Accelerating Scientific Advancement for Pediatric Rare Lung Disease Research

Report from a National Institutes of Health–NHLBI Workshop, September 3 and 4, 2015

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Abstract

Pediatric rare lung disease (PRLD) is a term that refers to a heterogeneous group of rare disorders in children. In recent years, this field has experienced significant progress marked by scientific discoveries, multicenter and interdisciplinary collaborations, and efforts of patient advocates. Although genetic mechanisms underlie many PRLDs, pathogenesis remains uncertain for many of these disorders. Furthermore, epidemiology and natural history are insufficiently defined, and therapies are limited. To develop strategies to accelerate scientific advancement for PRLD research, the NHLBI of the National Institutes of Health convened a strategic planning workshop on September 3 and 4, 2015. The

workshop brought together a group of scientific experts, intramural and extramural investigators, and advocacy groups with the following objectives: (1) to discuss the current state of PRLD research; (2) to identify scientific gaps and barriers to increasing research and improving outcomes for PRLDs; (3) to identify technologies, tools, and reagents that could be leveraged to accelerate advancement of research in this field; and (4) to develop priorities for research aimed at improving patient outcomes and quality of life. This report summarizes the workshop discussion and provides specific recommendations to guide future research in PRLD.

Keywords: rare disease; genomics; discovery; outcomes; children

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Pediatric rare lung diseases (PRLDs) comprise a spectrum of low-prevalence disorders collectively representing a substantial burden of morbidity, mortality, healthcare utilization, and caregiver costs. Although some PRLDs, such as cystic fibrosis (CF), have been the focus of longstanding research efforts, most PRLDs remain poorly understood. In the past decade, a subset of PRLDs has been a focus

of study by the Children's Interstitial and Diffuse Lung Disease Research Network and others. Concerted efforts to organize this field have included development of consensus diagnostic criteria, implementation of standardized terminology, and publication of clinical practice guidelines (1–3). Schemes to classify children's interstitial and diffuse lung disease, including by age of onset, by

pulmonary or systemic origin, vascular, immunologic, or other suspected etiology, are useful and can be modified to incorporate additional PRLDs (Table 1).

Although remarkable advances have been made for some conditions, progress for most PRLDs is impeded by poorly defined disease pathogenesis, lack of model systems for preclinical studies, and lack of definitive diagnostic tests, molecular targets, specific

Table 1. Examples of pediatric rare lung diseases

Category and Subtypes	Specific Examples and Etiologies
Disorders of lung development	
Diffuse developmental disorders	Alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV); associated with disruption of <i>FOXF1</i>
	Acinar dysplasia
	Congenital alveolar dysplasia
Lung growth abnormalities	Pulmonary hypoplasia
	Bronchopulmonary dysplasia
Pulmonary interstitial glycogenosis	Diffuse form or patchy form in conjunction with altered lung development
Congenital malformations	Congenital pulmonary airway malformations
	Bronchogenic cysts
	Pulmonary sequestration
	Airway malformations
	Others
Genetic disorders of surfactant metabolism	Associated with disruption of <i>SFTPB</i> , <i>SFTPC</i> , <i>ABCA3</i> , and <i>NKX2-1</i> ; Others, candidate genes/gene variants not identified
Pulmonary alveolar proteinosis	GM-CSF autoantibodies
	Associated with disruption of <i>CSF2RA</i> and <i>CSF2RB</i>
	Lysinuric protein intolerance
	Other secondary PAP mechanisms
Neuroendocrine cell hyperplasia of infancy	Associated with <i>NKX2-1</i> mutation; others, etiology not identified
Cystic fibrosis	Associated with disruption of <i>CFTR</i>
Primary ciliary dyskinesia	Associated with disruption of <i>DNAH5</i> , <i>DNAI1</i> , <i>DNAI2</i> , <i>CCDC114</i> , <i>ARMC4</i> , <i>LRR6</i> , <i>HEATR2</i> , <i>SPAG1</i> , <i>DNAAF1</i> , <i>DNAAF2</i> , <i>CCDC39</i> , <i>CCDC40</i> , <i>RSPH4</i> , <i>RSPH9</i> , and multiple other genes (>30) identified; others, candidate genes/gene variants not identified
Pulmonary vascular disorders	
Pulmonary venoocclusive disease	
Pulmonary capillary hemangiomatosis	Associated with disruption of <i>EIF2AK4</i>
Hereditary hemorrhagic telangiectasia	Associated with disruption of <i>ACVRL1</i> , <i>ENG</i> , and <i>SMAD4</i>
Congenital lesions (hemangiomas, others)	
Isolated pulmonary capillaritis	
Pulmonary arterial hypertension	Associated with disruption of <i>BMPR2</i> ; multiple other genes identified
	Others, candidate genes/gene variants not identified
	Associated with altered lung development, lung diseases, other systemic disorders, and other conditions or exposures
Lymphatic disorders	
	Pulmonary lymphangiectasia
	Generalized lymphatic anomaly (lymphangiomatosis)
	Kaposiform lymphangiomatosis
	Others
Related to systemic diseases	
Connective tissue (rheumatologic) disorders	
Metabolic or lysosomal storage diseases	Niemann-Pick, Gaucher disease, numerous others
Sarcoidosis	
Dyskeratosis congenita	Associated with disruption of <i>TERT</i> , <i>TERC</i> , <i>DKC1</i> , <i>TINF2</i> , and <i>RTEL1</i>
Langerhans cell histiocytosis	
Associated with immunodeficiency syndromes	Follicular bronchiolitis, lymphocytic interstitial pneumonia; multiple genetic etiologies
Neurocutaneous syndromes	Neurofibromatosis, tuberous sclerosis complex, ataxia-telangiectasia, others
Hermansky-Pudlak syndrome	Lung disease associated with disruption of <i>HPS1</i> , <i>AP3b1</i> , and <i>HPS4</i>
Sickle cell disease	
Others	
Other PRLDs	
Bronchiolitis obliterans	Postinfectious or post-transplant/pulmonary graft-versus-host disease
Hypersensitivity pneumonitis	
Eosinophilic pneumonia	
Radiation pneumonitis/fibrosis	

