Clinical Scope and Healthcare Utilization in Childhood Interstitial Lung Disease at a Tertiary Center

Lisa Young[1], Lance Feld[1], Laura Voss[1], Zeyu Nancy Li[1], Jessica Rice[1], Maureen B Josephson [1], Yun Li[1], and Sharon McGrath-Morrow[1]

[1]The Children's Hospital of Philadelphia

March 26, 2023

Abstract

Childhood interstitial lung disease (chILD) is a heterogeneous group of diffuse lung diseases (DLD) that can be challenging to diagnose. With relative rarity of individual entities, data are limited on disease prevalence, care patterns, and healthcare utilization. The objective of this study was to evaluate chILD prevalence and review diagnostic and clinical care patterns at our center. A single-center, retrospective cohort study was conducted of patients receiving care at the Children's Hospital of Philadelphia (CHOP) between January 1, 2019, and December 31, 2021. Through query of selected ICD-10 billing codes relevant for chILD/DLD, a total of 306 patients were identified receiving care during this period. Respiratory symptom onset was documented to have developed before two years of age for 40% of cases. The most common diagnostic categories included those with oncologic disease (21.2%), bronchiolitis obliterans (10.1%), and connective tissue disease (9.5%). Genetic testing was performed in 49% of cases, while 36% underwent lung biopsy. Hospitalization at CHOP had occurred for 80.4% of patients, with 45.1% ever hospitalized in an intensive care unit. One-third of children had required chronic supplemental oxygen. Seven (2.3%) patients died during this three-year period. Collectively, these data demonstrate the scope of chILD and extent of health care utilization at a large volume tertiary care center. This approach to cohort identification and EMR-driven data collection in chILD provides new opportunities for cohort analysis and will inform the feasibility of future studies.

Introduction

Childhood interstitial lung disease (chILD), also referred to as diffuse lung disease (DLD), is a heterogenous group of disorders with overlapping clinical, radiographic, and pathologic characteristics. While chILD is considered rare, the incidence and prevalence are not well established.[1] Over the past 30 years, the scope of the field has expanded through recognition of specific disease entities. For example, surfactant protein B deficiency was first described in the early 1990's,[2] with reports of*SFTPC* and *ABCA3* mutations as causes of chILD in 2001 and 2005, respectively,[3; 4] followed by the definite description of Neuroendocrine cell Hyperplasia of Infancy (NEHI) in 2005.[5] After development of consensus terminology and lung biopsy classification, the first clinical practice guideline was published in 2013.[6-8] Further advances in molecular genetics and imaging technology have subsequently modified the diagnostic approach, though limited data are available on the clinical utility of genetic testing for chILD.

In 2012, a revision to the International Classification of Diseases (ICD) Ninth Revision added codes for several chILD disorders under an umbrella diagnosis of "Other alveolar and parietoalveolar pneumonopathy", which included code for surfactant mutations of the lung, NEHI, and other interstitial lung diseases of childhood.[9] The currently utilized tenth revision of ICD codes expanded the codes for systemic disease associated with pulmonary manifestations[10]. Billing codes have not previously been utilized as a case ascertainment method for research in chILD.

In this study, we sought to evaluate recent practices at a tertiary care medical center to better understand

chILD prevalence, care patterns, healthcare utilization, and outcomes. We identified diagnostic challenges and found substantial inpatient and multidisciplinary outpatient care utilization. By highlighting the scope of this patient population and associated care needs, this knowledge can be leveraged to inform healthcare delivery in the future.

*MethodsStudy population*A single-center, retrospective cohort study of patients receiving care at the Children's Hospital of Philadelphia (CHOP) was performed. This study was granted exempt approval with waiver of informed consent from the CHOP Institutional Review Board (IRB 19-016269). Patients were identified based on a query of selected ICD-10 billing codes (**Supplemental Table 1**) relevant for chILD/DLD. Medical records were then reviewed for patients who had either outpatient or inpatient pulmonary encounters between January 1, 2019, and December 31, 2021, curating cases for inclusion after chart review to confirm ILD/DLD diagnosis. Data collection included EMR data through September 28, 2022, allowing time for diagnostic testing and clinical follow up after initial evaluations.

*Study design and data collection*Outpatient and inpatient encounters, medication exposure data, and procedural history were obtained via electronic medical record (EMR) reports developed for this study. Supplemental chart review was performed, focused on assessment of diagnostic testing performed outside of CHOP and characterization of disease severity and outcomes. Study data were collected and managed using Research Electronic Data Capture electronic data capture tools hosted at CHOP.[11; 12]Disease categories or classification were designated by the study team based on the aggregate of available clinical data, genetic testing, imaging, and lung biopsy reports in the EMR.

