

The U.S. National Registry for Childhood Interstitial and Diffuse Lung Disease: Report of Study Design and Initial Enrollment Cohort

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Abstract

Childhood interstitial and diffuse lung disease (chILD) encompasses a broad spectrum of rare disorders. The Children’s Interstitial and Diffuse Lung Disease Research Network (chILDRN) established a prospective registry to advance knowledge regarding etiology, phenotype, natural history, and management of these disorders. This longitudinal, observational, multicenter registry utilizes single-IRB reliance agreements, with participation from 25 chILDRN centers across the U.S. Clinical data are collected and managed using the Research Electronic Data Capture (REDCap) electronic data platform. We report the study design and some elements of the initial Registry enrollment cohort, which includes 683 subjects with a broad range of chILD diagnoses. The most common diagnosis reported was neuroendocrine cell hyperplasia of infancy (NEHI), with 155 (23%) subjects. Components of underlying disease biology were identified by enrolling sites, with cohorts of interstitial fibrosis, immune dysregulation, and airway disease being most commonly reported. Prominent morbidities affecting enrolled children included home supplemental oxygen use (63%) and failure to thrive (46%). This Registry is the largest longitudinal chILD cohort in the U.S. to date, providing a powerful framework for collaborating centers committed to improving the understanding and treatment of these rare disorders.

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Childhood interstitial and diffuse lung disease (chILD) encompasses a broad spectrum of rare disorders. The Children’s Interstitial and Diffuse Lung Disease Research Network (chILD RN) established a prospective registry to advance knowledge regarding etiology, phenotype, natural history, and management of these

disorders. This longitudinal, observational, multicenter registry utilizes single-IRB reliance agreements, with participation from 25 chILDRN centers across the U.S. Clinical data are collected and managed using the Research Electronic Data Capture (REDCap) electronic data platform. We report the study design and some elements of the initial Registry enrollment cohort, which includes 683 subjects with a broad range of chILD diagnoses. The most common diagnosis reported was neuroendocrine cell hyperplasia of infancy (NEHI), with 155 (23%) subjects. Components of underlying disease biology were identified by enrolling sites, with cohorts of interstitial fibrosis, immune dysregulation, and airway disease being most commonly reported. Prominent morbidities affecting enrolled children included home supplemental oxygen use (63%) and failure to thrive (46%). This Registry is the largest longitudinal chILD cohort in the U.S. to date, providing a powerful framework for collaborating centers committed to improving the understanding and treatment of these rare disorders.

INTRODUCTION:

Childhood interstitial and diffuse lung disease (chILD) encompasses a broad spectrum of rare disorders. Recent estimates of disease prevalence range from 0.15 to 4.6 cases per 100,000 children, depending on the definitions and ascertainment methods utilized.¹⁻³ Despite increasing clinician awareness of chILD and improved diagnostic tools, the prevalence of these disorders is likely significantly underestimated.

While some types of chILD overlap with adult forms of interstitial lung disease, pediatric conditions have important differences in etiology, phenotype, and natural history.⁴⁻⁶ Many diverse causes of chILD are known, whereas mechanistic understanding remains unknown for many cases.⁶⁻⁸ The investigation of suspected chILD cases requires analysis of combinations of clinical presentation, imaging, lung biopsy pathology, and genetic testing. Disease severity at initial presentation varies widely both within and between disorders from birth to adolescence, encompassing a range of respiratory symptoms such as cough, dyspnea, exercise intolerance, recurrent lung infections, hemoptysis, and respiratory failure. Physical findings include tachypnea, crackles, wheezing, hypoxemia, and pneumothorax. Diagnosis may occur through lung imaging and/or pulmonary function testing (PFTs) in asymptomatic patients by family screening or screening of high-risk groups, such as children with connective tissue or immune-mediated disorders, oncologic disorders, or post-stem cell transplantation. Overall, chILD is associated with high healthcare costs and a heavy burden of care both chronically and with acute exacerbations.^{9,10}

