance, antibiotics

*The means by which altered peer review pulmonary diagnosis was primarily based on: clinical, imaging, pathology, genetics data

**Change in therapy observed following peer review. Usually no specific treatment changes were recommended by peer review