*Statistical analysis*We analyzed EMR data based on lifetime to date and the time period between 2019-2021. Descriptive statistics were utilized, with reporting of means and standard deviations (SD) for continuous variables and frequencies and percentages for categorical variables.

*Results Patient demographics and clinical characteristics*Through ICD-10 billing diagnoses, a total of 306 patients were identified as receiving care during this 3-year period. Demographic characteristics are summarized in **Table 1** . A slight majority (55%) of patients were male, and 77.1% were born as a result of full-term ([?] 37 weeks) pregnancies. More than half (56.2%) of the cohort identified as white race and two-thirds (66.7%) had private insurance, in comparison to white race for 53.3% and private insurance for 52.4% among all patients seen with outpatient encounters in the Division of Pulmonary and Sleep at CHOP during the same time period. For those patients with a documented age of onset of respiratory symptoms (n=231), 40.7% had respiratory symptom onset in the first two years of life, with 30.3% developing symptoms before six months of age. The onset of respiratory symptoms was not documented in the EMR for 24.5% of the cohort. Overall, 70 (22.9%) patients were referred for a second opinion after seeing a pulmonologist at another institution.

*Distribution of ILD diagnoses*DLD associated with oncologic disorders was the most common diagnostic category, accounting for 65 (21.2%) cases (**Table 2**). We also identified cases of bronchiolitis obliterans (n=31, 10.1%), DLD associated with connective tissue diseases (n=29, 9.5%), NEHI (n=28, 9.2%), environmental/toxic related lung injury (n=27, 8.8%), and alveolar hemorrhage disorders (n=23, 7.5%). Surfactant metabolic dysfunction was responsible for 19 cases (6.2%), while 15 cases (4.9%) had DLD associated with immune-related disorders. There were multiple other diagnoses for which three or fewer patients were identified (**Supplemental Table 2**). For 32 cases (10.5% of the cohort), a definitive diagnosis or classification could not be assigned based on EMR data. The overall cohort mean age at time of diagnosis was 7.3 years (SD 6 years).

Diagnostic testing and monitoring Almost all patients (92.2%) had chest computed tomography (CT) scans, with 220 (71.9%) patients having at least one chest CT between 2019-2021. Flexible bronchoscopy was performed in 97 (31.7%) patients ever in their lifetime, with procedures in 73 (23.9%) patients during the recent 3-year period. Echocardiography was performed in 195 patients (63.7%) ever in their lifetime and half (n=153, 50%) of patients during the 3-year period, with a mean of 2.1 (SD 2.7) procedures per patient per year.

Lung tissue sampling was performed in 110 (35.9%) patients in a variety of contexts (**Figure 1A**), with 72 (65.5%) patients having the procedure at our center at a mean age of 7.6 years (SD 6.3 years). Fifty-two (72.2%) patients had a wedge biopsy. In addition, there were 13 transbronchial biopsies, six lung nodule biopsies, three endobronchial ultrasound with transbronchial needle aspiration procedures, two lobectomies, two bronchial biopsies, two core needle biopsies, and one endobronchial mass excisional biopsy. Of the 23 patients identified with alveolar hemorrhage, most (n=20, 87%) underwent lung biopsy, resulting in histologic diagnosis of capillaritis in 50%**.** Over half (52.6%) of patients ultimately diagnosed with surfactant metabolic dysfunction underwent lung biopsy. Notably, 45 (40.1%) patients had a lung biopsy performed at an outside institution; seven of these patients subsequently had a lung biopsy repeated at our center.

In total, 149 (48.7%) patients underwent genetic testing relevant for their lung disease evaluation (**Figure 1B**), and 38 (25.5%) of tested patients had a diagnosis established by genetic testing (**Figure 2).** Alterations in genes impacting surfactant metabolism dysfunction accounted for 50% of positive results. CHOP providers ordered the testing for 22 (57.9%) of positive results. The 76-gene CHOP Comprehensive Pulmonary-Vascular Panel was performed for 41 cases and yielded positive results in four cases. Two patients were found to be compound heterozygous for variants in *ABCA3* , one patient was found to be heterozygous for a *de novo* pathogenic variant in *SFTPC* , and one patient was heterozygous for a pathogenic deletion within chromosome 14q12, which includes the *NKX2.1* gene. CHOP providers ordered other respiratory relevant genetic analyses in 61 patients, including single gene testing/targeted variant testing and targeted pulmonary gene panels for 47 patients, 14 of which resulted in a molecular diagnosis. Chromosomal microarray analyses were performed in 21 patients, all of which were non-diagnostic. Respiratory-relevant genetic testing was performed prior to referral to our center in 41 patients, with molecular diagnosis established by single gene testing/targeted variant testing and targeted pulmonary gene panels for 14 (37.8%) of 37 patients.