The Children's Interstitial and Diffuse Lung Disease Research Network (chILDRN) was established in 2004 in the U.S.¹¹ In addition to producing disease-specific reports, this network conducted two foundational studies. The first study applied a new classification scheme to lung biopsies from 187 infants with diffuse lung disease from eleven centers.⁴ A subsequent manuscript reported 191 lung biopsies in older children from ten institutions.⁵ These studies were crucial in defining the pathologic spectrum of chILD, but were retrospective studies limited by lung biopsy ascertainment. While there have been several registry reports from Europe, Australia, and New Zealand,^{2,3,12,13} there have as of yet been no prospective multicenter studies of chILD in North America.

Strategies to accelerate progress in this field were the focus of a workshop sponsored by the National Heart, Lung, and Blood Institute in 2015. The priority areas identified were to: (1) establish an interactive, data-driven, research community, (2) define the clinical phenotypes, epidemiology, and natural history, (3) identify pathogenic mechanisms, biomarkers, and pharmacotherapeutic targets, and (4) define, measure, and improve clinical outcomes.¹⁴

To provide a framework to address these unmet needs, we established a longitudinal observational study using single-IRB reliance agreements. The objectives are to advance knowledge concerning clinical features, management, and outcomes of infants and children with chILD disorders, while developing infrastructure to facilitate scientific advancement and clinical trials in this field. Here we provide a report on the development and study design of this registry and the characteristics of the initial enrollment cohort. Some of the results of this study have been previously reported in the form of an abstract.¹⁵

METHODS:

The National Registry for Childhood Interstitial and Diffuse Lung Disease is a longitudinal, observational, multicenter study which was initially approved by the Vanderbilt University Institutional Review Board (IRB #160427) in 2016. In 2019, the Children’s Hospital of Philadelphia (CHOP) became the data coordinating center and IRB of record (IRB #19-016138), now utilizing IRB Reliance Exchange. An open call for site participation was issued within the chILDRN in 2016 and offered through 2020, with sites volunteering to participate. Protocol and database training for participating site personnel are facilitated by the coordinating center via an online format. Data use agreements are coordinated from CHOP and aligned across participating sites.

Enrollment criteria are: age 0 to 21 years; diagnosis or suspected diagnosis of chILD; subject/parental/guardian permission (informed consent); and where appropriate, child assent. Both prevalent and incident patients seen clinically at chILDRN participating institutions or referred to a participating site for remote enrollment with informed consent may be enrolled. Data from clinical care are collected and organized using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at CHOP^{16,17}. Cross-sectional baseline data consist of demographics, clinical status, disease process / disease mechanism, and diagnosis or classification. The severity of illness score as developed by Fan, et al¹⁸, is used to classify clinical status at the time of Registry enrollment.

Descriptive statistics were used to characterize the study cohort. The utilization of genetic testing and lung biopsy were compared among different diagnoses or diagnostic categories using Chi-square tests. Plots were performed using GraphPad Prism version 9. Subjects included in the current analysis were enrolled prior to December 1, 2022, and with a minimum dataset of demographic information and disease classification. Missing data elements were handled as missing completely at random given ongoing data enrollment format of the prospective registry, with subject N reported for each data analysis.

RESULTS:

Study Enrollment and Demographics

In total, 25 sites have participated in the Registry, with 23 currently active sites who have IRB approval in reliance with subject enrollment under the CHOP IRB. Site activation was staggered ranging from 2016 to 2022 after completion of regulatory requirements. All sites are academic medical centers, and the number of enrolled subjects per site ranges from 1 to 135 (**Figure 1**). Specific enrolling sites are listed in Figure 1 legend and includes sites across 15 states. As of December 1, 2022, a total of 717 subjects are enrolled. As the Registry’s ongoing open enrollment format allows for temporarily incomplete data, here we report the 683 subjects with the minimum required dataset entered at time of data lock for this analysis. **Table 1** summarizes the cohort demographics. The median reported age at diagnosis was 22 months (interquartile range (IQR) 5, 86 months).

