Update on Diffuse Lung Disease in Children CrossMark

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Diffuse lung diseases in children, also called children's interstitial lung disease, are a diverse group of rare disorders that cause disturbances of gas exchange in the lungs. Although individually rare, there are many different forms of diffuse lung disease in children, and collectively these disorders are associated with significant morbidity and mortality, as well as health-care resource utilization. Over the past several years, there have been many significant advances in the field, including genetic discoveries and the development of clinical practice guidelines. This review summarizes recent advances in the understanding, diagnosis, and treatment of diffuse lung diseases in children.

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Diffuse lung diseases in children are a heterogeneous group of rare conditions that cause significant morbidity and mortality in affected individuals. Estimates of disease prevalence range from 0.13 to 16.2 cases per 100,000,¹ compared with other rare childhood diseases such as cystic fibrosis that have a prevalence of 1 per 3,000 in white subjects in the United States.² Interstitial lung disease is perhaps the best recognized subgroup of diffuse lung disease, and the terms “interstitial lung disease” and “diffuse lung disease” are often used interchangeably in pediatrics. Because some of the specific entities grouped under these umbrella terms lack disruption of the interstitium, “diffuse lung disease” is the more accurate term.

The rarity, complexity, and heterogeneity of diffuse lung disease in children pose

challenges in both clinical care and research efforts. The need for multicenter collaboration to improve approaches to diagnosis and treatment of children with these disorders has resulted in the formation of research networks, including the Children's Interstitial Lung Disease Research Network in North America and the Children's Interstitial Lung Disease-European Union. Several recent studies suggest that childhood interstitial lung disease is often underrecognized^{3,4} and associated with high health-care resource utilization.¹ One primary area of progress is recognition that the forms of diffuse lung disease affecting children aged < 2 years are often distinct from the forms most common in adults.⁵ In contrast, diffuse lung disease in older children has much greater overlap with adult disorders.

ABBREVIATIONS: ABCA3 = gene encoding adenosine 5'-triphosphate-binding cassette family member A-3; ANCA = antineutrophil cytoplasmic antibody; ATS = American Thoracic Society; COPA = coat-omer-associated protein alpha; GM-CSF = granulocyte-macrophage colony-stimulating factor; NEHI = neuroendocrine cell hyperplasia of infancy; *NKX2-1/TTF-1* = gene encoding thyroid transcription factor-1; PAP = pulmonary alveolar proteinosis; PFT = pulmonary function test; *SFTPB* = gene encoding surfactant protein B; *SFTPC* = gene encoding surfactant protein C

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Progress in the field of diffuse lung diseases in children has been spurred by genetic discoveries, recognition of distinct forms of lung disease in young children, and development of a new classification paradigm. The present review focuses on advances made in the field of diffuse lung disease over the past 4 years, particularly with respect to clinical practice guidelines and high-impact findings in specific disease entities.

Practice Guidelines and Management Strategies

The first practice guideline for the diagnosis and management of diffuse lung disease in children was published by the American Thoracic Society (ATS) in 2013.⁶ This document summarizes many years of collaborative efforts to firmly define the discipline of childhood interstitial lung disease and is a fundamental advance in the field. Impetus for the guideline was prompted by growing recognition that childhood diffuse lung diseases, particularly in infancy, are often distinct from adult lung diseases. This conclusion was most clearly illustrated by a study from Deutsch et al⁵ that used 187 lung biopsy specimens from 11 pediatric centers to describe the histopathologic spectrum of diseases in children aged < 2 years. The subsequent classification scheme emphasized disorders more prevalent in infancy and thus provided a foundation for the ATS guideline. The guideline committee used a standardized method to collect, review, and grade the available evidence to inform recommendations focused on the evaluation, diagnosis, and management of infants and young children with diffuse lung diseases.

In the ATS guideline, the term “chILD syndrome” (ie, children’s interstitial and diffuse lung disease) was used to describe the constellation of unexplained respiratory signs and symptoms, such as tachypnea, hypoxemia, crackles, and diffuse abnormalities on chest imaging, that should prompt further evaluation for possible diffuse lung diseases.⁶ A critical first step is to exclude other, more common causes of diffuse lung disease such as infection or cystic fibrosis.^{6,7} Once these common causes are excluded, the clinical status of the patient is important; children who are critically ill or whose condition is rapidly progressing require a more aggressive approach to diagnosis. Laboratory testing may have a role in specific clinical contexts. For example, a CBC count with differential can be helpful in diagnosing alveolar hemorrhage syndromes or pulmonary infiltrates with eosinophilia.⁸ Pulmonary function tests (PFTs) (including spirometry, lung

volumes, and measurement of diffusing capacity) are commonly used in older children, whereas infant PFTs are considered on a case-by-case basis in infants and toddlers.