Whole exome sequencing (WES) was performed in 58 (38.9%) patients, was ordered by CHOP providers in 42 (72.4%) instances and was diagnostic for six (10.3%) patients. Positive findings resulted in diagnoses of CHOPS syndrome (n=2), ataxia telangiectasia (n=2), lysosomal storage disease (n=1), and one diagnosis of an immune-related disorder (*STAT1* gain-of-function variant). Two of the patients diagnosed through WES also had non-diagnostic targeted pulmonary gene panels, including one patient with CHOPS syndrome and one with lysosomal storage disease (GM1 gangliosidosis).

In examining the diagnostic categories of patients who underwent genetic testing within the overall cohort, NEHI made up the largest group (n=21, 14.1%), followed by those with ILD not otherwise specified (NOS) (n=19, 12.8%), surfactant metabolic dysfunction (n=18, 12.1%), DLD associated with connective tissue disorders (n=16, 10.7%), and bronchiolitis obliterans (n=14, 9.4%). Patients with surfactant metabolic dysfunction and those ILD NOS were among those most likely to have undergone genetic testing (94.7% and 82.6%, respectively, **Figure 1B**).

Both genetic testing and lung biopsy were performed in 63 (20.6%) unique patients. Those with alveolar hemorrhage disorders were the largest subgroup (n=12, 19.0%), followed by nine (14.3%) patients with DLD associated with connective tissue disease and seven (11.1%) patients with surfactant metabolic dysfunction. We analyzed the time order of testing for the 20 patients who had the CHOP Comprehensive Pulmonary-Vascular Panel and lung biopsy performed, as we could confirm the order timing within our institution. Eleven patients had lung biopsy performed prior to genetic testing, while eight had genetic testing performed first. One patient had lung biopsy performed on the same day that genetic testing was initiated. Ultimately, six patients who had a lung biopsy later had a genetic diagnosis established.

*Outpatient care utilization*Within this cohort, nearly all patients (96.1%) received outpatient pulmonary care at our center. A mean of 2.8 (SD 2.6) outpatient pulmonary visits per patient per year occurred between 2019-2021. Cardiology, endocrinology, and gastroenterology were other highly utilized medical subspecialties (**Figure 3**). At our center, more patients had encounters with nutrition and physical therapy than with speech and language pathology or occupational therapy.

*Hospitalizations*We quantified the hospitalization events using EMR data for hospital days at CHOP both

for lifetime to date and for the 3-year period from 2019-2021. In their lifetime, 246 (80.4%) patients had ever been hospitalized at CHOP, while nearly half (n=138, 45.1%) had ever been hospitalized in an intensive care unit (ICU). Between 2019-2021, 176 (57.5%) patients were hospitalized, with a mean of 42.1 (SD 80.6) hospital days and 3.1 (SD 3.5) hospitalizations per hospitalized patient. ICU admission occurred in 82 patients, reflecting 26.8% of all chILD patients and 46.6% of the hospitalized chILD patients, and accounting for a mean of 38.4 (SD 93.2) ICU days and 1.8 (SD 1.9) ICU hospitalizations per ICU hospitalized patient. When considering hospitalization burden across the entire cohort, the mean number of hospitalization events per patient was 1.8 (SD 3.0) during this 3-year period, with 0.5 (SD 1.3) ICU hospitalization events per patient.

In examining hospitalization data based on diagnostic category from 2019-2021, the largest group of hospitalized patients was DLD associated with oncologic disorders (n=34, 19.3%). Other groups of patients who accounted for the most hospitalizations were patients with environmental/toxic related lung disease (n=26, 14.8%), bronchiolitis obliterans (n=16, 9.1%), alveolar hemorrhage disorders (n=16, 9.1%), and DLD associated with connective tissue disease (n=19, 10.8%). Within each of these disease categories, most patients were hospitalized at least once in their lifetime (**Figure 4A**). Between 2019-2021, the percentage of ICU hospitalization by disease category was greatest for patients with surfactant metabolic dysfunction (42.1%), alveolar hemorrhage disorders (30.4%), and DLD associated with oncologic disorders (27.7%) (**Figure 4B**)**.**

*Medication utilization*Medication exposure most relevant for treatment of chILD/DLD was examined. Due to the EMR driven, retrospective methodology of our study, medication exposure was defined as documentation of an inpatient order or presence of medication on the medication list associated with an outpatient encounter. In examining lifetime exposure, 78% of patients had some form of oral and/or intravenous corticosteroid ever prescribed, and 57% were prescribed intravenous corticosteroids (methylprednisolone). Between the years of 2019 and 2021, 10.5% of patients were prescribed intravenous corticosteroids, while 29.4% had oral and/or intravenous corticosteroids prescribed.

