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REAL-WORLD DATA SOURCES FOR PHARMACOEPIDEMIOLOGIC RESEARCH OPEN ACCESS

Success of the German Cystic Fibrosis Registry

Lutz Naehrlich[1] | Manuel Burkhart[2] | Registry Working Group of the German CF Registry

[1]Department of Pediatrics, Justus-Liebig-University, Giessen, Germany | [2]Mukoviszidose Institut gGmbH, Bonn, Germany

Correspondence: Lutz Naehrlich (lutz.naehrlich@paediat.med.uni-giessen.de)

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ABSTRACT

The German Cystic Fibrosis (CF) Registry (GCFR) is a national General Data Protection Regulation–compliant centralised database sponsored by the German Cystic Fibrosis Association (Mukoviszidose e.V.) and based on informed consent for each participating patient, ethical approval, and data protection votes. The aims of the GCFR are to optimise quality of care for CF at the centres, generate epidemiologic overviews, address research questions related to improved CF care, and inform caregivers, patients (aimed at patient empowerment), and health authorities and industry (aimed at care planning and pharmacovigilance). Established in 1995, the Registry has captured data on > 9600 individuals with a combined total of more than 140 000 annual assessments with an estimated coverage rate of > 90%. Patient data are collected after informed consent and confirmed diagnosis of CF, or a CFTR-related disorder, or a screening-positive inconclusive diagnosis of CF (i.e., CFSPID). The registry collects core, encounter, and annual health data. Data include demographics, anthropometrics, lung function, microbiology, CF-specific complications and chronic medications, hospitalisations, demand-oriented antibiotic therapies, and outcomes (death and transplants). Real world and pharmacovigilance studies have been published and additional research underway; there is a formal process for requesting access to the GCFR.

1 | Data Resource Basics

Cystic fibrosis (CF) is an inherited, chronic-progressive disease with an incidence of 1:4800 live births [1], resulting in 150–200 new diagnoses each year in Germany. Most children are diagnosed in the first months of life, but diagnosis can be delayed until adulthood in up to 5.6% of cases. People with CF are treated in one of 85 CF centres (as of 2022) in cooperation with general practitioners, paediatricians and pneumologists and transferred from paediatric to adult care after reaching age 18 years. In 2022, a total of 60.1% of those with CF who had annual follow-up data in Germany were adults (age ≥ 18 years), and the median age of survival was 56.9 years (5-year period, 2017–2021) [2].

The aims of the German Cystic Fibrosis Registry (GCFR) are to optimise quality of care for CF at the centres, generate epidemiologic overviews, address research questions related to improved CF care and inform caregivers, patients (aimed at patient empowerment) and health authorities and industry (aimed at care planning and pharmacovigilance). The national, centralised database is sponsored by the German Cystic Fibrosis Association (Mukoviszidose e.V.) and based on informed consent from each participating patient, ethical approval (Justus-Liebig-University Giessen, Germany, AZ 24/19), and data protection votes from relevant authorities.

In 1995, the GCFR started as the Qualitätssicherung Mukoviszidose (Cystic Fibrosis Quality Assurance Project). It was led by Martin Stern until 2012, when Lutz Naehrlich became medical lead. The GCFR was hosted by the Centre for Quality and Management in Health (Hannover, Germany) and was funded/sponsored by Mukoviszidose-Hilfe e.V. (later Christian-Herzog-Stiftung) during 1995–2012 and by the Mukoviszidose e.V. since 1995 [3]. Former German CF registry activities include

Members of working group of the German CF Registry are provided in Appendix A.