CT scans are a central modality for the evaluation of most diffuse lung disease. A high-resolution, controlled ventilation chest CT scan is the recommended technique for children with suspected interstitial lung disease.⁶ Intravenous contrast can be used to aid evaluation of mediastinal structures, such as mediastinal lymphadenopathy; however, contrast is not necessary for most forms of interstitial lung disease or for evaluation of pulmonary vasculitis. In some diseases, chest CT scans can be diagnostic and obviate the need for further testing, such as for neuroendocrine cell hyperplasia of infancy (NEHI) or postinfectious bronchiolitis obliterans.^{9,10} In other diseases, chest CT scans may suggest a diagnostic pattern and guide further testing. For example, the presence of diffuse ground-glass opacities with septal thickening is common for disorders of surfactant metabolism but does not distinguish among the different genetic mechanisms.¹¹

Genetic testing has a growing role in the evaluation of diffuse lung disease in children, with multiple disorders having an identified genetic cause.^{6,7} For hospitalized neonates with respiratory failure not attributable to other causes, consideration should be given to testing for both disorders of surfactant metabolism, including mutations in adenosine 5'-triphosphate-binding cassette family member A-3 (*ABCA3*), surfactant protein B (*SFTPB*), surfactant protein C (*SFTPC*) and mutations or deletions in *NKX2-1*/thyroid transcription factor-1 (*TTF-1*), and *FOXF1*, which is associated with alveolar capillary dysplasia with misalignment of the pulmonary veins.⁶ *FOXF1* testing is especially important if the neonate has severe pulmonary hypertension. Children may not present with *SFTPC*, *ABCA3*, and *NKX2-1* mutations at birth but rather in the first year of life or later.¹² Genetic testing should be performed by a laboratory approved according to the Clinical Laboratory Improvement Amendments; a list of available tests can be found at www.genetests.org. Current recommendations are to perform genetic testing for surfactant dysfunction prior to a lung biopsy in most cases.

Although there have been advances in discovering heritable causes of diffuse lung disease in children, it is also important to consider environmental mechanisms,

which are often overlooked without a detailed clinical history and sufficient index of suspicion. For example, bronchiolitis obliterans is a recognized consequence of acute respiratory infection, including episodes caused by adenovirus, mycoplasma, and others, although the risk factors are poorly understood. Furthermore, recent reports have detailed epidemics of diffuse lung disease in Korea that have been attributed to humidifier disinfectant.¹³ Lastly, hypersensitivity pneumonitis is likely an underrecognized cause of diffuse lung disease in children, with reports from Europe highlighting the clinical significance of this disease.^{14,15}

Lung biopsy is still required for definitive diagnosis of many diffuse lung diseases in children, such as pulmonary interstitial glycogenosis, alveolar simplification, pulmonary vasculitis/capillaritis, lymphoproliferative disorders, and disorders of surfactant metabolism not identified by genetic testing. A lung biopsy should be considered when results of noninvasive testing do not define the disease. Consensus guidelines for the handling of lung biopsy specimens, including fixation for electron microscopy, have been developed to optimize the diagnostic yield in children.¹⁶

Although refinements and modifications to the classification scheme developed by Langston et al¹⁶ have been proposed over time,^{4,17} the system overall provides a useful framework with which to approach diffuse lung disease in children. The classification scheme was recently applied to 191 lung biopsy specimens from a cohort of children aged 2 to 18 years.¹⁸ These findings reported by Fan et al¹⁸ emphasize that a large portion of diffuse lung disease in older children occurs in association with immunodeficiency and autoimmune disease, thus more closely mirroring adult disease.

