Pediatric Pulmonology

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ORIGINAL ARTICLE OPEN ACCESS

Genetic Testing Utilization in the U.S. Registry for Childhood Interstitial and Diffuse Lung Diseases

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Received: 17 December 2024 | **Revised:** 2 March 2025 | **Accepted:** 17 March 2025

Funding: Financial support was provided by the National Institutes of Health, the Children's Discovery Institute at St. Louis Children's Hospital, and the Children's Hospital of Philadelphia.

Keywords: childhood interstitial lung disease (chILD) | genetic testing | rare lung diseases

ABSTRACT

Introduction: Childhood interstitial and diffuse lung diseases (chILD) comprise a diverse group of rare disorders. Identifying the underlying cause is crucial for treatment, prognosis, and estimating recurrence risk. The objective of this study was to assess the utilization of genetic testing for subjects enrolled in the United States National Registry for ChILD, a multicenter observational study.

Methods: Genetic data from participating sites were reviewed and analyzed in relationship to clinical characteristics.

Results: Of 609 children enrolled from 22 centers, genetic testing was performed for 55.5% ($n = 338$). Genetic testing results were positive (diagnostic) for 22.8% ($n = 77$), negative for 60.7% ($n = 205$), and uncertain for 16.6% ($n = 56$). Most testing was performed through gene panels (55.9%), followed by exome sequencing (ES) or whole genome sequencing (WGS) (26.9%), single

For a complete list of The ChILD Registry Collaborative, see the Acknowledgments section.

gene testing (24.6%), and/or chromosomal microarray (11.8%). For participants with positive (diagnostic) genetic testing results, the majority were diagnosed through gene panel (33.8%; $n = 26$) or single gene testing (32.5%; $n = 25$). The most common diagnosis confirmed by genetic testing was *SFTPC*-associated surfactant metabolism dysfunction. Of the 59 subjects with unclassified ILD, only 22% ($n = 13$) had undergone ES or WGS, 61% ($n = 36$) had received panel testing, and 27% ($n = 16$) did not have any genetic testing reported.

Conclusion: The utilization of genetic testing has been variable in infants and children enrolled in the ChILD Registry. Additional efforts are needed to develop genetic testing recommendations for children with suspected ILD. Furthermore, there is opportunity for broader utilization of ES/WGS and genetic discovery for children with lung disease of unclear etiology.

1 | Introduction

Childhood interstitial and diffuse lung diseases (chILD) include over 200 rare and diverse disorders. Although clinical awareness of chILD is increasing, the broad spectrum of phenotypes can make diagnostic evaluation challenging. Some disorders within this heterogenous group have known molecular etiologies, while specific genetic underpinnings have not been identified to date for other forms of chILD [1]. The American Thoracic Society (ATS) clinical practice guidelines for chILD and the European Respiratory Society (ERS) guidelines, as well as the more recent ERS Clinical Research Collaboration for chILD (ERS CRC chILD-EU) recommendations, all include use of genetic testing within diagnostic algorithms based on clinical context [2–4].

Pathogenic variants in the gene encoding surfactant protein B (*SFTPB*) were the first genetic cause of childhood ILD identified in 1993 [5]. As accessibility and genomic technologies have improved, genetic discovery has identified novel molecular causes of chILD [6]. For example, genetic mechanisms recognized in recent years include COPA syndrome, ILD associated with *RAB5B*, and *CCR2* deficiency [7–9]. While the total number of genetically determined chILD entities globally is unknown, prior registry studies from Europe have reported that a genetic cause is currently identified in approximately 20% of patients with chILD in European cohorts [4, 10]. Given the changing landscape of genetic testing, this study aimed to assess the utilization of diagnostic genetic testing for participants enrolled in the United States National Registry for Childhood Interstitial and Diffuse Lung Diseases (US ChILD Registry) [11].

2 | Methods

The U.S. National Registry for Childhood Interstitial and Diffuse Lung Diseases is a longitudinal, observational, multicenter study which was initiated in 2016, with coordination at the Children's Hospital of Philadelphia (CHOP) since 2019 (IRB #19-016138) [11]. Enrollment criteria are as follows: age 0–21 years; diagnosis or suspected diagnosis of chILD; subject/parental/guardian permission (informed consent); and when appropriate, child assent. The study population includes both prevalent and incident infants and children seen clinically at participating institutions or referred to a participating site for remote enrollment with informed consent. Data from clinical care are collected and organized using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at CHOP [12, 13]. The study design and characteristics of the original enrollment cohort have been previously reported [11].

Subjects included in the current analysis were those enrolled before July 1st, 2023, for whom the Genetics forms were completed in the Registry. A subject was considered to have had genetic testing performed if any of the following testing modalities were documented: pulmonary-relevant single gene testing or gene panels, exome sequencing (ES), whole genome sequencing (WGS), and/or chromosomal microarray. Genetics overread was performed by a genetic counselor (LV) in consultation with study investigators. Descriptive statistics were used to characterize the study cohort and reported as unadjusted values. Plots were performed using R (version 4.4.0). 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.