Spectrum of Diagnoses

The 683 subjects were classified by site investigators in the following categories: lung developmental dysplasia; alveolar growth disorder; surfactant dysfunction; pulmonary alveolar proteinosis due to other causes; pulmonary interstitial glycogenosis; neuroendocrine cell hyperplasia of infancy (NEHI); bronchiolitis obliterans; alveolar hemorrhage; chILD associated with connective tissue or immune-mediated disorders; other specific or multisystem disorders; environmental / toxic / drug related chILD; or unclassified ILD (**Table 2**). To date, the most frequent diagnosis is NEHI, with a total of 155 subjects comprising 22.7% of all registry enrollment. The second most frequent diagnosis is ILD associated with connective tissue or immune-mediated disorders (113 subjects, 16.5%). For 11% of enrolled subjects, the diagnostic designation was ‘unclassified ILD’ (**Figure 2**).

Within these broader categories, subclassifications or specific diagnoses could be subsequently selected by site investigators. For example, within the surfactant metabolic dysfunction category, surfactant protein-C gene (*SFPTC*) is most frequently reported (37 subjects; 45.1% of surfactant metabolic dysfunction category), while ILD due to *ABCA3* disruption is reported in 30 (36.6%) of subjects. The most frequently enrolled

subtype of bronchiolitis obliterans is post-infectious (34 subjects, 45.3% of bronchiolitis obliterans category).

Classification of Disease Process

Subjects are also classified according to the suspected underlying biologic process(es) based on available clinical, genetic, radiologic, and pathologic data. Reporting site investigators identified subjects as having interstitial fibrosis (n=112), airway disease (n=198), pulmonary hemorrhage (n=82), altered intrinsic lung development (n=104), pulmonary alveolar proteinosis (n=30), immune deficiency or dysregulation (n=134), or eosinophilic disorders (n=20). Among the 112 subjects with a fibrotic disease process, 34 (30.4%) had connective tissue or immune-mediated disorders and 25 (22.3%) had surfactant dysfunction. If an individual experienced multiple co-existing disease processes, then each contributing biologic mechanism was recorded. For example, 74% of subjects characterized as having a fibrotic disease process were designated to have an additional type of disease process present (e.g., immune dysregulation; airway disease).

Approach to Diagnosis

Of the 683 subjects analyzed to date, 579 have notation about whether genetic testing was performed, and 544 have designation about history of lung biopsy. Across all diagnoses reported in the Registry, 58% (n=336) of subjects have undergone genetic testing and 39% (n=214) have had a lung biopsy (**Figure 3**). Genetic testing utilization among the five most frequent diagnoses (surfactant metabolic dysfunction, NEHI, bronchiolitis obliterans, immune-mediated / connective tissue related, and unclassified ILD), ranged from 40% for NEHI to 93% for surfactant metabolic dysfunction. The frequency of lung biopsy differed among the most frequent diagnoses (p -value = 0.0028), with the lowest among subjects with NEHI (27%) and bronchiolitis obliterans (25%) and the highest among subjects with surfactant metabolic dysfunction (48%) and unclassified ILD (46%).

Morbidity and Outcomes

Table 3 summarizes the clinical status of enrolled subjects at time of Registry enrollment using Fan severity of illness score¹⁸. While a quarter of subjects were asymptomatic, the lifetime morbidity experienced by the children in this cohort is substantial. Overall, 63% of subjects had a history of home supplemental oxygen use, and 12% required chronic (>3 weeks) invasive mechanical ventilation, with an additional 13% requiring chronic non-invasive ventilatory support. Failure to thrive occurred in 46% of subjects during their clinical course.