Hydroxychloroquine was prescribed for 10.5% (n=32) of the overall cohort across their lifetime, with 7.8% (n=24) of the cohort receiving hydroxychloroquine between 2019 and 2021 at a mean age of 10.6 years (SD 6.4) at the time of the first prescription. The most frequent underlying diagnoses for patients prescribed hydroxychloroquine were surfactant metabolic dysfunction (n=11, 45.8%) and DLD associated with connective tissue disease (n=7, 29.2%). Pirfenidone was prescribed for eight (2.6%) patients, including three with DLD associated with oncologic disease, two with DLD associated with connective tissue disease, and one each with bronchiolitis obliterans, surfactant metabolic dysfunction, and fibrotic lung disease of unknown etiology.

*Respiratory support and Outcomes*In the overall cohort, 32.7% had ever required chronic home supplemental oxygen, 12.4% had ever received chronic non-invasive respiratory support, and 4.6% underwent tracheostomy for chronic invasive respiratory support. The mean age at time of tracheostomy placement was 4.8 (SD 6.1) years. Chronic supplemental oxygen use was prevalent in patients with NEHI, accounting for 24% of the group with home supplemental oxygen use in general.

Of the 306 patients seen between 2019-2021, seven (2.2%) patients had died as of January 1, 2022, including four with DLD associated with oncologic disorders, one with DLD associated with connective tissue disease (juvenile dermatomyositis with pulmonary involvement), one with surfactant metabolic dysfunction (*SFTPC*), and one with DLD associated with immune-related disorders (severe combined immunodeficiency disease). Five deaths were to due respiratory failure, while in two patients cause of death was not documented. Pulmonary fibrosis was associated with mortality in four patients, including the one with connective tissue disease (juvenile dermatomyositis), one with ILD due to *SFTPC* , and two with prior history of oncologic disease. Further, thirteen patients underwent lung transplantation including four patients with surfactant metabolic dysfunction, three with DLD associated with oncologic disorders, two with vascular disease not otherwise specified, and one each with alveolar capillary dysplasia, bronchiolitis obliterans, pulmonary capillary hemangiomatosis, and ILD of unknown etiology. The four patients with surfactant metabolic dysfunction

who underwent lung transplant included two patients heterozygous for variants in *ABCA3* , and two patients with surfactant protein C associated ILD. Two other patients were listed for lung transplant, and one was awaiting combined heart/lung transplant.

*Discussion*In this retrospective single center study, we used ICD-10 billing diagnoses to identify patients with chILD/DLD. This strategy allowed us to identify 306 children and adolescents with chILD/DLD who received care at a large volume tertiary care medical center between 2019 and 2021, providing new data on the scope of chILD. Furthermore, using EMR data collection, we provide the first report on health care utilization and hospitalizations in chILD in the United States (U.S.).

The diagnosis of chILD/DLD is challenging and there is uncertainty about incidence and prevalence. Published estimates are 0.13-16.2 cases per 100,000 children per year,[1] acknowledging reports are based on differing case definitions and study methodology. For example, the 2004 European Respiratory Society task force identified 185 cases of interstitial lung disease in children over a five-year period[13] and a 2018 study by the chILD European Union registry identified 575 patients across 82 centers from 16 countries over a three period.[14] In the U.S., the chILD Research Network reported 187 lung biopsy cases in children <2 years of age from 11 centers from 1999-2004 and 191 cases in children ages 2-18 from 12 centers over a four-year period.[6; 7]Additionally, Soares et al. performed a retrospective review at a mid-size single center, identifying 93 cases over an 18-year period.[15] Our study methodology did not differentiate incident cases from prevalent cases. Our cohort size may reflect a combination of the overall size of our children's hospital, the study methodology, and increased awareness and clinical suspicion for chILD in recent years. A substantial portion of cases were seen by pulmonologists at other centers prior to referral to our center, further limiting any population-based estimates and volume predictions for other pediatric centers. We do note that the size of our identified chILD cohort is very similar to the number of patients seen at our Cystic Fibrosis Center between 2019 and 2021.