Summary

- The German Cystic Fibrosis (CF) Registry is a national General Data Protection Regulation–compliant centralised database sponsored by the German Cystic Fibrosis Association (Mukoviszidose e.V.) and based on informed consent for each participating patient, ethical approval and data protection votes.
- Established in 1995, the Registry has captured data on > 9600 individuals with a combined total of more than 140 000 annual assessments.
- Patient data are collected after informed consent and confirmed diagnosis of CF, or a CFTR-related disorder or a screening-positive inconclusive diagnosis of CF (i.e., CFSPID). The registry collects core, encounter and annual health data.
- Data include demographics, anthropometrics, lung function, microbiology, CF-specific complications and chronic medications, hospitalisation, demand-oriented antibiotic therapies and outcomes (death and transplants).
- Real world and pharmacovigilance studies have been published and additional research underway.
- There is a formal process for requesting access to the German CF Registry. An application form and more details can be found using the following link: https://www.muko.info/englisch-version/registry.

multicentric CF databases coordinated by the CF centre in Frankfurt/Main (1980–1994), the Technical University Dresden (1978–1993, East German CF registry), and the Medical School Hannover (1990–1993), but these were not connected because of data protection considerations and differences among data sources.

An initial decentralised registry software called CFAS (Cystic Fibrosis Quality Assurance Software) replaced paper-based data collection in 1998. In 2007, a software update, Muko.dok, was developed by Axaris GmbH, Dornstadt/Germany, focused on visualisation and secondary use of data for clinical purposes (especially referral letters). In 2015, the company established a web-based version, Muko.web, accompanied by an up-to-date data protection framework that included a trust authority and General Data Protection Regulation compliance. In 2015, data management was placed under the oversight of the Hannover Medical School and shifted in 2018 to the Interdisciplinary Center for Clinical Trials (Interdisziplinäres Zentrum für klinische Studien, IZKS) at the University Medical Center, Mainz.

The GCFR is based on an annual data collection (Level 1) and has been augmented by encounter-based documentation since 1996 (Level 2) each at centre level. For the annual report, the annual data collection is aggregated for each patient across all caregiving centres per patient (Level 0). Since 1995 (as of 30 July 2023), data on 9686 individuals with 141 960 annual follow-up data have been collected. The database will be locked 6 months after the end of the calendar year in order to provide the data for research request and publish each year in autumn an annual report.

2 | Data Collected

The GCFR collects data of all individuals diagnosed with CF and associated disorders who are seen at participating CF centres and who provide informed consent. Although a CF diagnosis is the main inclusion criterion, in 2015, the GCFR also began to include patients with CFTR-related disorders and people classified as CF screening positive, inconclusive diagnosis (i.e., CFSPID), with allowance for a change in the clinical diagnosis over time.

In 2021, encounter-based documentation was available for more than 85% of all people with CF with follow-up data in the GCFR (Figure 1). The dataset contains core data such as sex, date and place of birth, ethnicity, diagnosis, diagnostic criteria met (including results of confirmatory tests such as the sweat test, genotyping for CF transmembrane conductance regulator gene variants and electrophysiology) and if applicable, maternal/paternal status, organ transplantation, date and cause of death or if lost to follow-up but alive, last date confirmed alive [4]. Annually collected and aggregated data from patient encounters include anthropometrics, pulmonary function tests, respiratory microbiology, CF-related laboratory tests, mental health screening, CF-related complications and CF-related therapies (including start/stop dates and reason for stopping), episodes of antibiotic treatments (including reason) and hospitalisations (including reason).

The dataset reflects clinical practice and clinically relevant safety concerns. The data collection process for each encounter includes consideration of the period since the last encounter. For the annual dataset, the clinical status and lung function reported closest to the patient's birth date without exacerbation were used until data collection year 2014. From 2015, for patients age ≥ 6 years who have undergone a lung function measurement, the encounter with the best forced expiratory volume in the first second as a percentage of predicted values (FEV1%) and the associated height and weight measurements have been selected for recording. In cases of missing FEV1 measurements and for children under age 6 years, the last available height and weight measurements for the reporting year are used.

Until 2014, the annual dataset remained unchanged. A major update was introduced in 2015 because of major changes in clinical practice and to harmonise registry data with data from international CF registries such as the European CF Society Patient Registry. In addition to the 2015 update of the annual dataset, minor updates have been introduced subsequently. The publicly available data dictionary records these changes, including the dates of changes [4].

Until 2012, annual follow-up data were collected until death or lung transplantation. Since 2013, follow-up after transplantation has been queried, and a follow-up query for all people with CF in the GCFR without follow-up-data has been established to close the gap between loss to follow-up or to transplantation and death.