(Continued)

Table 1. (Continued)

Category and Subtypes	Specific Examples and Etiologies
Pulmonary alveolar microlithiasis Plastic bronchitis Others Unclassified or undefined	Associated with disruption of <i>SLC34A2</i> Associated with cyanotic heart disease, sickle cell disease, lymphangiectasia, and others

Definition of abbreviations: GM-CSF = granulocyte/macrophage colony-stimulating factor; PAP = pulmonary alveolar proteinosis; PRLDs = pediatric rare lung diseases.

therapies, or outcome measures (Table 2). Factors such as overlapping clinical and radiologic presentations, incomplete penetrance, and variation in timing of disease onset pose additional challenges for many PRLDs.

In September 2015, the NHLBI convened a group of clinicians, scientists, parents of children with rare disorders, and National Institutes of Health (NIH) staff to review and make recommendations regarding priority areas of research to accelerate scientific advancement of PRLD research and improve clinical outcomes and quality of life for children with PRLDs. The workshop was organized into four sessions focused on (1) the current state of PRLD research; (2) scientific gaps and barriers to increasing research and improving outcomes for PRLDs; (3) opportunities afforded by new technologies, tools, and reagents to accelerate PRLD research; and (4) approaches to link patients, clinicians,

and researchers. This report summarizes the workshop presentations and discourse and identifies priority areas of research and recommendations intended to guide future PRLD research.

Workshop participants reviewed PRLD scientific advances and highlighted the elements that had contributed to them. In particular, successful strategies in CF, primary ciliary dyskinesia (PCD), and pulmonary alveolar proteinosis (PAP) were discussed as instructive examples. In CF, a biomarker-based diagnostic test (sweat chloride) (4, 5) led to identification of a cohort of affected individuals. Application of what was then a new technology, “chromosomal walking and jumping,” yielded identification of the disease-causing gene (6). Patient advocacy organization support led to establishment of a clinical care network and evidence-based care guidelines, and creation of a therapeutics development network accelerated the

evaluation of new treatments. Building on extensive NIH-supported research elucidating molecular pathogenesis, collaboration between the CF Foundation and the pharmaceutical industry led to new pharmacotherapy targeting specific molecular defects, a prominent example of personalized medicine (7, 8). In all, a massive undertaking with contributions from clinicians, scientists, patients, patient advocacy organizations, the pharmaceutical industry, and NIH all contributed to the successes that have advanced research and improved clinical outcomes for patients with CF.

