Advancing precision medicine for acute respiratory distress syndrome


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Advancing Precision Medicine for Acute Respiratory Distress Syndrome

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Abstract

Acute respiratory distress syndrome (ARDS) is a heterogeneous clinical syndrome. Understanding of the complex pathways involved in lung injury pathogenesis, resolution, and repair has grown considerably in recent decades. Yet, to date, only therapies targeting ventilation-induced lung injury have consistently proven beneficial. Despite these gains, ARDS morbidity and mortality remain high. Many candidate therapies with promise in preclinical studies have been ineffective in human trials, at least in part due to clinical and biological heterogeneity that modifies treatment responsiveness in human ARDS. A precision medicine approach to ARDS seeks to better account for this heterogeneity by matching therapies to subgroups of patients that are anticipated to be most likely to benefit, identified in part by evaluating for heterogeneity of treatment effect in clinical trials. In October 2019, the National Heart, Lung, and Blood Institute convened a multidisciplinary workshop to explore research opportunities and challenges for accelerating precision medicine in ARDS. Topics of discussion included: (1) rationale and challenges for a precision medicine approach in ARDS; (2) the roles of preclinical ARDS models in precision medicine; (3) essential features of cohort studies to advance precision medicine; and (4) novel approaches to clinical trials to support development and validation of a precision medicine strategy. Although the workshop was conducted before the COVID-19 pandemic began, the pandemic has highlighted the urgent need for precision therapies for ARDS as the global scientific community grapples with many of the key concepts, innovations, and challenges discussed at this workshop.

Key Words: acute respiratory distress syndrome; precision medicine; clinical trials as topic
Key Messages

- Mortality and morbidity from ARDS remain high. Phenotypic heterogeneity (clinical and biological) is inherent in ARDS and likely to influence response to therapy, yet remains poorly understood.

- Preclinical models are invaluable for understanding specific biologic processes and identifying targetable nodes in pro-injury and pro-resolution pathways, yet cannot fully replicate ARDS heterogeneity.

- Multicenter observational cohorts that collect clinical, physiological, radiological, and biological data and samples in a harmonized and feasible manner will facilitate deep phenotyping of patients and identify mechanistic pathways for subsequent interrogation with preclinical models (i.e. “reverse translation”) and for potential targeted intervention.

- Development of rapid, practical diagnostic assays that can yield results within minutes to a few hours to support predictive and prognostic enrichment approaches will be important for molecular signature-guided therapy in trials or clinical practice.

- Platform trials with a master protocol, with or without adaptive features, may facilitate efficient simultaneous and/or sequential testing of multiple candidate therapies, accelerate detection of treatment-responsive subgroups, and create a discovery pipeline for ARDS pharmacotherapies drawing from repurposed or novel drugs.

- Discovery is accelerated by collaboration and coordination among key stakeholders, including sponsors, regulatory agencies, industry, academia, patient advocates, and the broader medical community.
**Introduction**

Acute respiratory distress syndrome (ARDS) occurs in one-quarter of all critically ill patients who require mechanical ventilation.\(^1\) Despite substantial gains in preventing ventilation-induced lung injury,\(^2\) ARDS remains associated with substantial mortality and with long-term morbidity among survivors.\(^3\)\(^-\)\(^5\)

To date, no specific pharmacotherapy has proven effective for ARDS. Countless agents that showed promise in preclinical studies have been ineffective in human trials, a gap attributed in part to clinical and biological heterogeneity in human ARDS.\(^6\) A precision medicine approach is intended to address explicitly how such underlying heterogeneity influences response to therapy among different patients with the same diagnosis.\(^7\)

Limited ability to rigorously identify potential sources of heterogeneity has hampered feasibility of a precision medicine approach to ARDS. Growing evidence suggests that subsets of patients, identified through combined clinical-molecular multivariable phenotyping, may exhibit differential response to therapies deemed ineffective for the overall population,\(^8\)\(^-\)\(^10\) renewing hope for bringing a precision medicine approach to ARDS.