3 | Results

3.1 | Study Population

As of July 1st, 2023, a total of 609 Registry subjects at 22 participating centers had available genetic testing history entered in the Registry. Demographics and clinical characteristics of the study population at the time of data review (July 1st, 2023) are shown in Table 1, with comparison between those subjects with and without genetic testing. Of the 609 subjects reviewed, 54.5% were male and 45.5% were female. The median age at the time of genetic testing was 2.6 years. While the median current age of all Registry participants was 11.6 years, the current median age was significantly younger for those who had genetic testing in comparison to those children who did not have genetic testing (median 10.6 years (IQR 6.8, 16.5) vs. 13.6 years (IQR 7.9, 18.7), $p = 0.0004$). No differences in overall genetic testing utilization were observed based on self-reported race or ethnicity.

3.2 | Spectrum of Diagnoses and Genetic Testing Rates

Information on clinical diagnostic category was available for 581 subjects (95.4%), with incomplete data submitted from sites for 28 subjects (Table 2). The most common diagnostic categories were neuroendocrine hyperplasia of infancy (NEHI) ($n = 142$, 24.4%) and ILD/DLD associated with connective tissue or other immune mediated disorders ($n = 85$, 14.6%). The highest rate of genetic testing was reported for subjects with surfactant metabolic dysfunction ($n = 73$, 97.3%), while subjects with environmental/toxic/drug related chILD had the lowest rate of genetic testing ($n = 3$, 23.1%). Within the Registry, a

TABLE 1 | Demographic characteristics of Registry subjects with and without genetic testing.

Demographic characteristic	Total ($n = 609$)	With genetic testing ($n = 338$)	Without genetic testing ($n = 271$)	p value[a]
Sex, n (%)				
Male	332 (54.5)	188 (55.6)	144 (53.1)	0.567
Female	277 (45.5)	150 (44.4)	127 (46.9)	
Current age, years	$n = 608$	$n = 337$	$n = 271$	
Median (IQR)	11.6 (10.53)	10.6 (9.78)	13.6 (10.78)	0.0004
Age at time of genetic testing, years	$n = 303$	$n = 303$		
Median (IQR)	2. 6 (8.60)	2. 6 (8.60)	N/A	
Race, n (%)				0.457
White	420 (69.0)	233 (68.9)	187 (69.0)	
Black or African American	59 (9.7)	30 (8.9)	29 (10.7)	
Asian	22 (3.6)	12 (3.6)	10 (3.7)	
Native Hawaiian or Other Pacific Islander	2 (0.3)	0 (0)	2 (0.7)	
American Indian/Alaskan Native	6 (1.0)	2 (0.5)	4 (1.5)	
More than one race	46 (7.6)	30 (8.9)	16 (5.9)	
Unknown or not reported	54 (8.9)	31 (9.2)	23 (8.5)	
Ethnicity, n (%)	$n = 608$	$n = 338$	$n = 270$	
Hispanic or Latino	95 (15.6)	58 (17.2)	37 (13.7)	0.502
Not Hispanic or Latino	459 (75.5)	250 (74.0)	209 (77.4)	
Unknown or not reported	54 (8.9)	30 (8.9)	24 (8.9)	

Abbreviation: IQR, interquartile range.
[a]unadjusted p value.

TABLE 2 | Case classification for enrolled subjects and rate of genetic testing for each primary diagnosis/category.

Primary diagnosis/category[a]	Registry subjects, n (%)	Underwent genetic testing, n (% of category)
NEHI	123 (24.4)	55 (38.7)
ILD/DLD associated with connective tissue or other immune mediated disorders	85 (14.6)	46 (54.1)
Surfactant metabolic dysfunction	75 (12.9)	73 (97.3)
Bronchiolitis obliterans	73 (12.6)	28 (38.4)
Alveolar hemorrhage disorders	49 (4.5)	18 (36.7)
Other specific or multisystem disorders	36 (6.2)	27 (75.0)
Alveolar growth disorder	26 (4.5)	19 (73.1)
Environmental/toxic/drug related	13 (2.2)	3 (23.1)
Pulmonary interstitial glycogenosis	13 (2.2)	11 (84.6)
Lung developmental dysplasia	6 (1.0)	5 (83.3)
Pulmonary alveolar proteinosis	4 (0.7)	2 (50.0)
Unclassified ILD	59 (10.2)	43 (72.9)

[a]Classification data incomplete for 28 registry subjects.