As highlighted by the ATS guideline,⁶ treatment strategies for diffuse lung disease continue to be limited, in part due to the rarity and heterogeneity of these disorders in children. Supportive care, including proper nutrition, immunizations, and use of supplemental oxygen for hypoxemia, are the focus of management, absent definitive therapies for most forms of diffuse lung disease in children.^{6,7} When severity warrants, systemic corticosteroids (either oral or intravenous) are a mainstay of therapy; however, there is little to no evidence to support this approach.⁶ NEHI is a notable exception, as corticosteroids have not been found to be helpful in most cases.¹⁹ In contrast, pulmonary vasculitis generally requires significant immune suppression, often with cyclophosphamide or rituximab.²⁰⁻²⁴ Treatment for

connective tissue disease-interstitial lung disease also focuses on immune suppression.²⁵

Recently, the Children's Interstitial Lung Disease-European Union group published practice guidelines for children ages 0 to 16 years.⁷ Although their approach to evaluation and diagnosis of diffuse lung disease was similar to that of the ATS guidelines, they provide a new focus on therapeutic approaches. Author consensus and a Delphi process were used to develop recommendations aimed at standardizing therapies. This process highlighted the limited quality evidence to inform therapeutic choices for most forms of interstitial lung disease in children and the need for future trials.

Neuroendocrine Cell Hyperplasia of Infancy

Since the first article on NEHI was published in 2005, an additional 14 papers from six countries have subsequently detailed the clinical, physiologic, radiologic, and histologic features of this rare disorder.^{9,19,26-37} A primary advance in this area is the growing recognition that NEHI can be diagnosed by using a chest CT scan without the need for lung biopsy. Brody et al⁹ first fully described the radiologic features of NEHI in 2010. CT scans from biopsy-proven NEHI cases were reviewed (along with scans from disease control subjects) by two pediatric radiologists blinded to diagnosis based on the lung biopsy results. The characteristic findings of ground-glass opacities in the right middle lobe, lingula, and medial segments of the upper and lower lobes, in the absence of other significant parenchymal abnormalities, were shown to be specific to NEHI and are now considered pathognomonic for NEHI in a compatible clinical context (Fig 1). Finally, Gomes et al³³ also demonstrated the consistency of this imaging pattern in NEHI, including evidence of improvement or complete resolution of ground-glass opacities over time, consistent with the known clinical course of this disease. In summary, with a compatible clinical picture, chest CT scans are now considered sufficient to diagnose NEHI without performing a lung biopsy. This approach has significantly reduced morbidity by decreasing the need to conduct biopsies.

Infant PFTs may also have a role in supporting a diagnosis of NEHI syndrome. Kerby et al³² compared infant PFTs from 37 children with NEHI vs children undergoing hematopoietic stem cell transplantation. Patients with NEHI exhibited a predominant air trapping disorder as evidenced by a markedly elevated functional residual capacity or residual volume/total

Figure 1 – A-C, Examples of CT scan findings in three patients with neuroendocrine cell hyperplasia of infancy (NEHI). Black arrows indicate ground-glass opacities in the medial portion of either the upper or lower lobes while red arrows indicate ground-glass opacities in the right middle lobe or lingula. Patients A and B have typical CT patterns for NEHI, whereas patient C has a much more subtle pattern consistent with NEHI. Patients A and B are siblings with NEHI. C1 shows a CT scan performed at 5 months of age, and C2 shows a repeat CT scan on the same subject at 3 years of age. Note the resolution of ground-glass opacities in this case.

lung capacity ratio with proportionate reductions in forced expiratory volume in the first 0.5 s and FVC.

A lung biopsy is occasionally still required to diagnosis NEHI, particularly in cases in which the typical pattern is not seen on the CT scan. Results of the lung biopsy in NEHI generally show a seemingly benign pattern with no significant alveolar changes, although mild airway inflammation is occasionally noted.^{19,34} Small bronchioles contain an increased number of bombesin-positive pulmonary neuroendocrine cells.³⁴ Chromogranin is used in some pathology laboratories to stain for

neuroendocrine cells; however, it does not sufficiently stain cells in NEHI and should therefore be avoided.¹⁹ Because pulmonary neuroendocrine cells are present in the normal lung and increased in a variety of clinical contexts, including bronchopulmonary dysplasia, airway injury, pulmonary hypertension, and others, the presence of pulmonary neuroendocrine cells alone is not specific for a NEHI diagnosis. When lung biopsy is necessary, morphometric quantitation of the increased number of pulmonary neuroendocrine cells as well as neuroendocrine bodies can be used to distinguish NEHI from other diseases.³⁴

Finally, there is evidence that NEHI has a heritable component. A report from Popler et al³⁵ described nine patients from four families with NEHI, suggesting a possible genetic mechanism for NEHI. A 2013 publication reported a mutation in *NKX2-1* in an individual with NEHI and multiple family members with lung disease, although mutations in this gene have not been associated with NEHI in other cases to date.²⁹ In addition, there are a number of additional cases of familial NEHI for which a genetic cause has not yet been identified.