The distribution of diagnoses of identified patients is also instructive in considering the spectrum of chILD and the care delivery models. Our chILD cohort highlights the large number of patients with systemic diseases with lung involvement or pulmonary complications, particularly those with history of oncologic, connective tissue, and immune-mediated diseases. Immunocompromised patients accounted for approximately one quarter of chILD cases. Disorders that typically present in infancy, including NEHI, surfactant metabolic dysfunction, and diffuse developmental lung diseases were less prominent in our cohort than in prior lung-biopsy based studies. Reflecting the time period of our study, we found a notable group of adolescent patients with e-cigarette or vaping associated lung injury (EVALI), with either abnormalities on chest CT or lung function. However, based on our clinical experience, we suspect that the billing query approach underestimated the number of patients receiving care for EVALI during this time.

We were particularly interested in examining the utilization and impact of genetic testing in our cohort, as many prior studies have relied heavily on lung biopsy classification. Although 51% of the cohort had respiratory disease directed genetic testing, a molecular diagnosis was identified in only 38 cases, reflecting 25.5% of those tested and 12.4% of the overall cohort. Despite advances in understanding the genetic underpinnings of chILD, this data suggests opportunity for further discovery and application of newer genomic technologies in a more comprehensive manner. In addition to limitations in diagnostic yield, barriers to testing may include cost and/or insurance coverage, other access barriers, and turn-around-time for acutely ill patients.[14; 16-18] The potential value of negative genetic testing results should also be acknowledged and further examined. While a subset of patients at our center had both lung biopsies and genetic testing, further prospective studies are needed to examine how both positive and negative genetic results impact clinical care decisions.

In addition to ambulatory medical care utilization, chILD patients were frequently hospitalized, including in the ICU. While oncology patients were the largest group, and our data do not allow us to delineate whether the hospitalization was primarily attributable to lung disease, patients with a broad representation of chILD etiologies were hospitalized across the age spectrum. Comprehensive data were not available

on hospitalization and testing performed outside our institution, though the frequency of second opinion referrals and outside lung biopsies suggests that our data underestimate the overall healthcare utilization of this cohort. A recently published prospective, longitudinal study by Seidel et al. evaluated healthcare utilization and medical costs in chILD among 445 patients in 10 European countries, reporting a high health care economic burden.[19] The authors found that outpatient care, inpatient hospital admission rates and inpatient hospital days were high, though decreased over time as follow up was performed upwards of five years after baseline data was obtained. Medical costs were reported to be highest in those with diffuse developmental disorders and diffuse parenchymal lung disease of unclear etiology in the non-neonate. While our study does not directly consider the medical cost of chILD, our data demonstrate the impact to patients, families, and the healthcare system in the U.S.

Our study highlights the power of EMR-derived data but also identified some opportunities and challenges. First, historical data are limited for older patients, as the current EMR system was implemented about 10 years ago. Because hospitalization billing diagnoses are assigned administratively and not by medical providers at our center, chart review would be required to determine whether lung disease was a primary or secondary indication for hospitalization events in many cases. ILD diagnosis benefits from multidisciplinary case review, and we suggest development of standardized approaches to document the outcome of such reviews, as well as other discrete data elements in the EMR that inform individual patient care and population management. For example, although we know that the age of symptom onset is important for the differential diagnosis in a patient with suspected chILD, this information was not documented in the EMR for 24.5% of our cohort. Lastly, there are limitations in using current ICD billing codes for the purposes of case ascertainment, due to inconsistent use and incomplete correlation with disease categorization in some cases.

In summary, this single tertiary-care referral center report elucidates key aspects of the scope of clinical care and healthcare utilization in chILD, including limitation in current genetic testing and diagnostic capabilities. Further, we demonstrate that use of an EMR approach has the potential to provide new opportunities for cohort analysis that will inform the feasibility of future studies in chILD. Better understanding of these disease processes and mechanisms to monitor patients are needed to advance clinical care delivery and improve outcomes.

Acknowledgements

We thank the Clinical Research Unit, a subset of the CHOP Center for Data-Driven Discovery in Biomedicine, for support for EMR data collection. We thank Devaney Camburn and Emily Madonia for management of the Rare Lung Diseases Frontier Program and Jason Rinde for assistance with administrative data.

References

1. Vece TJ, Young LR. 2016. Update on diffuse lung disease in children. Chest. 149(3):836-845.

2. Nogee LM, de Mello DE, Dehner LP, Colten HR. 1993. Brief report: Deficiency of pulmonary surfactant protein b in congenital alveolar proteinosis. N Engl J Med. 328(6):406-410.