The registry data support reporting from three perspectives: an annual snapshot of the CF population in Germany, the overall surviving CF population and an estimation of the general CF population. The annual report relies on only those

people with CF who have annual follow-up data in the calendar year, characterising a single annual cohort each year. For example, the annual report from 2019 included a cohort of 6471 people living with CF and annual follow-up data [5]. Based on follow-up information (status living or dead in the calendar year), 7250 people with CF were represented in the CF registry for 2019.

In addition to this annual snapshot, the report allows for estimation of the general CF population. For example, the 2019 annual report covered 89.3% of the living CF population (Figure 1), with age-dependent variation ranging from 99.1% among those age 0–4 years to 80.0% among those age ≥ 50 years (Table 1). Transition from paediatric to adult care contribute to the observed decrease in young adults (Table 1). Based on our informed personal experience, the non-consent rate in this registry is ~5%. Taking this proportion into account, we estimate that there were 7613 people in the general CF population, so that the registry represented 95% coverage of the living CF population for the year 2019.

Various measures are incorporated into the GCFR to ensure data quality. The data elements are harmonised, well defined, well perceived by the CF centres and described in data coding documents and up-to-date user guides. The Muko.web software is user friendly and includes helpful hints, displays of data completeness for each encounter and each data element ('quality dashboard'), comparison with previous encounters, quality checks for implausible or out-of-range data entries and data overviews for important data elements at the centre or individual patient level, with benchmarks against national averages. The data management provides a service desk, training and updates for the centres and their staff at regular intervals, along with a newsletter and performance of quarterly rather than annual data queries for encounter-based documentation to minimise missing entries and discrepancies. Patients who are lost to follow-up are traced each year individually by the trust authority at the IZKS. In 2019, datasets were complete for annual data of 98% of all people with CF.

Data validation visits at the CF centre level have been performed since 2018 at 20 centres, with checks of selected core and annual datasets for 567 randomly selected people with CF against the medical health records (Table 2). During 2018–2023, genetic information has rarely been incorrect (1.9%), but a genetic report was missing in 23.6% of cases. Centres were instructed to retrieve the original genetic report or re-genotype the pwCF. In up to 12%, the best FEV1% value (level 1 documentation) and