Motivated by these advances, the Division of Lung Diseases within National Heart, Lung, and Blood Institute (NHLBI) convened a workshop in October 2019 to establish research opportunities and explore potential roadblocks for accelerating precision medicine in ARDS. Invited experts in preclinical studies, human translational research, and clinical trials of ARDS were joined by experts in precision medicine and adaptive trial design outside of ARDS. This report summarizes presentations and discussions from the group, weighing the current state of research relevant to advancing precision medicine in ARDS and proposing strategic coordination
of future research from bench to bedside. Summary statements from workshop participants were
developed (Tables 1 and 2). Of note, this workshop took place prior to the COVID-19 pandemic
caued by the novel coronavirus, SARS-CoV-2. The early experience with COVID-19, which has
become a common cause of ARDS, highlights the extensive heterogeneity of phenotypes that can
occur from even a single precipitant of lung injury and the need for high-efficiency trials to rapidly
test candidate therapies. As such, workshop attendees, many of whom have been directly involved
in COVID-related clinical research, added a brief discussion of salient aspects of the pandemic to
this manuscript.

Why Precision Medicine for ARDS

The concept of precision medicine encapsulates what practicing clinicians strive to do
every day: deliver care tailored to the individual patient that maximizes potential benefit and
minimizes risks. The extent to which this approach is attainable in practice may depend partly on
the ability to characterize patients prospectively in a manner that identifies likely treatment
responsiveness. Other fields that pair molecular diagnostics with targeted therapies (e.g. BRAF
inhibitors for melanoma or estrogen/progesterone/HER2 receptor targeting in breast cancer11,12) or
identify and refine biomarker-defined subgroups for targeted therapies through rigorous cohort
characterization (e.g. subphenotyping severe asthma13) provide important examples of the value
in identifying and targeting treatment-responsive subphenotypes to improve patient outcomes.
ARDS by its definition is an inherently heterogeneous clinical syndrome. Therapeutic discovery
is likely to be accelerated by subphenotyping patients according to mechanistic drivers that can be
made clinically accessible and actionable.
Clinically overt sources of heterogeneity

ARDS is a diffuse lung injury characterized by alveolar inflammation and disruption of the alveolar-capillary barrier. In practice, however, neither alveolar inflammation nor barrier function is measured routinely. ARDS diagnosis instead has broad syndromic criteria and requires clinical judgment regarding the presence and etiology of pulmonary edema, introducing inter-clinician variability and, as a result, phenotypic heterogeneity. Yet, even a more precise definition would not eliminate the substantial clinically overt heterogeneity of ARDS.

Respiratory physiology is routinely used to subtype ARDS patients, albeit with mixed results. Lower PaO2:FiO2 correlates with higher incidence of diffuse alveolar damage on autopsy, but PaO2:FiO2 is influenced substantially by ventilator settings and does not consistently differentiate treatment responsiveness. Stratification of ARDS by PaO2:FiO2 has yielded some success, however, with positive trial results for a proning strategy in patients who have PaO2:FiO2 less than 150; whether patients with higher PaO2:FiO2 might respond to the same interventions is less clear.

Ventilation-induced lung injury may be an important effect modifier of treatment responsiveness, but the differential impact of ventilator strategies on lung injury is not readily detectable at bedside. Instead, global respiratory mechanics and the degree of ventilator support required are routinely used to characterize ARDS patients. Geographic distribution of lung injury (sometimes categorized radiographically as focal or diffuse ARDS) signifies regional mechanical heterogeneity, correlates with biomarkers of alveolar epithelial injury, and has prognostic value, but is of unclear value in predicting treatment response and is not consistently characterized in practice.
ARDS has often been characterized as direct (pulmonary) or indirect (extrapulmonary) based on whether the injurious risk factor originated in the lungs (e.g. pneumonia, aspiration) or elsewhere (e.g. abdominal sepsis, pancreatitis, transfusion-related). Direct ARDS exhibits more alveolar epithelial injury, less endothelial injury, and greater risk of progression to fibrosis compared to indirect ARDS. Clinical predictors of mortality may also differ between direct and indirect ARDS. However, identifying the cause and origin of lung injury is fraught with imprecision. Patients often have no identifiable risk factor, and direct and indirect injury often occur together. Additionally, categorization by direct or indirect precipitant does not address whether the injurious stimulus is transient (e.g. transfusion, trauma, aspiration) or sustained over days (e.g. infection, pancreatitis).