Disorders of Surfactant Metabolism

Disorders of surfactant metabolism encompass diseases resulting from both defects in surfactant production and degradation and are considered the topic most responsible for defining the field of childhood interstitial lung disease. Inheritance patterns depend on the underlying genetic mechanism, with variable yet overlapping age of presentation among different genetic mechanisms (Table 1). For example, surfactant protein B deficiency and some subtypes of *ABCA3* deficiency present with neonatal respiratory failure. *ABCA3* deficiency, *SFTPC* mutations, and pulmonary alveolar proteinosis (PAP) due to granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor mutations may also present with milder symptoms in neonates or with chronic lung disease in older children or adults.¹² Mutations and deletions in *NKX2-1*, which encodes for TTF-1, cause a large spectrum of presentations both in younger and older children.³⁸ Autoimmune PAP due to GM-CSF autoantibodies typically presents in older children. Secondary PAP can occur as a consequence of a number of disorders, including infections (particularly *Pneumocystis jiroveci* pneumonia) after hematopoietic stem cell transplantation and in association with hematologic disorders.³⁹⁻⁴³

Diagnostic methods have changed with the availability of clinical genetic testing such that genetic testing is

recommended prior to lung biopsy for most cases, with the goal of obviating the need for lung biopsy. Importantly, genetic testing likely only identifies 60% to 75% of patients with disorders of surfactant metabolism; thus, a lung biopsy may still be indicated if results of genetic testing are negative.⁵ A recent study also suggests that lipidomic analysis of bronchoalveolar lavage fluid could aid in case identification.⁴⁴

Treatment options for surfactant production disorders continue to be limited, although there have been some reports of clinical improvement with systemic corticosteroids and/or hydroxychloroquine.^{7,45-51} Unfortunately, none of the treatments for surfactant disorders has been rigorously tested in controlled trials. Lung transplantation is an option and is at least as effective as lung transplantation for other diseases, with similar 5-year survival rates.⁵² Notably, a report by Liptzin et al⁵³ described prolonged mechanical ventilation as an alternative to lung transplantation in patients with interstitial lung disease due to *SFTPC* mutation.

An area of recent advance in this field relates to greater understanding of how genotype affects phenotype both in *ABCA3* mutations and in *SFTPC* mutations. Wambach et al⁵⁴ reported on 185 infants with *ABCA3* deficiency and categorized their mutations as null-null, null-other, and other-other. In patients with null-null mutations, all presented in the first year of life, with no subjects surviving past 1 year of life without a lung transplantation. Subjects with at least one non-null mutation often had significant respiratory disease; however, approximately 35% of subjects lived past 1 year of life with no need for a lung transplantation. This information is invaluable when counseling parents of sick neonates.

The relationship between mutation type and phenotype is less clear for *SFTPC* mutations, which are associated with variable penetrance and age of onset even within

TABLE 1] Genetic Disorders of Surfactant Metabolism

Gene	Inheritance Pattern	Neonatal Presentation?	Childhood Presentation?	Extrapulmonary Findings
<i>SFTPB</i>	AR	Yes; predominant	Extremely rare	None reported
<i>ABCA3</i>	AR	Yes; common	Yes; common	None reported
<i>SFTPC</i>	AD Spontaneous	Occasional	Yes, predominant	None reported
<i>NKX2-1</i>	AD deletions	Yes	Yes	Chorea, hypotonia, hypothyroidism
<i>CSF2RA</i> <i>CSF2RB</i>	AR	Rare	Yes; predominant	None reported

AD = autosomal dominant; AR = autosomal recessive.