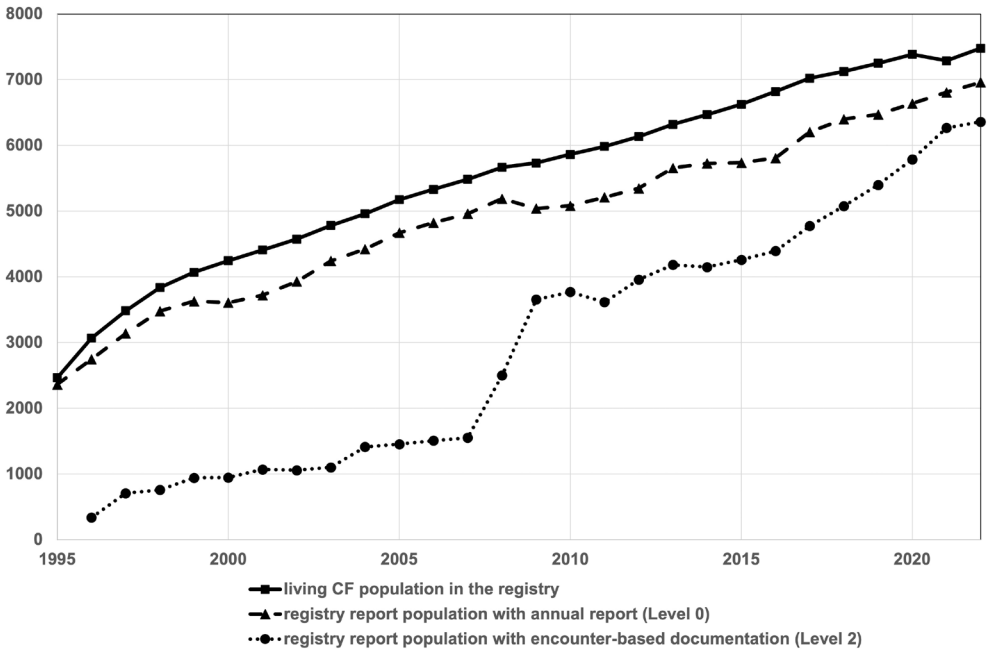

FIGURE 1 | Annual count of people with cystic fibrosis (CF) in the German CF Registry divided by registry report population (encounter-based documentation, or Level 2; annual report, or Level 0) and living CF population in the registry from 1995 to 2022.

TABLE 1 | People with cystic fibrosis (CF) in the German CF Registry (GCFR) with annual follow-up data (AFUD) (the GCFR annual report population) and without annual follow-up data (the GCFR living population) for 2019, by age ranges.

Age range, years	0–5	6–11	12–17	18–29	30–39	40–49	≥ 50	Total
With AFUD	877	897	925	1814	1120	522	316	6471
Without AFUD	8	34	43	275	211	129	79	779
Total	885	931	968	2089	1331	651	395	7250
% (with AFUD/total)	99.1%	96.3%	95.6%	86.8%	84.1%	80.2%	80.0%	89.3%

TABLE 2 | Accuracy and consistency of annual onsite data validation visits during 2018–2023 (20 centres and annual data set for 567 people with cystic fibrosis).

Data elements	Consistent and accurate (%)
Sex	100
Birth date	99.7
Transplantation	99.6
Height	92.9
Weight	90.1
Forced expiratory volume in the first second	88.0
Mutation[a]	74.5
Chronic use of inhaled antibiotics	89.2
Chronic use of rhDNAse	97.9
Use of pancreatic enzymes	97.4
CFTR modulator[b]	94.2
Chronic infection with *Pseudomonas aeruginosa*	95.6
Chronic infection with *Burkholderia cepacia* complex	99.3
Liver disease	93.7
Diabetes mellitus	97.9
Haemoptysis	95.6

Abbreviations: CTFR, cystic fibrosis transmembrane conductance regulator; rhDNAse, recombinant human DNase I.
[a]Checked against original genetic reports as data source.
[b]Checked only since 2023 and in 155 people with CF.

corresponding weight/height were not documented. Some variables, such as liver disease, need a clearer definition. Overall, however, the accuracy and consistency of the selected core and annual data have exceeded 95%.

3 | Data Resource Use

The GCFR is used to inform the individual patient (with the aim of patient empowerment), the centres (with the aim of improved patient care and quality control) and health authorities and industry (with the aim of improved planning of care and pharmacovigilance) and to enable research to improve CF care at the national and international levels [6]. Since 2006, a harmonised annual data set has been shared yearly with the European Cystic Fibrosis Society Patient Registry [7].

Since 1995, the GCFR has published a publicly available annual report to inform caregivers, patients, health authorities, and industry in a timely way about current CF epidemiology and longitudinal changes over time [8]. Since 2018, a patient and family version with additional background information has been available [9].

Quality improvement has been a focal point of the GCFR from the beginning. In the web-based software, CF centres can directly access individual patient and centre overviews and benchmark with other CF centres. An open benchmarking project was begun in 2004 with 12 CF centres and now includes 35 centres that participate in encounter-based documentation, with reported improvements in care [10].

Research requests have been supported to inform understanding of CF epidemiology, changing demographics, outcomes and treatments. For example, 2023 publications based on registry data have covered the real world impact of elexacaftor/tezacaftor/ivacaftor [11], survival-adjusted FEV1%/body mass index percentiles for people with CF [12], chronic inhaled antibiotic therapy [13] and atypical mycobacteria [14].