Other clinically overt factors could influence disease course and therapeutic responsiveness in ARDS. Supportive therapies including differing approaches to fluid management and sedation contribute additional clinical heterogeneity that may influence both patient outcomes and therapeutic responsiveness. Some commonly prescribed medications used to treat underlying diseases, including beta-blockers and beta-agonists, statins, and inhaled and systemic corticosteroids, may directly influence host response to lung injury. Environmental factors such as smoking, alcohol use, and ambient air quality may modify the biological response to pulmonary insults. In infection-associated ARDS, different pathogen species and strains precipitate lung injury via different virulence mechanisms and pathogen-host interactions. While evaluating heterogeneity in respiratory mechanics has proven useful to guide interventions targeting ventilation-induced lung injury, clinically obvious heterogeneity has been less helpful for therapies targeting other pathways of ARDS pathogenesis.
Clinically occult sources of heterogeneity

Early studies of the molecular biology of ARDS indicated that substantial heterogeneity exists between patients.\textsuperscript{36} Biomarkers of key pathways including inflammation, coagulation, alveolar epithelial injury, and vascular endothelial activation can differ considerably between patients,\textsuperscript{37–39} suggesting a role for molecular subphenotyping to deconvolute heterogeneity.

Analyses of clinical and biological data from trials and observational cohorts have identified two subphenotypes, distinguished in part by degree of inflammation, circulatory shock, and multiorgan failure, which appear to exhibit differential response to multiple treatments in secondary analyses of clinical trials.\textsuperscript{8–10,40,41} Parsimonious prediction models based on these analyses\textsuperscript{42} warrant prospective testing.

Better understanding of the drivers of molecular heterogeneity may help identify new therapeutic targets. Clinical heterogeneity undoubtedly accounts for some biological variation, but not all. Genetic predisposition helps shape the response to infectious and sterile pro-inflammatory stimuli that may precipitate ARDS, yet also influences resolution and repair.\textsuperscript{43} For certain lung infections, genetic polymorphisms influence pathogen-host interaction directly.\textsuperscript{44} Genetically predicted plasma concentrations of sRAGE (soluble receptor for advanced glycation end products, an inflammatory mediator and alveolar epithelial injury marker) and angiopoietin-2 (a marker of endothelial activation) are associated with risk of ARDS during sepsis.\textsuperscript{45,46} Polymorphisms in genes encoding cell matrix proteins, VEGFR-1 (vascular endothelial growth factor receptor 1), and haptoglobin also correlate with ARDS risk.\textsuperscript{47–49} Together, these findings suggest genetic polymorphisms may be an important source of biological heterogeneity in lung injury, resolution, and repair.
Differences in the lung and gut microbiomes also may contribute to ARDS heterogeneity. While proximal airways are lined with commensal bacteria, healthy alveoli are resistant to bacterial growth, providing few nutrient substrates and containing bactericidal surfactant. However, as lung injury develops, alveolar flooding by protein-rich liquid and surfactant inactivation together create a more welcoming environment for bacterial growth, which may drive further inflammation and injury in a positive feedback loop. Lung bacterial overgrowth may occur, and translocated gut bacteria and associated pathogen-associated molecular patterns may enter the alveolus. Therapeutic implications of this dysbiosis are not well understood.