For the 527 subjects with outcome data available, 31 (6%) have died since enrollment. The diagnoses of those who died were immune-mediated or connective tissue disease (n=10), bronchiolitis obliterans (n=6), unclassified (n=4), other specific or multisystem disorders (n=4), surfactant dysfunction (n=2), environmental/toxic/drug related (n=2), lung developmental dysplasia (n=1), alveolar growth disorder (n=1), and pulmonary alveolar proteinosis (n=1). No deaths occurred in children with NEHI. Sixteen subjects in the registry underwent lung transplant with primary indicated diagnoses of surfactant metabolic dysfunction (n=5), bronchiolitis obliterans (n=3), unclassified chILD (n=3), alveolar growth disorder (n=2), lung developmental dysplasia (n=1), chILD associated with connective tissue or immune-mediated disorders (n=1), and other specific or multisystem disorder (n=1). Four deaths occurred among lung transplant recipients.

DISCUSSION:

This U.S. National Registry for ChILD provides a large cohort of subjects poised to support a broad scope of ongoing and future studies. In contrast to prior publications from the chILDRN, the scope of the Registry differs in that ascertainment is prospective, does not require lung biopsy, and does not require definitive diagnosis prior to enrollment, thus including the full spectrum of chILD cases. IRB reliance and data sharing provide robust infrastructure and feasibility for future detailed analyses of specific disease subtypes and planning for clinical trials.

International registries for rare lung diseases in children have developed in recent years, enabling cohort identification and providing valuable data including disease prevalence, morbidity, and healthcare utilization

in certain countries¹⁻³. While here we report the largest prospective cohort to date in the U.S., the study was not designed to capture incidence or prevalence data for patients in a controlled manner. Approximately two-thirds of subjects have been enrolled from five centers. Because study enrollment is currently dependent on the availability of internal resources to screen and identify eligible subjects, administer informed consent, and enter study data, we cannot conclude whether the distribution of subjects reflects disease prevalence at U.S. centers based on regional population, referral patterns, or other factors. The participating sites were self-selected and represent an extensive but incomplete geographic distribution, with fewer centers from the southern and western U.S. The distribution of race and ethnicity as reported in the Registry is similar to the 2020 U.S. Census Data, though direct comparison is limited as the Registry allows for selection of “unknown or not reported” for both race and ethnicity.¹⁹ Additional centers have subsequently indicated interest to join the Registry, and the goal is to further expand participation. Interestingly, our cohort recruitment occurred primarily in the outpatient pediatric pulmonology setting at most sites, with fewer subjects than expected with infant disorders, likely reflecting limited enrollment through neonatal or pediatric intensive care units. This primarily outpatient enrollment pattern may also have resulted in an underestimation of mortality. While the chILD RN has always been a multidisciplinary network from its inception, we think it will be important to continue to expand registry enrollment referrals from neonatologists, critical care physicians, geneticists, radiologists, and pathologists, as well as other subspecialists such as rheumatologists, immunologists, and oncologists, who see substantial numbers of infants and children with or at-risk for chILD.

For the U.S. Registry, subjects could be enrolled with clinically suspected chILD without a specific diagnosis, whether due to ongoing clinical evaluations or currently unclassifiable findings. This subgroup reflects an important clinical and scientific challenge and an opportunity to improve care for children with diffuse lung disease. While prior studies have classified subjects by specific diagnosis or diagnosis category, this registry additionally invited designation of the suspected underlying disease process(es) (e.g., interstitial fibrosis, airway disease, immune-mediated), enabling a framework for therapy and research in the absence of specific diagnosis. While advances in defining the molecular basis of chILD hold great promise for precision medicine, we also anticipate that approaches which focus on the common biologic processes involved in chILD will continue to be useful for future clinical trials.^{20,21}