3. Nogee LM, Dunbar AE, 3rd, Wert SE, Askin F, Hamvas A, Whitsett JA. 2001. A mutation in the surfactant protein c gene associated with familial interstitial lung disease. N Engl J Med. 344(8):573-579.

4. Bullard JE, Wert SE, Whitsett JA, Dean M, Nogee LM. 2005. Abca3 mutations associated with pediatric interstitial lung disease. Am J Respir Crit Care Med. 172(8):1026-1031.

5. Deterding RR, Pye C, Fan LL, Langston C. 2005. Persistent tachypnea of infancy is associated with neuroendocrine cell hyperplasia. Pediatr Pulmonol. 40(2):157-165.

6. Deutsch GH, Young LR, Deterding RR, Fan LL, Dell SD, Bean JA, Brody AS, Nogee LM, Trapnell BC, Langston C et al. 2007. Diffuse lung disease in young children: Application of a novel classification scheme. Am J Respir Crit Care Med. 176(11):1120-1128.

7. Fan LL, Dishop MK, Galambos C, Askin FB, White FV, Langston C, Liptzin DR, Kroehl ME, Deutsch

GH, Young LR et al. 2015. Diffuse lung disease in biopsied children 2 to 18 years of age. Application of the child classification scheme. Ann Am Thorac Soc. 12(10):1498-1505.

8. Kurland G, Deterding RR, Hagood JS, Young LR, Brody AS, Castile RG, Dell S, Fan LL, Hamvas A, Hilman BC et al. 2013. An official american thoracic society clinical practice guideline: Classification, evaluation, and management of childhood interstitial lung disease in infancy. Am J Respir Crit Care Med. 188(3):376-394.

9. Popler J, Lesnick B, Dishop MK, Deterding RR. 2012. New coding in the international classification of diseases, ninth revision, for children's interstitial lung disease. Chest. 142(3):774-780.

10. Icd-10-cm coding for interstitial lung diseases. 2015. In: Plummer AL, editor. Coding & Billing Quarterly: American Thoracic Society.

11. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. 2009. Research electronic data capture (redcap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 42(2):377-381.

12. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, McLeod L, Delacqua G, Delacqua F, Kirby J et al. 2019. The redcap consortium: Building an international community of software platform partners. J Biomed Inform. 95:103208.

13. Clement A, Force ERST. 2004. Task force on chronic interstitial lung disease in immunocompetent children. Eur Respir J. 24(4):686-697.

14. Griese M, Seidl E, Hengst M, Reu S, Rock H, Anthony G, Kiper N, Emiralioglu N, Snijders D, Goldbeck L et al. 2018. International management platform for children's interstitial lung disease (child-eu). Thorax. 73(3):231-239.

15. Soares JJ, Deutsch GH, Moore PE, Fazili MF, Austin ED, Brown RF, Sokolow AG, Hilmes MA, Young LR. 2013. Childhood interstitial lung diseases: An 18-year retrospective analysis. Pediatrics. 132(4):684-691.

16. Temple SEL, Ho G, Bennetts B, Boggs K, Vidic N, Mowat D, Christodoulou J, Schultz A, Gayagay T, Roscioli T et al. 2022. The role of exome sequencing in childhood interstitial or diffuse lung disease. Orphanet J Rare Dis. 17(1):350.

17. Saddi V, Beggs S, Bennetts B, Harrison J, Hime N, Kapur N, Lipsett J, Nogee LM, Phu A, Suresh S et al. 2017. Childhood interstitial lung diseases in immunocompetent children in australia and new zealand: A decade's experience. Orphanet J Rare Dis. 12(1):133.

18. Terwiel M, Borie R, Crestani B, Galvin L, Bonella F, Fabre A, Froidure A, Griese M, Grutters JC, Johannson K et al. 2022. Genetic testing in interstitial lung disease: An international survey. Respirology. 27(9):747-757.

19. Seidl E, Schwerk N, Carlens J, Wetzke M, Cunningham S, Emiralioglu N, Kiper N, Lange J, Krenke K, Ullmann N et al. 2022. Healthcare resource utilisation and medical costs for children with interstitial lung diseases (child) in europe. Thorax. 77(8):781-789.

Table 1: Demographics of the cohort.