portion of enrolled subjects had ILD/DLD that was not able to be assigned to a specific diagnostic category and thus were termed "unclassified ILD/DLD" by the study site. Among these 59 subjects, the identification of ILD/DLD occurred through variable combinations of imaging (83%), lung biopsy (44%) or other clinical and laboratory findings. Additionally, of the 59 subjects reported to have "unclassified ILD," 43 (73%) had genetic testing performed, while 27% ($n = 16$) did not have any genetic testing reported. For those with "unclassified ILD" who did have genetic evaluation, 61% had gene panel testing and

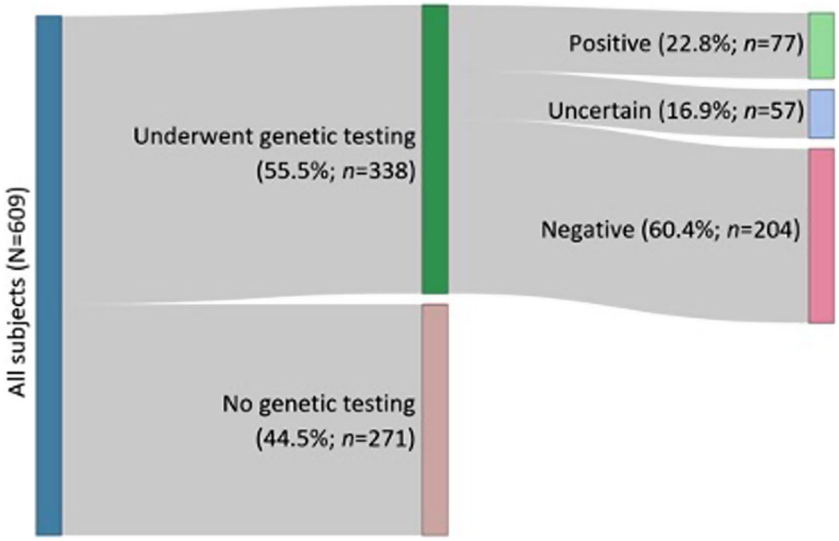

FIGURE 1 | Genetic testing utilization and outcome for U.S. ChILD Registry subjects. Of the 609 subjects, 338 underwent genetic testing. Positive outcome refers to genetic testing that was diagnostic and identified underlying genetic cause for subject's pulmonary symptoms. Uncertain outcome refers to subjects who had genetic testing that identified variants of uncertain significance (VUS) in relevant genes, subjects with limited genetic information, or identification of variants in candidate genes. Negative outcome refers to subjects who had genetic testing, but it did not identify any disease-causing variants and a possible genetic explanation for subject's pulmonary symptoms. [Color figure can be viewed at wileyonlinelibrary.com]

22% underwent exome sequencing/whole genome sequencing (ES/WGS).

3.3 | Genetic Testing Utilization and Findings

Of the 609 Registry subjects reviewed, 338 (55.5%) had genetic testing performed. Among these, 77 (22.8%) subjects had a positive result and 204 (60.4%) had negative genetic testing. There were 57 (16.9%) subjects who received an uncertain result, which included variants of uncertain significance (VUS) in genes related to pulmonary disease or variants in candidate genes, as well as subjects with limited genetic information available in the Registry to complete a detailed over-read (Figure 1). We examined testing outcomes based on self-reported race and ethnicity. Among those who received genetic testing, positive results were reported in 21.4% of White participants and 25.7% of non-White individuals, while 57.9% of White participants and 64.9% of non-White individuals had negative genetic testing results ($p = 0.08$ by Fisher's exact test). Among participants who self-reported as Hispanic ($n = 58$), 14 (24.1%) received positive genetic testing results, as compared to 22.0% of non-Hispanic Whites and 27.6% of non-Hispanic Black individuals ($p = 0.3259$ by Fisher's exact test).

A total of 438 instances of molecular genetic tests were reported for the 338 Registry subjects that had genetic testing performed. Multiple genetic tests or genetic testing modalities were completed for 23.1% (78) of subjects. Gene panels were the most common genetic test modality for subjects, with a total of 200 panels (45.7% of all tests ordered) reported across 189 subjects (55.9%). ES/WGS and targeted testing were the second and third most common tests, respectively. ES/WGS was obtained for 26.9% of subjects and made up 20.8% of all genetic tests performed, while targeted testing was reported for 24.6% of subjects and made up 19.6% of all genetic testing completed. A smaller proportion of subjects had microarrays (11.8%) or other types of testing, including karyotypes, transcriptome analysis, telomere testing, or unspecified modality (5.2%) (Figure 2A–B). Of subjects with "unclassified ILD" who underwent a genetic evaluation, gene panels were performed for 61% and ES/WGS for 22% of subjects.