The registry data also support pharmacovigilance in the best interest of the patients, CF caregivers and health authorities. Based on a 2015 European Medial Agency (EMA) initiative to use registry data for pharmacovigilance [15], the GCFR since 2019 has contributed to pharmacovigilance studies required by EMA at the national (EUPAS43022, EUPAS20990, EUPAS30550) and international (via the European Cystic Fibrosis Society Patient Registry) levels by providing anonymised, aggregated data supporting safety and efficacy monitoring of new therapies for CF. As an example, the German CF Registry data contribute to the multinational registry-based study on effectiveness of lumacaftor/ivacaftor initiation in children with CF aged 2–5 years on disease progression [16].

During the COVID pandemic, the GCFR collected COVID cases involving people with CF in Germany, presented up-to-date information about how COVID affected this patient population, and shared the data with a global CF registry group to increase knowledge about the impact of COVID for people with CF and related risk factors [17–19].

A pilot project, MUKO.me, began in 2023 with the aim of enhancing patient participation in the registry. The project involves giving people with CF direct online access to their individual patient overviews and the ability to interact with the CF centres through instruments such as questionnaires related to aspects of quality of life, which will be added to the data collection.

4 | Strengths and Weaknesses

Since 1995, the GCFR has served as a high-quality, longitudinal real world CF data source with high coverage. Encounter-based documentation in an increasing number of patients over the last decade (Figure 1) has generated additional granularity, especially for analysing the effects of new medications. A caveat is that automatic aggregation of encounter data can result in some missing information if the timing occurs after the last encounter of the calendar year.

The coverage of the GCFR relies on the commitment of each respective CF centre because registry participation is not obligatory by national law, in contrast to cancer and transplantation

registries. Mukoviszidose e.V. has sponsored the GCFR since 1995, offers grants for the centres to support data entry, and is committed to the long-term sustainability of the data source.

General data protection laws in Germany preclude data linkage with screening laboratories for newborns, the transplantation registry and the death registry. This lack of linkage access is a major obstacle to tracking an entire case evolution from diagnosis to death. After transplantation, many people with CF are followed up only in transplant centres rather than in CF centres. As noted, because of German laws, the transplantation registry does not crosslink with the GCFR, which results in a lost to follow-up scenario for the patient in the GCFR. Lost to follow-up queries could be closed or minimised with great effort in the German population registers. Furthermore, patients without an updated consent form had to be anonymised in 2020, which made tracking of their cases impossible and led to a slightly and inaccurately decreased follow-up rate for the living CF population in the GCFR.

5 | Data Resource Access

Personally identifying data (IDAT) and personal medical health data (MDAT) are collected as part of the GCFR and are stored separately on physically separate servers from two independent external service providers. Pseudonyms are used instead of personally identifying data and are automatically generated with the help of Mainzelliste, a web-based, centralised pseudonymisation service [20]. This service secure that all centres receive the same pseudonym for the same patient. In rare cases of ambiguity, the trusted authority at the IZKS can intervene. The data centre responsible for storing personally identifying and medical data are state of the art and meet current data protection and data security requirements. The communication between the registry components always takes place via encrypted connections (i.e., HTTPS). Keys and certificates used for this purpose correspond to the requirements described in the current baseline protection catalogues of the Federal Office for Information Security [21]. The system offers an audit trail for all data entries and data access.

Patient medical data documented in the registry can be viewed only by the CF registry's data management and statistics team and clinical team members, who can access the personal and medical data only for patients in their care including a retrospective view of the course of disease independent of centres involved. Research requests are processed exclusively by the registry's internal statistics team and sent to the applicant in the form of aggregated reports. Transfer of raw data to third parties is highly restricted. The process for research requests including the application form can be found at the GCFR website [4].

Author Contributions

L.N. and M.B. drafted reviewed the manuscript.

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Ethics Statement

The Justus-Liebig-University Giessen has granted an ethical approval (AZ24/19) for the collection and use of data into the GCFR. There are positive data protection votes for the GCFR from responsible data protection authorities. Each patient or their guardians provided written informed consent for collection of data, including use of pseudonymised data in research. A trust authority at the IZKS was established in 2018 and can view personally identifying data and safeguard patient data protection rights. This authority also will in the future be active as a potential interface with other research-related databases such as the transplantation registry that serve the purpose of the GCFR.