In PCD, a different approach was taken. The NIH Office of Rare Diseases and the National Center for Advancement of Translational Sciences established the Rare Diseases Clinical Research Network comprising clinicians, scientists, and patient advocacy organizations. One member, the Genetic Disorders of

Table 2. Examples of key advances and remaining hurdles for specific pediatric rare lung diseases

Specific Disease	Key Advances	Specific Gaps or Hurdles
Genetic disorders of surfactant metabolism (<i>ABCA3</i> , <i>SFTPC</i> , <i>NKX2.1</i>)	Delineation of genetic mechanisms Pathogenic mechanisms partially understood through development and study of cell and animal models	Natural history incompletely defined Need for greater identification and organization of patients for study Therapeutic targets insufficiently defined Need for systems for high-throughput testing of mutations and potential therapeutics Lack of validated biomarkers or outcome measures suitable for use in infants and young children
Neuroendocrine cell hyperplasia of infancy	Disease description Delineation of clinical, radiologic, physiologic, and histologic features and diagnostic criteria Patient advocacy	Epidemiology and natural history not sufficiently defined Need for greater identification and organization of patients for study Etiology not defined Lack of cell or animal models for modeling of disease Lack of validated biomarkers or outcome measures suitable for use in infants and young children

Figure 1. Paradigms for pediatric rare lung disease (PRLD) research. The descending black arrow in the center depicts key steps along a linear pathway leading from disease description to development of an effective therapy. In this paradigm, elucidation of disease phenotype(s) and pathogenic mechanism(s) are central to identification of molecular targets that can be developed into biomarkers/diagnostics and novel therapeutics. In rare disease research, a “front-door” approach and iterative collaboration of patients, researchers, and clinicians are required. Facilitating communication among these stakeholders provides the critical foundation needed to achieve advancement in PRLDs. See text for further details.

Mucociliary Clearance Consortium, has systematically identified PCD-causing genetic mutations and developed new strategies to improve diagnostic approaches and care for patients with PCD (9–13). A patient advocacy organization, the PCD Foundation, developed in parallel and is now working to establish care centers following the model developed by the CF Foundation.

Another success story was presented for PAP. The serendipitous identification of an animal model of PAP provided a critical pathogenic clue (14). Subsequent NIH-supported basic, clinical, and translational research led to development of highly specific diagnostic tests, elucidation of disease pathogenesis, and novel molecular pathogenesis-based pharmacotherapeutic approaches that are now in clinical testing (15–20). Workshop participants also discussed the critical role of patient advocacy in rare disease research. Phelan-McDermid syndrome, a genetic cause of autism spectrum disorder (ASD), was highlighted as a prominent example of the power of patient/family involvement in advancing research (21–26).

These examples illustrate that research advances can be driven in various ways in PRLD. Notwithstanding, certain elements are recurrent, including methods to identify individuals with specific PRLDs;

collaboration among clinicians, scientists, and patients; support from NIH and patient advocacy organizations; and empowerment of the patient community (Figure 1). In the remainder of this workshop report, we review gaps in knowledge/challenges to overcome, identify novel strategies and technologies, and discuss approaches to empowering the patient community with potential to accelerate advancement of PRLD research. The recommendations developed during the workshop were approved by all workshop participants and have been synthesized and organized within the following four priority areas.

Priority Area 1: Establish an Interactive, Data-driven, PRLD Research Community

A primary challenge in the nascent field of PRLD research and advocacy is that patients, expert clinicians, and biomedical researchers are often separated across institutions and geographies and lack a common platform to connect or communicate. Patients and families with PRLDs do not yet have a “clearinghouse” of information and means of connection to the medical research complex. Those patients, clinicians, and researchers who do manage to contact one another

typically do so on an *ad hoc* or case-by-case basis. Expertise, model systems, and data resources remain isolated, and the economies of scale from centers of excellence are not realized.

Furthermore, inherent limitations of health information technology, such as firewalls and other security measures, limit access, sharing, and aggregation of both healthcare data (housed across multiple non-interoperable electronic health record systems) and biological samples (obtained with myriad diverse consents) across diverse and often geographically separated groups of individuals. Patients, clinicians, and researchers often are unable to access and share the necessary clinical and “-omics” data. Even when patient communities have managed to acquire their health system data and samples, they lack turnkey toolkits to share and analyze them. For example both patient-driven and researcher-driven rare disease groups end up funding development of their own registries, biobanks, survey platforms, and tools to collect patient-reported outcomes.