Both genetic testing and lung biopsy were performed for 135 Registry subjects. For 24 children, genetic testing results were positive, including diagnoses of *SFTPC* ($n = 10$), *ABCA3* and *NKX2-1* ($n = 2$ each), and *COPA* and *STING1* ($n = 1$ each). In examining the timing of lung biopsy and genetic testing, data on test timing were available for 18 of the 24 cases. Among these, lung biopsy was performed before genetic testing in seven cases (years ranging from 2005 to 2022) and occurred concurrent with genetic testing in six cases (range 2011–2020). For five children where lung biopsy was performed after genetic testing, the time gap ranged from 6 weeks to 12 years, though further details of the clinical circumstances were not available.

While gene panels were the most frequently ordered genetic testing modality, they had the lowest diagnostic yield (13% positive). The highest diagnostic yield was observed for targeted testing (29.1% positive), followed by microarray (20% positive). ES/WGS had a diagnostic yield of 14.3%, and it returned an uncertain result in 13.2% of cases. Despite panel testing having a low percent positive yield, based on frequent use of these panels, most subjects with positive genetic testing results were diagnosed through gene panels (33.8%). Targeted testing was the basis for a positive diagnosis in 32.5% of Registry participants. The most common diagnoses made through genetic testing were surfactant protein-C (*SFTPC*) associated surfactant metabolism dysfunction ($n = 21$; 27.3%), thyroid transcription factor-1 (*NKX2-1*)-related disorders ($n = 10$; 13.0%), and ATP binding cassette transporter A3 (*ABCA3*)-associated surfactant metabolism dysfunction ($n = 7$; 9.1%) (Table 3). The genetic evaluation for Registry participants varied and included at least one of 14 chILD-related genes for 78.1% of subjects that