individual affected families.⁵⁵ In a recent article by Kroner et al,⁵⁶ subjects with a mutation in the BRICHOS domain of *SFTPC* were more likely to present in the first year of life, although long-term survival was not correlated with specific mutations. Peca et al⁵⁷ examined histopathologic and electron microscopy findings for correlation with *SFTPC* mutations. A number of changes were noted in lamellar bodies; however, no consistent changes were noted in contrast to distinct findings reported in association with *ABCA3* and *SFTPB* mutations.^{58,59}

Mutations and deletions in *NKX2-1*, the gene encoding TTF-1 (a major transcription factor that regulates many genes, including those involved in surfactant protein production), are a recognized cause of isolated diffuse lung disease in children. Hamvas et al³⁸ reported 21 subjects with mutations in *NKX2-1* and found substantial phenotypic variation in pulmonary disease; the most common neurologic presentation was hypotonia. Some subjects had severe respiratory failure shortly after birth similar to patients with *SFTPB* mutations, whereas others had recurrent pulmonary infections, potentially attributable to a loss of innate immunity provided by surfactant proteins A and D. The histopathologic changes were also variable, with some subjects having patterns associated with disorders of surfactant metabolism such as desquamative interstitial pneumonia and PAP, while other subjects had alveolar growth abnormalities or changes consistent with chronic infection. *NKX2-1* mutation should be suspected in any infant with hypotonia, congenital hypothyroidism, and lung disease, referred to as the brain-lung-thyroid syndrome. However, it should be emphasized that the disease is heterogeneous, and mutations in *NKX2-1* should be part of the differential for any pediatric patient with unexplained diffuse lung disease, even in the absence of hypothyroidism or neurologic disease.

Finally, a number of intriguing advances have been made in the treatment of PAP caused by mutations in GM-CSF receptor subunits. PAP is a form of diffuse lung disease that occurs from accumulation of surfactant proteins in the alveolar spaces. Pulmonary macrophages, under the regulation of GM-CSF, are critical for surfactant recycling and clearance.⁶⁰ PAP in young children is most often due to mutation in the *CSF2RA* or *CSF2RB* genes that encode the α and β subunits, respectively, of the GM-CSF receptor.⁶¹⁻⁶³ PAP from *CSF2RA* mutations typically presents in early childhood.

Currently, the only established treatment is repeated whole lung lavage.⁶⁴ Recent publications have reported on a potential novel treatment for PAP caused by GM-CSF receptor mutations. In *csf2rb*^{-/-} mice that have an analogous disease to human PAP, a macrophage transplantation consisting of either wild-type murine macrophages, gene-corrected macrophages from mutant mice, or normal human macrophages resulted in significantly improved surfactant clearance and homeostasis.⁶⁵⁻⁶⁷ Furthermore, the effects lasted for up to 9 months, longer than the average life span of a pulmonary macrophage, indicating that a normal population of pulmonary macrophages can be established in the lungs of the affected mice. If these findings can be recapitulated in humans, they would significantly improve therapy for this form of PAP and could potentially be curative.

Pulmonary Vasculitis

Pulmonary vasculitis most often presents in older children and has garnered increased focus due to disease severity and management implications. Although multiple disorders are associated with pulmonary hemorrhage, the most common causes in children are the antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides and idiopathic pulmonary capillaritis.⁸ Granulomatosis with polyangiitis, microscopic polyangiitis, and Goodpasture's syndrome are often diagnosed according to the presence of autoantibodies and renal disease. In contrast, because bronchoscopy and imaging (Fig 2) cannot distinguish capillaritis from idiopathic pulmonary hemosiderosis, a lung biopsy is required to diagnose idiopathic pulmonary capillaritis.⁶⁸

While most reports on pulmonary vasculitis in children have been small case series, a larger study of 66 children with ANCA-associated vasculitis from Sacri et al⁶⁹ reported a female predominance and an average age of diagnosis of 11.5 years. Importantly, this cohort illustrated the chronic nature of the disease, with a relapse rate of > 50% within 5 years of diagnosis. Renal disease was prominent in children with ANCA-associated vasculitis, emphasizing the need for monitoring and treatment.