Conflicts of Interest

L.N. is the medical lead of the German CF Registry, the pharmacovigilance study manager of the European CF Society Patient Registry and the principal investigator for GCFR and ECFSPR based pharmacovigilance studies for Chiesi Farmaceuti S. p. A. and Vertex Pharmaceuticals. M.B. is employee of the Mukoviszidose Institut gGmbH, Bonn, Germany, a non-profit limited company of the Mukoviszidose e.V.

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Appendix A

Registry Working Group of the German CF Registry

Ines Adams (Kinderklinik, Otto-von-Guericke Universität Magdeburg), Andreas Artlich (Klinik für Kinder und Jugendliche, Oberschwabenklinik (OSK) gGmbH, Ravensburg), Manfred Ballmann (Kinder- und Jugendklinik Pneumologie und Allergologie, Universitätsmedizin Rostock), Joachim Bargon (Klinik für Pneumologie, Frankfurter Rotkreuz-Kliniken e.V., Frankfurt), Monika Bauck (Klinik für Kinder- und Jugendmedizin II, Pädiatrische Pneumologie, Phillipps Universität Marburg), Stefan Blaas (Zentrum für Pneumologie, Klinik Donaustauf), Ingrid Bobis (4. Medizinische Klinik Christiane Herzog-Zentrum Nord, Städtisches Klinikum Kiel), Sebastian Bode (Klinik für Kinder- und Jugendmedizin, Universitätsklinikum Ulm), Folke Brinkmann (Campus Lübeck, Klinik für Kinder-und Jugendmedizin Universitätsklinikum Schleswig Holstein, Lübeck), Susanne Büsing (Zentrum für Kinder- und Jugendmedizin, Christliches Kinderhospital Osnabrück), Malte Cremer (Zentrum für Kinder- und Jugendmedizin, Allgemeine Pädiatrie, Klinikum Frankfurt (Oder)), Doris Dieninghoff (Lungenklinik Merheim, Kliniken der Stadt Köln). Stefanie Dillenhöfer (St. Josef Hospital—Klinik für Kinder- und Jugendmedizin—Christiane Herzog-Zentrum UKRUB—Katholisches Klinikum Bochum), Anna-Maria Dittrich (Klinik für Pädiatrische Pneumologie Christiane Herzog-Zentrum Medizinische Hochschule Hannover (MHH), Helmut Ellemunter Tirol Kliniken GmbH Kinder- und Jugendheilkunde—Mukoviszidose-Zentrum Medizinische Universität Innsbruck/Austria), Sebastian Fähndrich (Klinik für Pneumologie, Universitätsklinikum Freiburg), Rainald Fischer (Lungenheilkunde München Pasing, München), Sara Lisa Fleser (Klinik für Allgemeine Pädiatrie und Neonatologie Universitätsklinikum des Saarlandes, Homburg), Norbert Geier (Klinik für Kinder- und Jugendmedizin Klinikum am Gesundbrunnen, Perinatalzentrum SLK-Kliniken Heilbronn), Nikola Gjorgjevski (Kinder- und Jugendmedizin, Helios Kliniken Schwerin), Ute Graepler (Klinik für Kinder- und Jugendmedizin, Universitätsklinikum Tübingen), Matthias Griese (Kinderklinik und Kinderpoliklinik im Dr. von Haunerschen Kinderspital, LMU Klinikum der Universität München), Jörg Große-Onnenbrink (Klinik für Kinder- und Jugendmedizin Allgemeine Pädiatrie, Universitätsklinikum Münster), Jutta Hammermann (Universitäts-Mukoviszidose-Centrum, Universitätsklinikum Carl Gustav Carus, Dresden), Helge Hebestreit (Kinderpoliklinik Christiane Herzog-Zentrum Unterfranken, Universitätsklinikum Würzburg), Andrea Heinzmann (Zentrum für Kinder- und Jugendmedizin, Universitätsklinikum Freiburg) Inka