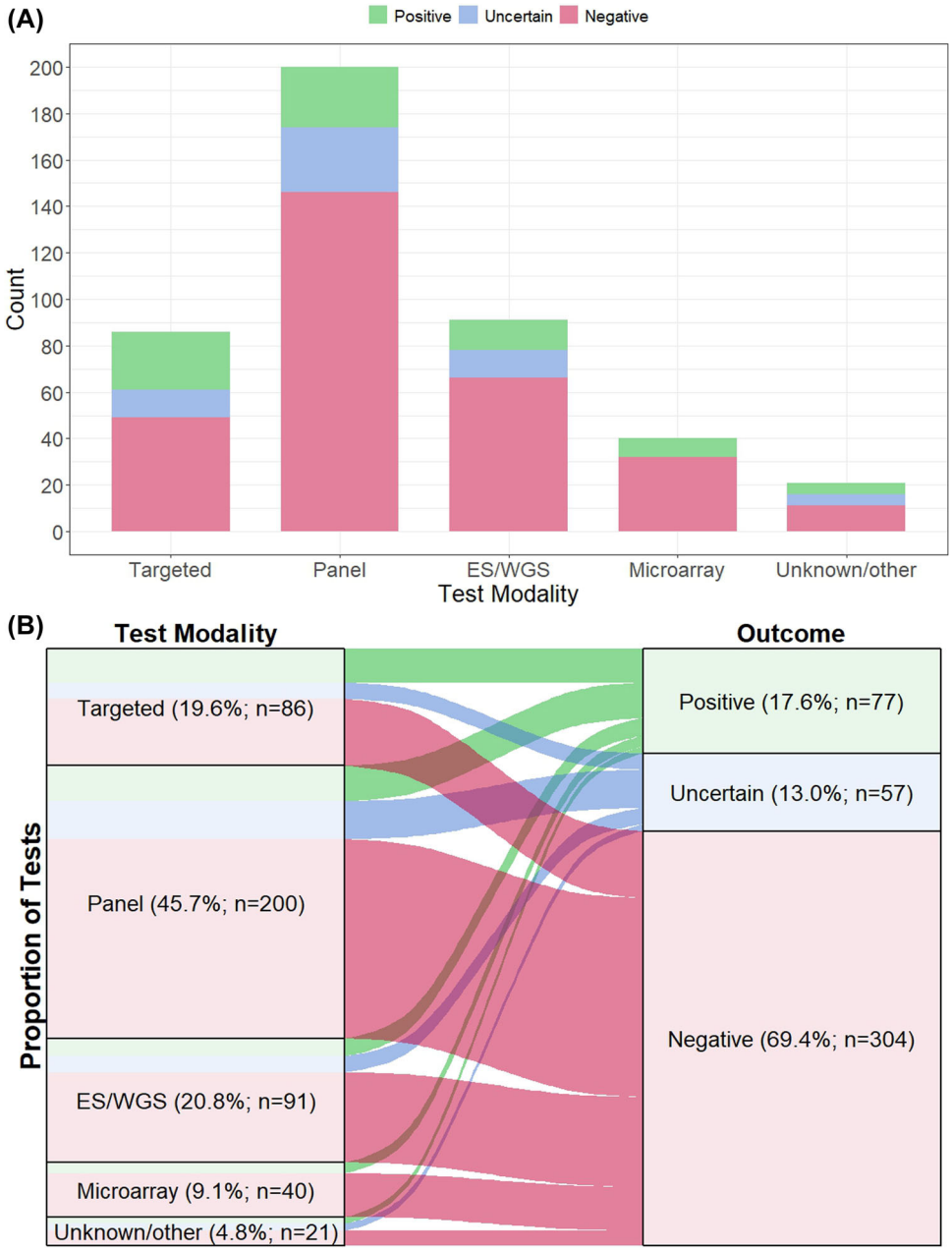

FIGURE 2 | Genetic testing modalities ordered and diagnostic yield. (A) Total number of genetic tests ordered and the diagnostic outcome by testing modality. Across the 338 subjects that underwent genetic testing, 434 different instances of genetic testing were reported. Total number of individual tests is indicated along the Y axis. (B) Genetic testing modality proportions and diagnostic yield. Targeted refers to single gene sequencing or targeted variant analysis. Other test modalities include karyotypes, telomere testing, and transcriptome analysis. Unknown refers to instances when a specific test modality was not documented in registry form. Abbreviations: ES/WGS, exome sequencing/whole genome sequencing. [Color figure can be viewed at wileyonlinelibrary.com]

underwent genetic testing (Supporting Information S1: Table 1). There were 50 children whose genetic evaluation did not include any of the 14 genes, but instead had targeted testing of other genes, a microarray, or different types of gene panels such as a primary ciliary dyskinesia or albinism panel.

For Registry participants that underwent genetic testing for chILD, there was a shift in the landscape of genetic testing modalities over time. Between 2007 and 2023, there was an increase in the utilization of ES/WGS. Use of ES/WGS was first reported in 2013, at which time it accounted for 5% of testing ($n = 1$ of 20 total) but eventually increased to 37% of testing ($n = 10$ of 27 total tests) in 2021. Gene panels were a consistently popular genetic testing approach, with more than 35% of Registry participants receiving panel testing in any given year (Figure 3).

4 | Discussion

Progress in the field of chILD has occurred over the past 30 years through a combination of genetic discoveries, lung biopsy classification, identification of chILD-associated disorders (e.g., rheumatologic, post-stem cell transplant), and improved understanding of

TABLE 3 | Positive genetic testing results.

Positive Genetic Analysis ($n = 77$)	n	%
SFTPC-associated surfactant metabolism dysfunction	21	27.3
NKX2-1-related disorders	10	13.0
ABCA3-associated surfactant metabolism dysfunction	7	9.1
RTEL1-associated dyskeratosis congenita	3	3.9
Rubenstein Taybi syndrome	3	3.9
Trisomy 21	3	3.9
Autoimmune interstitial lung, joint, and kidney disease	2	2.6
Hermansky-Pudlak syndrome[a]	2	2.6
MECP2 duplication syndrome	2	2.6
Noonan syndrome	2	2.6
TBX4-associated pulmonary disease	2	2.6
Other positive genetic diagnosis[b]	20	26.0

[a]Hermanksy-Pudlak syndrome was attributed to pathogenic variants in *HPS1* and *AP3B1*.
[b]Other positive genetic diagnoses include 2q32 deletion syndrome; multisystem associated smooth muscle dysfunction: *ACTA2*; ataxia telangiectasia: *ATM*; Blau syndrome: *NOD2*; chronic granulomatous disease: *CYBB*; familial autoinflammatory syndrome, with or without immunodeficiency: *SOCS1*; fibrodysplasia ossificans progressiva: *ACVR1*; ichthyosis vulgaris: *FLG*; FLNA deficiency; alveolar capillary dysplasia: *FOXF1*; hypohidrotic ectodermal dysplasia: *EDA1*; Menkes syndrome: *ATP7A*; congenital disorder of glycosylation type IIb: *MOGS*; Niemann-Pick type B: *SMPD1*; prolidase deficiency: *PEPD*; telomere syndrome: *TERT*; hyper-IgE syndrome: *STAT3*; STING-associated vasculopathy, infantile-onset: *STING1*; thrombocytopenia-absent radius syndrome: *RBM8A*; TBCK syndrome.

the underlying pathobiological mechanisms. These advances provide a framework for more specific diagnoses amidst a heterogeneous group of rare disorders. While genetic testing has become more widespread in some areas of pediatric healthcare including the neonatal intensive care unit [14–16], limited data are available about the utilization of clinical genetic testing for children with diffuse and interstitial lung diseases. In data from 22 children's hospitals focusing on chILD, we found that just over half of children enrolled in the Registry had undergone genetic testing and that 12.6% received a genetic diagnosis. Most participants had not undergone ES or WGS.