Historically, the initial treatment for pulmonary vasculitis has been prolonged courses of cyclophosphamide and systemic corticosteroids, with significant adverse effects.²¹ A different model was adopted in the 1990s with the use of cyclophosphamide for shorter treatment

Figure 2 – A-C, Imaging and histopathology in idiopathic pulmonary capillaritis. A, Chest radiographic findings of diffuse infiltrates in a 5-year-old presenting with anemia and cough without hemoptysis. B, Representative chest CT findings including ground-glass opacities (white arrow) and septal thickening (black arrow). There are also diffuse infiltrates, which can be seen in the setting of severe, acute bleeding. Note that the findings on chest radiograph and CT scan are indistinguishable from idiopathic pulmonary hemosiderosis. C, Lung biopsy specimen from the same patient shows the typical findings on histopathology with red blood cells in the airspaces, hemosiderin-laden macrophages (blue arrow), and neutrophils in the interstitium along capillaries (asterisk). Magnification $\times 400$. Histopathology courtesy of Dr Norma Quintanilla.

courses as an induction phase of therapy, followed by maintenance with less toxic medications, including methotrexate or azathioprine.^{22,23} Although not studied in pediatric patients, alternative long-term therapy protocols for ANCA-associated vasculitis have been assessed in recent studies. Rituximab has been used as a substitute for cyclophosphamide for induction, likely because it has a superior safety profile.²⁴ Guillevin et al⁷⁰ reported that when rituximab was given every 6 months for 18 months as maintenance therapy following an initial induction with cyclophosphamide, the 2-year relapse rates improved from 29% in the azathioprine group to 5% in the rituximab group. In another study,

Calich et al⁷¹ found that using rituximab for both induction and maintenance produced outcomes similar to other maintenance regimens, although with a decrease in the total glucocorticoid need. These data suggest that rituximab may be a promising therapy, given its potential for long-term relapse-free survival.

Genetic Causes of Immune Dysregulation and Diffuse Lung Disease

The increased availability of advanced genetic sequencing techniques, including whole exome sequencing, has expanded the understanding and scope of diffuse

lung diseases in children. Several recent publications highlight the power of this technology and potential promise for uncovering the etiology and disease pathogenesis.

Watkin et al⁷² reported a genetic cause of immune dysregulation that causes familial pulmonary hemorrhage and arthritis. Five families were identified with multiple affected individuals with pulmonary hemorrhage. Exome sequencing revealed mutations in the alpha subunit of coatamer-associated protein (COPA). COPA is part of a complex, coatamer-associated protein I that regulates retrograde transport from the Golgi to the endoplasmic reticulum. Defects lead to increased endoplasmic reticulum stress and increased autophagy, both of which can lead to autoimmunity.

In another recent discovery, Lo et al⁷³ identified a new genetic cause of common variable immunodeficiency in which a significant number of patients had lymphocytic interstitial pneumonia. Patients were found to have mutations in *LRBA*, which encodes a protein that is likely involved in trafficking CTLA4, a potent inhibitor of immune function expressed by T_{reg} cells. Indeed, the patients with severe lung disease significantly improved with treatment with abatacept, a CTLA4 agonist.

Finally, Milner et al⁷⁴ described gain of function mutations in *STAT3* that lead to autoimmunity. The study patients had lymphocytic interstitial pneumonia in addition to other features of immune dysregulation, including autoimmune hemolytic anemia, autoimmune thrombocytopenia, autoimmune neutropenia, and scleroderma features. The exact cause of the immune dysfunction is not known; however, it may be related to delayed dephosphorylation of *STAT3*, which leads to decreased T_{reg} function and increased T_H17 activity, both of which can cause autoimmunity. Taken together, these advances demonstrate how genetic discovery in children with diffuse lung diseases is rapidly defining etiology and underlying biology and thus provides promise for much-needed therapeutic advances.

Conclusions

The field of diffuse lung disease in children has evolved significantly in recent years, driven by robust phenotyping, refined classification, and genetic discoveries. Although NEHI and disorders of surfactant metabolism continue to be areas of focus in this field, forms of diffuse lung disease in older children, including ANCA-associated vasculitis, are gaining momentum. Finally, new genetic causes of specific forms of diffuse lung disease, notably

PAP due to *CSF2RA* and *CSF2RB* mutations, pulmonary hemorrhage due to *COPA* mutations, and lymphocytic interstitial pneumonia due to mutations in *LRBA* and *STAT3*, are exemplars of transformative progress in the field. Although advances have occurred, therapy is lacking for most forms of diffuse lung disease in children. The formation of international research networks holds promise for translating scientific advances to the therapeutic trials greatly needed in this field.

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