Demographics	**N = 306**
Sex Male Female	169 (55%) 137
Race White Other Black Multiple races Asian Not documented Native Hawaiian or Other Pacific Islander	172 (56.2%) 60
Ethnicity Not Hispanic or Latino Hispanic or Latino Not documented	257 (84.0%) 47
Gestational Age Full-term[1] Pre-term[2] Not documented	236 (77.1%) 54
Insurance Medicaid only Medicare only Private only Self-pay	100 (32.7%) 1

[1]Full-term is defined as gestational age [?] 37 weeks.[2]Pre-term is defined as gestational age < 37 weeks.

Table 2: Primary diagnosis or disease category for cohort of 306 cases.

Primary Diagnosis or Disease Category	**Number of cases (% of total)**	**Age at diagnosis, years (mean ± SD)**
DLD associated with Oncologic Disorders*	65 (21.2%)	8 ± 4.8
Bronchiolitis Obliterans (not HSCT or oncology related)	31 (10.1%)	5.3 ± 4.8
DLD associated with Connective Tissue Diseases**	29 (9.5%)	8.4 ± 5.3
Neuroendocrine cell Hyperplasia of Infancy	28 (9.2%)	1.9 ± 2.7
Environmental/Toxic related***	27 (8.8%)	17.3 ± 1.6
Alveolar Hemorrhage Disorders	23 (7.5%)	4.5 ± 2.6
Surfactant Metabolic Dysfunction	19 (6.2%)	2.5 ± 4.3
DLD associated with Immune-related Disorders[#]	15 (4.9%)	7.0 ± 4.9
Ataxia Telangiectasia	8 (2.6%)	4.8 ± 2.9
Diffuse Lung Disease NOS ILD NOS Vascular Disease NOS Cystic Lung Disease NOS Developmental Lung Disease NOS	32 (10.5%) 23 (7.5%) 5 (1.6%) 3 (1%) 1 (<1%)	n/a
Others[$]	29 (9.5%)	n/a

DLD: diffuse lung disease; HSCT: Hematopoietic stem-cell transplantation; NOS: not otherwise specified and without specific diagnosis or classification

*Includes status post chemotherapy/radiation therapy and status post stem cell transplant

**Includes systemic lupus erythematosus, systemic juvenile inflammatory arthritis, dermatomyositis

*** Includes e-cigarette or vaping associated lung injury or other inhalation injury

[#] Incudes chronic granulomatous disease, severe combined immunodeficiency, common variable immunodeficiency

[$]Others represent diagnoses with 3 or fewer cases. See supplemental Table 1 for complete list.

Figure 1: Lung biopsy and genetic testing occurrences by primary disease category.

A. Data is based on the 110 unique patients, 35.9% of the overall cohort, who underwent lung biopsy. B. Data is based on the 149 unique patients, 48.7% of the overall cohort, who underwent genetic testing. NEHI: Neuroendocrine cell Hyperplasia of Infancy; ILD NOS: interstitial lung disease not otherwise specified

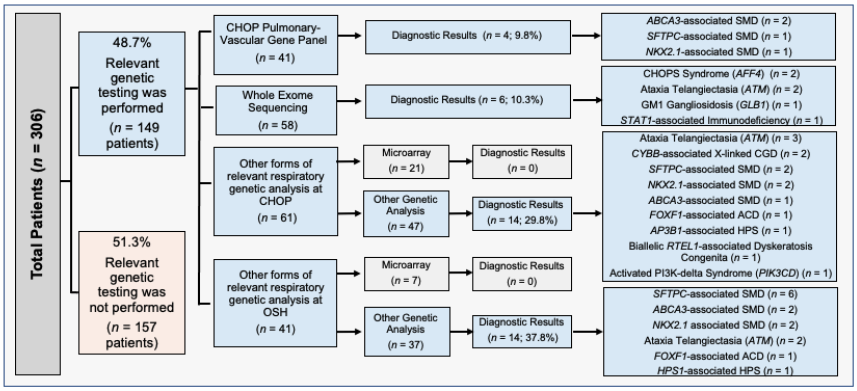

Figure 2: Map of genetic testing practices in this cohort. Of 306 patients in the cohort, 149 had relevant genetic testing performed. The map details the type of testing and diagnostic results. Note that the total of 149 patients includes one patient with SFTPC-associated surfactant metabolic dysfunction whose EMR lacked documentation of which lab performed the testing. The CHOP Pulmonary and Vascular Disease panel is a targeted gene panel containing 76 genes associated with conditions including, but not limited to, respiratory distress syndrome, surfactant metabolic dysfunction, alveolar capillary dysplasia, primary ciliary dyskinesia, interstitial lung disease, and other inherited pulmonary-vascular disorders. Other genetic analysis refers to single gene testing/targeted variant testing and targeted respiratory-related gene panels.