Our study captured data from clinical genetic testing performed over a period of 24 years, thus representing a time with broad variation in available genetic testing technologies. Even at given point in time, the composition of genes and numbers of genes included for analysis has differed substantially across available panels for ILD in different genomic labs. Further, the diagnostic rate observed in our study is likely impacted by inconsistent utilization of updated genetic testing or reanalysis of previous genetic data. For children who did not have genetic testing or follow-up testing with ES/WGS after negative panel results, data was not available about the potential reasons or barriers. Thus, our study reflects historical genetic testing utilization, but not necessarily the prevalence of genetic conditions in this cohort.

Genetic diagnoses in chILD have been reported within patient cohorts, electronic medical records, and registries across the world in recent years [10, 11, 17–21]. Limited data are available on the types of testing, timing, and detailed information on genetic testing outcomes among infants and children with chILD. Identification of genetic diagnoses within childhood disorders have notable implications for treatment, childhood to adult transition, future disease progression, associated co-morbidities, recurrence risk, and risk for other family members [22, 23]. Further, while chILD diagnoses are associated with significant morbidity during childhood and adolescence, there are implications for adult disease including pulmonary fibrosis [24–26]. There is increasing focus on personalized medicine and use of genetic and genomic information for diagnostic, prognostic, and therapeutic options in the pediatric and adult literature, including for pulmonary fibrosis [27]. This is also an area of interest in pediatric disease, as identification of detailed genetic variants and underlying disease pathogenic mechanisms may impact treatment options [28]. For example, diagnosis may inform decisions about timing of referral for lung transplantation, and transplant data has been reported for infants, children, and adults with genetic disorders of surfactant metabolism [29, 30]. Challenges in access to genetic testing are not only a pediatric issue; an international survey of patients, relatives, and pulmonologists previously reported that even in adult ILD, genetic testing guidelines, access, and availability are variable [31].

Given the progress in genetic testing technologies over the past several decades, one ongoing question in the evaluation for chILD is whether genetic testing may reduce the need for invasive lung biopsy and/or provide complementary information. In reviewing this cohort, we identified 24 infants and children with genetic testing results that may have precluded the need for lung biopsy within their evaluations. Given the discovery of new genetic etiologies of chILD over time and the marked change in turn-around-time for genetic testing results, it is unknown whether the genetic diagnostic results were received before or after the lung biopsy was obtained in these cases. Therefore, this historical data should be interpreted with caution. With more rapid return of genetic results, we would anticipate that at least some such cases might be diagnosed in the future without lung biopsy. In addition to diagnostic information, for children with diffuse and interstitial lung disease, genetic testing may also non-invasively provide prognostic information, and in some cases, personalized therapies. However, given variable genotype-phenotype correlations, there may still be an additive role for lung biopsy to guide therapies in selected cases even if a genetic diagnosis is established [32]. In future studies, it will be useful to capture data on whether genetic testing is initiated in the inpatient or outpatient setting, enabling assessment of impact of other components of healthcare utilization.

While the most common diagnoses made via genetic testing in Registry participants are consistent with the most common genetic causes of chILD reported in the literature, there were a considerable number of individuals whose pulmonary symptoms were found to be part of an underlying systemic genetic condition through genetic testing. Many of these conditions, like the immune mediated genetic causes of chILD, *CYBB*-related chronic granulomatous disease, *TBX4* deficiency, and *FLNA* deficiency, are not routinely included in lung disease