Recognizing these challenges and opportunities, we make a series of recommendations toward developing a “front door” to the PRLD community, thereby creating an entry point to engage patients, families, and clinicians, linking them to PRLD research and equipping them with scalable, reusable, common core data infrastructures and biomedical resources. Patients and patient advocacy groups can and should play a central role in this process by promoting disease awareness, facilitating communication among patients and researchers, establishing registries, and perhaps most importantly in framing the research agenda. Social media and web-based tools should be used to connect patients with rare disorders to one another, to clinicians with expertise in managing their condition, and to bench scientists studying the pathogenesis of the disease. The development of regulatory-compliant, scalable informatics platforms, such as the Informatics for Integrating Biology and the Bedside (i2b2), offer a means to provide researchers with existing large-scale clinical data sets for “discovery” research and to integrate these clinical data with large “-omics” datasets (27–29).

Recommendations

- Facilitate connection among PRLD clinicians, investigators, patients/families, and patient communities interested in PRLD research, including international collaboration.
 - Develop a sustainable network of clinicians, research labs, patient advocacy organizations, and patient communities.
 - Create a web-based front door to the organized PRLD clinical/research/patient community.
 - Develop an online presence for the network with profiles of PRLD-oriented clinicians, investigators, and patient groups.
 - Attract young/new investigators and encourage established investigators to enter/collaborate with the PRLD research field.
 - Support the necessary personnel and processes to facilitate matchmaking across stakeholders for clinical care, research, and advocacy.
- Facilitate sharing patient-level and aggregate clinical and research PRLD data and samples.
 - Develop a standardized research consent process to facilitate participation in PRLD studies.
 - Develop a scalable, reusable, common core infrastructure (for example, based on i2b2) to query and share electronic health record (EHR) data from PRLD encounters, diagnostic evaluations, and hospitalizations.
 - Develop policies, procedures, and tools to make patient-directed sharing of EHR data seamless across sites.
 - Use emerging mobile health technologies and apps to collect patient-reported outcomes.
 - Establish standardized biobanking protocols with uniform consents.
 - Develop strategies to promote understanding and use of genomic data by a greater community of investigators and medical providers.
- Leverage existing clinical research networks and information.
 - Enable patient-, family-, and community-led research with tools including turnkey registries and N-of-1 study frameworks.
- Facilitate enrollment of patients with PRLDs into the NIH Undiagnosed Diseases Network and collaboration between PRLD investigators and the Undiagnosed Diseases Network (<http://undiagnosed.hms.harvard.edu/>).
 - Adapt robust information platforms (e.g., i2b2), for sharing and analyzing PRLD data.
 - Encourage further development of interactions between the PRLD community and the Rare Diseases Clinical Research Network (www.rarediseasesnetwork.org).
 - Use Clinical and Translational Science Award program sites as a network of clinical sites to facilitate the study of patients with PRLDs.
 - Assemble, collate, curate, and provide information on institutional PRLD clinical and research programs.
- Establish centers of excellence in PRLD research. Such centers could function to:
 - Provide advanced clinical evaluation and care of patients with PRLDs.
 - Provide a reusable common core infrastructure permitting the interrogation and study of multiple distinct PRLDs.
 - Publish information to promote awareness and education about PRLDs among patients, their families and physicians, the medical community, and the general public.
 - Provide models of healthcare and its delivery that can promote early, accurate, and cost-effective evaluation and diagnosis of children with PRLDs.
 - Conduct and facilitate clinical research in PRLDs.

Priority Area 2: Define the Clinical Phenotypes, Epidemiology, and Natural History of PRLDs

Many distinct entities and categories of disorders are encompassed within PRLD (Table 1). The incidence and prevalence of most of these disorders is unknown. Many patients with PRLDs likely remain undiagnosed or incompletely diagnosed, due to the overlap of clinical features of PRLDs with many more common disorders, such as asthma or pneumonia.

The lung's limited repertoire of response to injury also results in radiologic and histopathologic overlap of otherwise disparate inciting processes. Defining and refining distinct disease phenotypes remains an essential step in advancing progress within PRLD. Furthermore, effectively clustering patients on the basis of distinctive phenotypes provides opportunity to elucidate common pathogenesis. Lessons learned from successes with other PRLDs, such as CF, PCD, and PAP, highlight the importance of defining distinctive clinical phenotypes through effective diagnostic criteria, easily accessible and reliable diagnostic testing (e.g., CF sweat test), and molecular phenotyping.

The expansion of information technology, including EHRs, research database infrastructures parallel to the EHR, large-scale research databases and patient registries, social media, and the growing use of "big data" in healthcare, provide an unprecedented set of opportunities to identify patients with PRLD (30–33). Improved understanding of the natural history of PRLD is needed to provide prognostic information to patients and families and is essential for designing clinical trials.