Abbreviations: CHOP: Children's Hospital of Philadelphia; HPS: Hermansky-Pudlak Syndrome; OSH: outside hospital; SMD=surfactant metabolism dysfunction

Figure 3: CHOP subspecialty outpatient care utilization. Data is based on outpatient clinic visits by medical subspecialty for the overall cohort for the time period between 2019 and 2021 and lifetime as documented in the EMR.

Figure 4: Hospitalization by primary disease category. A. Overall hospitalizations between 2019-2021 and both lifetime. B. ICU hospitalizations, between 2019 and 2021 and lifetime. NEHI: Neuroendocrine cell Hyperplasia of Infancy.

Supplemental Tables

Supplemental Table 1: ICD-10 billing codes utilized for cohort identification.

ICD-10 codes likely specific for ILD/DLD diagnosis	Diagnosis
D18.0	Pulmonary capillary hemangiomatosis
D86.0	Sarcoidosis of lung
I78.8	Isolated pulmonary capillaritis
J42	Bronchiolitis Obliterans (or Follicular Bronchiolitis)
J67.9	Hypersensitivity pneumonitis due to unspecified organic dust
J70.1	Radiation-induced pulmonary fibrosis
J82.81	Chronic eosinophilic pneumonia
J84.01	Pulmonary Alveolar Proteinosis
J84.02	Pulmonary alveolar microlithiasis
J84.03	Idiopathic pulmonary hemosiderosis
J84.09	Other alveolar and parieto-alveolar conditions
J84.10	Pulmonary fibrosis
J84.117	Desquamative interstitial pneumonitis
J84.83	Surfactant dysfunction due to genetic disorder

ICD-10 codes likely specific for ILD/DLD diagnosis	**Diagnosis**
J84.841	Neuroendocrine cell Hyperplasia of Infancy
J84.842	Pulmonary Interstitial Glycogenosis
J84.843	Alveolar capillary dysplasia with vein misalignment
J84.848	Other interstitial lung diseases of childhood
J84.89	Interstitial lung disease due to systemic disease
J84.9	Interstitial pulmonary disease, unspecified
J98.4	Diffuse lung disease
M05.10	Diffuse interstitial rheumatoid disease of lung
M33.01	Juvenile dermatomyositis with pulmonary involvement
Q33.8	Congenital pulmonary alveolar capillary dysplasia
Z87.09	History of interstitial lung disease
ICD10 codes potentially associated with ILD/DLD*	**Diagnosis**
D71	Chronic Granulomatous Disease
D72.1	Eosinophilic disorder
D81.9	Severe Combined Immunodeficiency Disease
D83.9	Common Variable Immunodeficiency
E70.331	Hermansky Pudlak Syndrome
E75.19	GM1 Gangliosidosis
F45.8	Restrictive lung disease
G11.3	Ataxia Telangiectasia
I27.23	Pulmonary veno-occlusive disease
I77.6	Vasculitis
J18.9	Inflammation of lung
J47.9	Bronchiectasis without acute exacerbation
J98.2	Interstitial emphysema
K50.90	Crohn's disease
M08.20	Juvenile idiopathic arthritis, systemic onset
M30.1	Eosinophilic granulomatosis with polyangiitis
M61.10	Fibrodysplasia ossificans progressiva
Q33.0	Congenital cystic lung
Q82.4	Ectodermal dysplasia
R04.89	Pulmonary hemorrhage
R91.1	Lesion of lung
R93.89	Abnormal chest CT
T14.90XA	Inhalation injury
T66.XXXS	Radiation injury, sequela
U07.0	E-cigarette or vaping use-associated lung injury
Z94.81	S/P allogeneic bone marrow transplant
Z94.84	History of peripheral stem cell transplant

***** Chart review required to evaluate for ILD/DLD manifestations

Supplemental Table 2: Other diagnostic categories.

Primary Diagnosis or Disease Category
Pulmonary Alveolar Proteinosis
Pulmonary Interstitial Glycogenosis
Hermansky Pudlak Syndrome
DLD associated with Renal Disorders

Primary Diagnosis or Disease Category
DLD associated with Gastrointestinal Disorders
Pulmonary Alveolar Microlithiasis
Alveolar Capillary Dysplasia
Others Lysosomal Storage Disease Ectodermal Dysplasia Chronic Eosinophilic Pneumonia CHOPS Syndrome Idiopathic Hy

DLD: diffuse lung disease