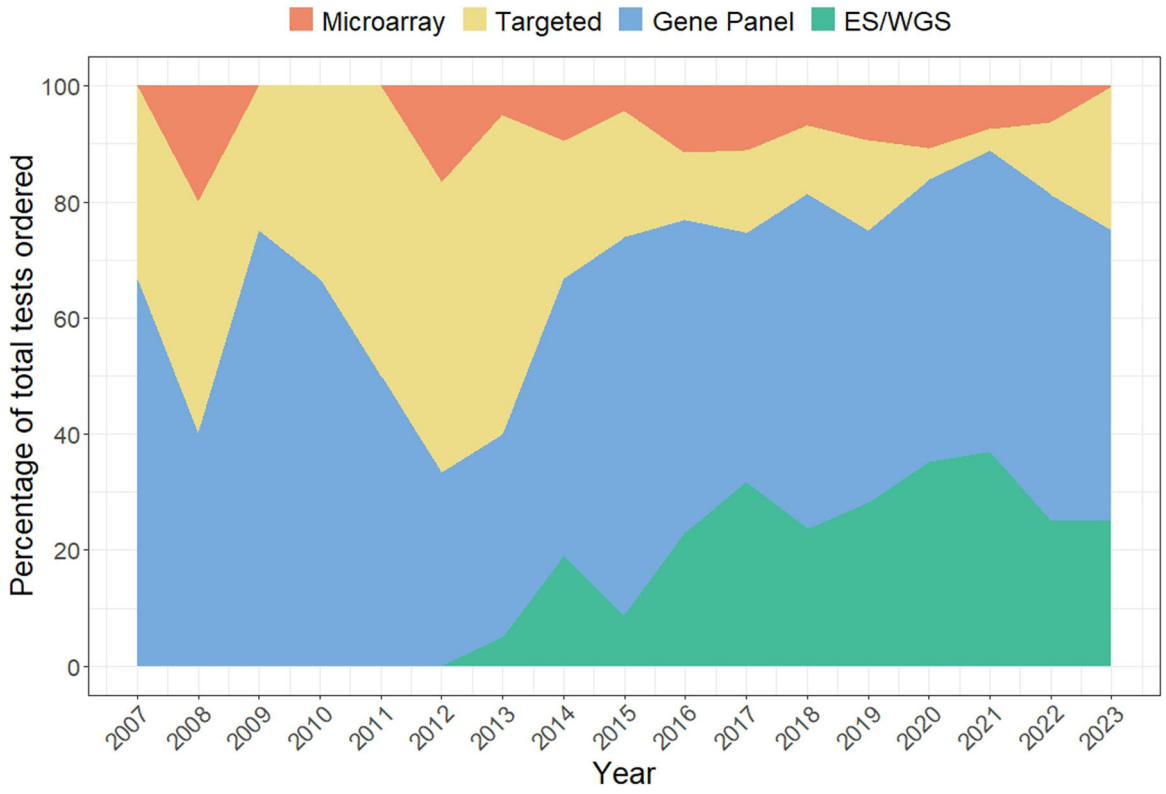

FIGURE 3 | Genetic testing modality ordered by year. Between 2007 and 2023, 373 different genetic tests were ordered for Registry subjects. The chart only includes reported instances of microarrays, targeted testing, gene panels, and ES/WGS. Data shown does not include genetic testing performed before 2007 or tests for which year of test was not documented in the Registry. From 1999 to 2007, a maximum of four genetic tests were reported for any given year. Abbreviations: ES/WGS, exome sequencing/whole genome sequencing. [Color figure can be viewed at wileyonlinelibrary.com]

gene panels, and the diagnoses were made via ES or WGS in these cases. While many labs offer gene panels that include genetic causes of ILD, as well as large panels for inborn errors of immunity, it is difficult to find a panel that includes both, even though these conditions can have overlapping clinical presentations and lung imaging findings. It is also important to acknowledge that the presentation of ILD/DLD often overlaps with other multisystem disorders that include pulmonary phenotypes. Gene panels had the lowest diagnostic yield for Registry participants, likely due to a combination of factors, including the wide range in the number of genes analyzed and the fact that no single panel is sufficiently comprehensive, particularly in a historical context before expansion of current panels. The U.S. ChILD Registry and previous studies [33, 34] have shown that lung disease or respiratory involvement can be seen in a variety of genetic conditions, and therefore, a broader genetic testing approach through ES or WGS could improve diagnostic yield and shorten the diagnostic odyssey for affected infants and children.

In considering the advances in sequencing technologies and informatics capabilities, recent studies have demonstrated the improved yield of WGS relative to other testing modalities. Wojcik et al recently reported a diagnostic yield of approximately 8% for WGS among both a diverse research cohort and in a selected clinical cohort of individuals who had previously undergone other genetic testing [35]. Further evidence supporting the role for WGS comes from the Genomic Medicine for Ill Neonates and Infants (GEMINI) study, which compared diagnostic yield for genomic sequencing with a targeted neonatal gene-sequencing test. In this study of 400 hospitalized infants with clinical suspicion for a genetic disorder, the diagnostic yield of genomic sequencing was 49% versus 27% with the targeted gene-sequencing test, though the time to return of results was longer for genomic sequencing [36]. As this field advances, with reduced costs and increased access, including some centers performing broad sequencing in house, ES/WGS may now return faster than commercial targeted panels. While overall cost–benefit analyses will depend on the nature of the population tested, another factor to consider is that WGS also generally obviates the need for microarray testing, thus influencing cost considerations of WGS compared to performing both ES and microarray.

This study has several limitations. First, since it uses registry-derived data from 22 different sites, there is variation in site reported data and genetic testing reports – ranging from mis-interpreted implications of genetic findings (e.g., monoallelic variant in an autosomal recessive condition, variants of uncertain significance, etc.) to data entry errors when transcribing. This highlights the importance of involving a clinician with expertise in genetics to review and potentially overread reports/site entries. Additionally, as referenced previously, ascertainment bias is present in this registry study format. Limited enrollments from the neonatal intensive care unit likely resulted in an under-representation of cases with some genetic diagnoses that are often lethal in the newborn period, such as SP-B deficiency, ABCA3 deficiency due to biallelic loss-of-function variants, or alveolar capillary dysplasia due to *FOXF1*

variants. Other retrospective case series and clinical practice experience suggest that many infants and children with genetic etiologies of ILD are not yet included in this Registry [17, 18, 23]. It is also important to acknowledge that the identification of an environmental contribution to lung disease such as post-infectious bronchiolitis obliterans or EVALI does not exclude the potential for monogenic or more complex genetic underpinnings.