Held (Praxis Kinderärzte im Friesenweg, CF Centrum Altona Kinder- und Jugendärztliche Gemeinschaftspraxis, Hamburg), Manfred Käding (Praxis für Kinder- und Jugendmedizin, Poliklinik Chemnitz), Petra Kaiser (Klinik für Kinder- und Jugendmedizin Christiane Herzog-Zentrum Eltern-Kind-Zentrum Prof. Hess, Bremen), Wolfgang Kamin (Klinik für Kinder- und Jugendmedizin Pulmologie/Allergologie, Evangelisches Krankenhaus Hamm (EVK)), Axel Kempa (Fachklinik Löwenstein, SLK-Kliniken Heilbronn, Löwenstein), Alexander Kiefer (Kinder- und Jugendmedizin, Klinik St. Hedwig, Regensburg), Birte Kinder (Klinik für Kinder- und Jugendmedizin, Dietrich Bonhoeffer Klinikum, Neubrandenburg), Bastian Klinkhammer (Zentrum für Kinder- und Jugendmedizin, Helios Klinikum Krefeld), Cordula Koerner (Klinik für Kinder- und Jugendmedizin, Marien Hospital Wesel gGmbH, Wesel), Holger Köster (Klinik für Pädiatrische Pneumologie und Allergologie, Neonatologie und Intensivmedizin Klinikum Oldenburg AöR), Markus Kratz (Klinik für Kinder- und Jugendmedizin Baden-Baden Balg, Klinikum Mittelbaden gGmbH, Baden-Baden), Stefan Kuhnert (Medizinische Klinik und Poliklinik II, Justus-Liebig-Universität Gießen), Peter Küster (Kinder- und Jugendmedizin, Clemenshospital Münster), Kerstin Landwehr (Klinik für Kinder- und Jugendmedizin Schwerpunkt Kinder-Pneumologie, Evangelisches Klinikum Bethel, Bielefeld), Simone Lehmkühler (Klinik für Kinder- und Jugendmedizin Pädiatrische Pneumologie und Allergologie, Universitätsmedizin Mannheim), Michael Lorenz (Klinik für Kinder- und Jugendmedizin, Universitätsklinikum Jena), Eva Lücke (Klinik für Pneumologie, Otto-von-Guericke-Universität Magdeburg), Rolf Mahlberg (Innere Medizin 1, Klinikum Mutterhaus der Borromäerinnen, Trier), Jochen Mainz (Klinikum Westbrandenburg Pädiatrische Pulmologie und Allergologie, Medizinische Hochschule Brandenburg (MHB)), Jochen Meister (Klinik für Kinder- und Jugendmedizin, HELIOS Klinikum Aue), Philipp Meyn (Fachkliniken Wangen, Klinik für Pneumologie Waldburg Zeil Kliniken, Wangen), Susanne Nährig (Campus Innenstadt Medizinische Klinik—Pneumologie LMU Klinikum der Universität München), Anna Nolde (II. Medizinische Klinik und Poliklinik Sektion Pneumologie, Universitätskliniken Eppendorf UKE, Hamburg), Thomas Nüßlein (Klinik für Kinder- und Jugendmedizin, Gemeinschaftsklinikum Mittelrhein, Koblenz), Claus Pfannenstiel (Kinderarztpraxis Laurensberg Aachen), Anne Pfülb (Klinik für Kinder- und Jugendmedizin, Klinikum Memmingen), Maike Pincus (Klinik für Kinder- und Jugendmedizin Pulmologie und Allergologie, Helios Klinikum Berlin Buch, Berlin), Margarethe Pohl (Zentrum für Kinder- und Jugendgesundheit Kinderpneumologie, Kinderklinik Dritter Orden, Passau), Krystyna Poplawska (Klinik für Kinder- und Jugendmedizin Pädiatrische Pneumologie und Allergologie, Universitätsmedizin Mainz), Freerk Prenzel (Klinik und Poliklinik für Kinder- und Jugendmedizin, Universitätsklinikum Leipzig), Silke van Koningsbruggen-Rietschel (Klinik für Kinder- und Jugendmedizin, Universitätsklinikum Köln), Felix C. Ringshausen (Klinik für