Recommendations

- Define and refine individual PRLD phenotype definitions.
 - Collect, vet, and curate clinical and research data on individual PRLDs to improve the specification of individual PRLD phenotypes. Implement processes to build and refine community consensus around definitions based on these data.
 - Develop advanced computational methods to derive new phenotypes from datasets and natural language processing methods to find novel patterns of PRLD in clinical notes.
 - Develop and validate biomarkers to improve diagnostic accuracy and molecular phenotyping of patients with PRLD.
 - Use the improved disease descriptions to develop additional International Classification of Disease-10th revision codes to improve tracking of individual PRLDs.

2. Study the epidemiology and natural history of individual PRLDs.
 - Identify patients with PRLD in EHR and insurance claims data to estimate the incidence and prevalence of and collect aggregated, anonymized data on PRLD prevalence.
 - Conduct observational studies to improve knowledge of trajectories of patients with specific PRLDs.
 - Develop and validate biomarkers to enhance characterization of the natural history and outcomes of specific PRLDs.
3. Provide aggregated, vetted information on the phenotype, epidemiology, and natural history of specific individual PRLDs to patients/families, clinicians, the medical community, and the general public.
 - Catalogue PRLDs and phenotypic descriptions. Consider contributing to existing knowledge bases (e.g., PheKB <https://phekb.org/>).

Priority Area 3: Identify Pathogenic Mechanisms, Biomarkers, and Pharmacotherapeutic Targets for PRLDs

PRLDs are enriched for genetic mechanisms and a single family or a few carefully phenotyped individuals can be informative. Exome and/or whole-genome sequencing of affected children and family members or refined cohorts of phenotypically similar patients have already led to the discovery of novel candidate genes associated with PRLDs (16, 34–40). Drawing again from successes with CF, PCDs, and PAP, determining the genetic and molecular basis of these disorders will be key steps in understanding pathogenesis and developing effective therapies for all PRLDs. Advances in genetic sequencing technologies have dramatically improved affordability, accessibility, and scope of genetic analyses. Collaboration between investigators, clinicians, and patients/families is critical to assemble well-phenotyped patient cohorts, acquire patient samples and biologic specimens, perform genetic analyses, study candidate genes and variants in functional model systems, and interpret and communicate results to stakeholders. Streamlining this pipeline from the

patient to the researcher and back as well as enhancing clinical and scientific collaborations are keys to advancing PRLD research.

Gene discovery must be coupled with model systems to understand the underlying biologic function; however, cellular and animal model systems to study specific lung cell types remain limited. Many of the currently available cell lines do not reliably replicate specific pulmonary cell types or relevant pulmonary biology or support study of the diverse entities comprising PRLD. Reprogramming somatic cells to induced pluripotent stem cells has enabled *in vitro* functional study of mutations within a patient-specific background for some diseases (41) and holds promise for PRLDs. Useful model systems should have clear read-outs of biological function (e.g., single-cell sequencing, reporter tools, structural/functional assays) to pinpoint activities of specific cell types and proteins at specific time points and account for the diversity, heterogeneity, and completeness of pulmonary developmental programs.

Accelerating progress within the PRLD field should draw on the many technological advances that have occurred in biomedical research, including huge strides in next-generation sequencing and genome-editing strategies (42, 43). These tools present the opportunity to identify causative gene mutations with a relatively small number of patients, facilitate the functional study of candidate genes and mutations in model systems, and even hold the promise of correcting patient-specific mutations *in vitro* with the eventual goal of correcting somatic cells *in vivo*.