Our data highlight many opportunities for future studies. First, it will be important to identify and reduce barriers to genetic testing for infants and children with suspected ILD, especially for those with chILD of unknown etiology. Clear recommendations are needed regarding the indications for genetic testing and recommended modalities in infants and children with diffuse lung disease, anticipating that WGS will play a larger role, particularly among inpatients. The increased use of WGS in neonatal intensive care units will likely identify additional infants with genetic etiologies for lung disease, and strategies are needed to enhance neonatology-pulmonology-genetics collaborations to care for these children and facilitate enrollment in studies to define genotype-phenotype correlations and outcomes. Further, as ES and WGS are expanding in availability, the field is primed for genetic discovery for causes of diffuse lung disease in childhood. We did not collect data on research reanalysis of sequencing data or follow-up investigations of potential candidate genes, but we are aware of such efforts ongoing at several centers. Given the high frequency of "non-diagnostic" results due to variants of uncertain significance, there is a potential avenue to invest additional efforts for VUS resolution, including coordinating parental testing, developing functional assays, and following up with laboratories regarding updates to classification. In this study, demographic information regarding race and ethnicity are self-reported and not specific ancestry data, and it is important to acknowledge the limitations of reference genetic databases with respect to ancestral diversity. Systematic recurring processes are needed to identify infants and children without defined etiology of their lung disease to facilitate expanded testing for those who only had panel testing and consider repeat testing as new genes are identified. Additionally, evaluating the impact of negative genetic testing results in this population is important, given the invasive nature of other evaluations including lung biopsy and overall complexities of the chILD diagnostic odyssey.

In conclusion, the U.S. ChILD Registry demonstrates varied utilization of genetic testing in infants and children with chILD. There is opportunity for broader utilization of ES/WGS and genetic discovery for children with ILD, especially for those with lung disease of unclear etiology. Additional studies are needed to delineate the clinical contexts surrounding genetic testing in this cohort and inform revised recommendations for utilization of genetic testing in chILD.

Author Contributions

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Acknowledgments

The authors thank all the research coordinators and study staff at the participating institutions for assisting with subject recruitment, consent, data entry, and oversight of regulatory processes.

ChILD Registry Collaborative

The following additional members of the chILD Registry Collaborative contributed to the collection and analysis of data presented in this manuscript: Carol Conrad, MD (Stanford University School of Medicine). Elizabeth Fiorino, MD (Cohen Children's Medical Center). Martha Fishman, MD (Boston Children's Hospital). Rebecca Gammell (Rainbow Babies & Children's Hospital). James Hagood, MD (University of North Carolina). Amjad Horani, MD (Washington University School of Medicine). Maureen Josephson, DO (Children's Hospital of Philadelphia). Erin Khan, MD (Children's Mercy Hospital Kansas City). Christin Kuo, MD (Stanford University School of Medicine). Geoffrey Kurland, MD (Pittsburgh Children's Hospital). Deborah Liptzin, MD (Colorado Children's Hospital). Katie Regan, MS, CGC (Boston Children's Hospital). Timothy Vece, MD (University of North Carolina). Supported in part by the NIH/NHLBI K24 HL143281 (LRY), NIH/NHLBI R01 HL170151 (LRY), Children's Hospital of Philadelphia (LRY), NIH/NHLBI R01 HL149853 (JAW), Children's Discovery Institute (JAW).

Conflicts of Interest

L.R.Y.: receives royalties from Wolters Kluwer for authorship in UpToDate, consultant for Boehringer Ingelheim pediatric advisory board (outside the submitted work). J.B.T.-W.: site investigator for Astra Zeneca (not related to interstitial lung disease). G.H.D.: Pathology consultant for Boehringer Ingelheim InPedILD trial; Pathology consultant for 4DMT. M.R.P – Site Investigator for Vertex Pharmaceuticals (not related to interstitial lung disease). W.A.G.: receives royalties from Wolters Kluwer for authorship in UpToDate. R.R.D.: receives royalties from Elsevier for editorship of Kendig and Wilmott's Disorders of the Respiratory Tract in Children, consultation for Boehringer Ingelheim pediatric advisory board and principal investigator for the INPEDILD and INPEDILD- ON trial. All other authors report no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. Some data have been previously presented in abstract form at the American Thoracic Society Conference 2024.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.