The utilization of lung biopsy and genetic testing varied for different types of disorders, reflecting evolving understanding of the pathophysiology and genetic mechanisms of different diseases. Importantly, the accessibility of different genetic testing options has changed considerably over the more than 20-year period during which these children were diagnosed and enrolled, and practice patterns of genetic testing continue to change rapidly. More than one-half of Registry subjects have had some type of genetic testing, including single gene testing, gene panels, karyotype analysis, chromosomal microarray, exome, or genome sequencing. Our current data do not capture clinical rationale for selected genetic testing, including impacts of insurance approval, turn-around-time, or patient/family preferences, which are all important areas for future study. Many sites found it challenging to locate genetic testing results in the electronic medical record, as results may come from clinical laboratories outside the site’s hospital system. Further, we found variable accuracy of the genetic information entered by sites such as incorrect data transcription or misinterpretation of the clinical implication of the genetic testing results. A future direction for the registry will be to utilize a genetic counselor or clinical geneticist to review the primary documentation of genetic testing results to enable collection of more detailed genetic testing results and facilitate central reclassification, when appropriate. These expanded workflows will become increasingly important as we anticipate that the increased use of exome and genome sequencing will lead to identification of new chILD disorders and could avoid the need for lung biopsy for some children.

Through ongoing longitudinal data collection, the U.S. National Registry for ChILD provides exciting opportunities for future clinical research. Additional studies are already underway to evaluate radiologic, genetic, and histopathologic disease features and correlations. As participating centers proceed with longitudinal data collection, the Registry will enable future analysis of natural history, treatment approaches, and outcome measures in chILD. The Registry will also facilitate clinical trials through identification of cohorts of

subjects with specific diagnoses or disease processes. Further, evaluation of quality of life, comorbidities, and clinical practice patterns will be important to optimize supportive care for affected children and their families. Alignment with recent international efforts¹⁻³ will expand these opportunities. As information about chILD disorders continues to grow through clinical, translational, and basic science research as well as efforts to expand the U.S. National Registry enrollment, we look forward to ongoing collaboration with the global pulmonary scientific community to better understand these rare diseases and improve the care of affected children and their families.

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Figure Legends

Figure 1. Subjects Enrolled by Registry Site.

Total n=683 from May 2016, to Dec 1, 2022. Site enrollment is represented above, numbered by the order in which site activation occurred. Subjects have been enrolled from the following participating centers (listed alphabetically): Boston Children’s Hospital (Boston, MA), Children’s Hospital of Colorado (Aurora, CO), Children’s Hospital Los Angeles (Los Angeles, CA), Children’s Hospital at Montefiore (Bronx, NY), Children’s Hospital of Philadelphia (Philadelphia, PA), Children’s Hospital of Pittsburgh (Pittsburgh, PA), Children’s Mercy (Kansas City, MO), Johns Hopkins Children’s Center (Baltimore, MD), Cohen Children’s Medical Center Northwell Health (North New Hyde Park, NY), Lucile Packard Children’s Hospital at Stanford (Palo Alto, CA), Lurie Children’s Hospital (Chicago, IL), Monroe Carell Jr. Children’s Hospital at Vanderbilt (Nashville, TN), North Carolina Children’s Hospital at UNC (Chapel Hill, NC), Oregon Health and Science University (Portland, OR), Rady Children’s Hospital of San Diego/ UC San Diego (San Diego, CA), Rainbow Babies and Children’s Hospital (Cleveland, OH), Riley Children’s Hospital (Indianapolis, IN), Seattle Children’s Hospital (Seattle, WA), University of California San Francisco Benioff Children’s Hospitals (San Francisco, CA), University of Michigan C.S. Mott Children’s Hospital (Ann Arbor, MI),

University of Missouri Children’s Hospital (Columbia, MO), Washington University School of Medicine / St. Louis Children’s Hospital (St. Louis, MO), Weill Cornell Medical Center (New York, NY).

Figure 2. Distribution of ChILD Diagnoses

Primary diagnoses and classification categories in the Registry as reported by site investigators. Note that 11% of cases were designed as unclassified chILD. *Other category includes groupings with small numbers of cases, including environmental/toxic/drug related, pulmonary interstitial glycogenosis, lung developmental dysplasia, pulmonary alveolar proteinosis, and specific multisystem disorders.

Figure 3. Genetic Testing and Lung Biopsy

Data are shown for the total registry population and the largest diagnoses or diagnostic categories. A) The rate of genetic testing utilization differs among diagnostic categories ($p < 0.0001$) B) The rate of lung biopsy differs among diagnostic categories ($p = 0.0028$).

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