Recommendations

1. Identify genetic factors driving the pathogenesis of specific PRLDs.
 - Develop strategies to identify patients/families with PRLD appropriate for evaluation by genomic sequencing.
 - Facilitate whole-exome and whole-genome sequencing in triads (e.g., patient plus biological parents).
 - Facilitate validation of results from exome and genome sequencing and use existing methods and develop novel high-throughput tools for functional assessment of identified genetic variants/candidate genes.
2. Extend analytic toolkits built on the shared infrastructure (Priority Area 1) to use diverse datasets for accelerating PRLD research.
 - Develop and extend software (e.g., transSMART [44]) and approaches to access, integrate, and analyze diverse data types including electronic medical records, genomic sequence data, and other data types.
3. Develop primary cell culture-based models of specific lung microenvironments (e.g., airway, alveolar, vascular, interstitium) and apply to the study of PRLDs.
 - Identify factors and culture conditions needed to establish specific lung airway epithelial cell, alveolar, and other lung-specific and non-lung-specific cell lineages.
 - Optimize lung epithelial air-liquid interface culture, three-dimensional culture models (e.g., alveolospheres, tracheospheres), and other cell culture-based models and apply these models for the study of specific PRLDs.
4. Develop, characterize, and validate available disease models of individual PRLDs.
 - Establish, validate, and share animal models of specific PRLDs.
 - Establish, validate, and share induced pluripotent stem cell-derived models of specific PRLDs.
 - Establish and share culture-based models of specific PRLDs using conventional primary cell-based methods.
5. Identify, validate, and translate biomarkers for clinical application in PRLD
 - Conduct clinical research studies to evaluate, validate, and translate novel biomarkers identified in disease model systems for use in defined PRLD patient groups.
6. Identify factors that modify the clinical presentation or course of PRLDs.
 - Identify factors (e.g., clinical, environmental, genetic, epigenetic) that contribute to disease progression or serve as protective factors.
 - Determine the impact of pulmonary vascular disease in PRLDs.
 - Determine the impact of treatment of other common disease mechanisms (e.g., targeting inflammation or fibrosis) in PRLDs.

Priority Area 4: Define, Measure, and Improve Clinical Outcomes for PRLDs

PRLDs are associated with high morbidity and sometimes mortality. Therapy is currently limited to supportive care for many PRLDs. A number of unique challenges exist to measuring and improving clinical outcomes for PRLDs, including lack of large patient numbers and resources for performing clinical trials, lack of ideal or “gold standard” outcome measures for PRLDs, and discordance between commonly used outcome measures and aspects of the disease most impactful to patients and their families (e.g., pulse oximetry or respiratory rate measurements vs. sleep quality). Many outcome measures drawn from the adult pulmonary community simply do not apply well to the pediatric population (e.g., 6-min-walk test for an infant with interstitial lung disease), and standard clinical trial designs demand larger numbers of phenotypically homogenous patients than are currently identified for most PRLDs. As such, a critical foundation is needed to translate scientific discoveries to clinical trials and achieve clinical impact in PRLD.

Recommendations

1. Develop novel and refine and validate existing clinically meaningful outcome measures for children with PRLD.
 - Establish clinically meaningful measures of functional status in infants and young children (e.g., sleep disturbance, feeding difficulty).
 - Develop at-home measures of cardiopulmonary function in pediatric patients (e.g., smart phone-based measures of heart rate, respiratory rate, and activity; internet-connected scales to measure body weight, patient-reported outcomes, and/or symptom logs.)
 - Identify and develop methodologies to monitor clinical outcomes and quality of life for use in young infants/young children/families with PRLD that are appropriate not only for observational studies but also for clinical trials.

- Develop and validate novel imaging and pulmonary function modalities as outcome measures in PRLDs
 - Develop and validate novel and clinically meaningful PRLD biomarkers based on pathobiology that are modifiable surrogates of clinically significant improvement and worsening.
 - Define digital phenotypes—characteristics that can be measured with new sources of digital data, including social media and mobile devices.
 - Conduct clinical studies to establish the age variation in the norms and clinical significance of the outcome measures.
2. Conduct clinical trials to evaluate and develop novel pharmacotherapeutics for PRLDs.
 - Conduct clinical trials to evaluate the safety and efficacy of novel pharmacotherapeutics for PRLDs.
 - Complement traditional clinical trials and observational studies with:
 - Observational studies using data from EHRs and insurance claims.
 - Pragmatic trials conducted within well-instrumented health systems using EHR-based approaches to track outcomes.
 - N-of-1 trials and other trial designs adapted for rare diseases (45).

Summary

PRLD research faces many hurdles, but it is also poised to produce discoveries that improve patient outcomes. Because of the large number of different PRLDs, novel strategies are needed to facilitate efforts in this field, retaining the strengths of disease-specific communities while also developing global connections across PRLD subgroups to create synergies. Discoveries in disease pathogenesis leveraging unique phenotypes in PRLD will also advance understanding of lung biology, lung health, and more common lung diseases. Acceleration of scientific advancement is likely to be facilitated by reducing barriers and the promotion of interaction of investigators and patients/families; development of strategies

permitting the sharing of information between patients, clinicians, and researchers; leveraging new technologies; and developing methods to empower patients in the research enterprise. Further collaboration, creativity, inspiration, and identification of resources will be necessary to implement these workshop recommendations aimed to accelerate scientific progress in PRLDs. ■

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