Pneumologie, Medizinische Hochschule Hannover (MHH)), Markus A. Rose (Zentrum für chronische Lungenerkrankungen, Christiane Herzog Transitionszentrum, Klinikum Stuttgart—Olgahospital, Stuttgart), Josef Rosenecker (Fachkliniken Wangen, Rehabilitationsklinik für Kinder und Jugendliche Waldburg-Zeil Kliniken, Wangen), Friederike Ruf (Pneumologie und Beatmungsmedizin, Robert Bosch Krankenhaus RBK, Stuttgart), Anette Scharschinger (Klinik für Kinder- und Jugendmedizin, Kinderpneumologie und Allergologie, Universitätsklinikum Augsburg), Martin Schebek (Pädiatrische Hämatologie und Onkologie, Psychosomatik und Systemerkrankungen, Klinikum Kassel), Sebastian Schmidt (Klinik für Kinder- und Jugendmedizin, Universitätsmedizin Greifswald), Sabina Schmitt-Grohe (Kinderklinik—Sozialpädiatrisches Zentrum, Universitätsklinikum Erlangen), Gudrun Schopper (Klinik für Kinder- und Jugendmedizin, Allergologie, Pneumologie, Umweltmedizin München, Klinik Schwabing, München), Antje Schuster (Klinik für Allgemeine Pädiatrie, Neonatologie und Kinderkardiologie UKD Universitätsklinikum Düsseldorf), Carsten Schwarz (Klinikum Westbrandenburg gGmbH, Potsdam), Christina Smaczny (Christiane Herzog CF-Zentrum, Universitätsklinikum Frankfurt), Olaf Sommerburg (Sektion Pädiatrische Pneumologie und Allergologie, Universitätsklinikum Heidelberg), Dana Spittel (Kinder- und Jugendmedizin, Helios Klinikum Erfurt), Mirjam Stahl (Klinik für Pädiatrie m. S. Pneumologie und Immunologie—Christiane Herzog-Zentrum Charité—Universitätsmedizin Berlin), Dirk Steffen (Innere Medizin, Luisenhospital Aachen), Florian Stehling (Klinik für Kinderheilkunde III, Christiane Herzog Centrum Ruhr, Universitätsklinikum Essen (AöR)), Simone Stolz (Akademisches Lehrkrankenhaus der Charité Klinik für Kinder- und Jugendmedizin Carl-Thiem-Klinikum Cottbus), Sivagurunathan Sutharsan (Ruhrlandklinik—Klinik für Pneumologie, Christiane Herzog-Zentrum Universitätsmedizin Essen), Klaus Tenbrock (Klinik für Kinder- und Jugendmedizin, Pädiatrische Pneumologie, Uniklinik RWTH Aachen), Tobias Tenenbaum (Klinik für Kinder- und Jugendmedizin, Sana Klinkum Lichtenberg, Berlin), Tina Teßmer (Klinik für Kinder- und Jugendmedizin, Klinikum Worms gGmbH), Wolfgang Thomas (Kinder- und Jugendmedizin, Klinikum Mutterhaus der Borromäerinnen, Trier), Christian Timke (Kinderklinik und Jugendmedizin, Christiane Herzog-Zentrum Nord, Städtisches Krankenhaus Kiel), Paul Vöhringer (Klinik für Kinder- und Jugendmedizin Pneumologie, Städtisches Klinikum Karlsruhe), Sabine Wege (Thoraxklinik Heidelberg gGmbH, Pneumologie und Beatmungstherapie, Universitätsklinik Heidelberg), Britta Welzenbach (Klinik für Kinder- und Jugendmedizin, Sozialpädagogisches Zentrum (SPZ), KJF Klinik Josefinum Augsburg), Heinrike Wilkens (Innere Medizin V—Pneumologie, Allergologie Beatmungs- und Umweltmedizin, Universitätsklinikum des Saarlandes. Homburg), Bettina Wollschläger (Medizinische Fakultät der Klinik für Innere Medizin I, Universitätsklinikum Halle (Saale) UKH, Halle), Sabine Zirlik (Medizinische Klinik 1 Schwerpunkt Pneumologie Universitätsklinikum Erlangen).