**Overarching Challenges to Precision Medicine for ARDS**

Workshop participants agreed that advancing precision medicine for ARDS holds considerable appeal and has a strong rationale (Table 1), but also faces considerable hurdles. Major obstacles include limited understanding of the key nodal points in the multiple pathways that mediate acute lung injury, and the difficulty of prompt identification of patients in whom specific pathways are deranged. The pathogenesis of acute lung injury involves a number of complex steps, including increased endothelial permeability, alveolar epithelial cell death and dysfunction, loss of surfactant function, activation of coagulation cascades, and triggering of complex innate immunity pathways in the lungs. The key nodes of these pathways that govern critical downstream events towards resolution and repair remain uncertain, and the importance of a specific pathway may differ between patients depending on etiology of lung injury, patient predisposition, and other factors.

Adding to the challenge, the timeframe for characterizing patients is short since ARDS develops rapidly, and treatments may be most effective when initiated early. For example, current
precision medicine approaches to staging and molecular classification of breast and lung cancer require days to weeks; yet in a recent trial of ARDS, 48- and 96-hour mortality were 10% and 16% respectively. Rapid assays will need to be developed to enable prompt biological phenotyping within minutes to a few hours. Proximate biospecimens, such as from bronchoalveolar lavage, require additional invasive procedures and have been obtained in a minority of large-scale human studies; even when collected, specimen acquisition and analysis protocols often differ between studies. Tissue samples are rarely obtained, both because of procedural risk and because the finding of diffuse alveolar damage does not substantially change treatment. Acute and chronic comorbidities vary and can influence the likelihood of developing and surviving from ARDS. Even if comorbidities do not modify biological treatment responsiveness, they undoubtedly influence risk of death attributable to ARDS. To add further complexity, there is no widely accepted surrogate endpoint for clinical trials in ARDS, complicating early-phase clinical studies.

Adapting Preclinical Investigations to Precision Medicine

*Need for rigorous preclinical models to advance precision medicine*

Animal models will never fully replicate the heterogeneity of human ARDS. Nevertheless, they remain essential for understanding more deeply the cellular and molecular drivers of disease and play an important role in developing a precision medicine strategy for ARDS (Table 2). Animal studies can be highly effective in modeling a specific biological feature of lung injury or treatable trait (e.g. endothelial barrier disruption), particularly when coupled with careful observation in human studies that can feasibly identify biomarkers of those targeted pathways.
Among the most powerful roles of animal models is to help define key nodes of mechanistic pathways that have been identified in rigorous human studies, a bedside-to-bench approach termed reverse translation (Figure 1). Once identified, these pathways and nodes may inform targets for drug development to be tested in subsequent trials.

Recent efforts to incorporate precision medicine in pediatric sepsis care offer an important example of how animal models could inform development of precision medicine for ARDS. Through a series of cohort studies, investigators developed a biomarker panel to predict mortality from pediatric sepsis in humans\textsuperscript{59} and subsequently found similar biomarkers were predictive of mortality in murine models of sepsis.\textsuperscript{60} The murine models were then used to test therapies targeting the predictive biomarkers, to determine whether they were causally related to outcomes and to identify other biological features (e.g. higher bacterial burden) of the group with high predicted mortality. This conservation of findings from bedside to bench may permit initial testing of candidate therapies in preclinical models to understand implications of biological heterogeneity and potentially inform trial design.\textsuperscript{60}

Reverse translation also may have an important role in understanding why some promising candidate treatments are not beneficial in human clinical trials. For example, heterogeneity of treatment effect by latent class subphenotype was observed in an ARDS trial of simvastatin\textsuperscript{8} but not a related trial of rosvastatin.\textsuperscript{61} Taking this clinical observation back to relevant preclinical models could help identify pivotal mechanistic determinants of a differential response to simvastatin as compared to rosvastatin for clinically defined ARDS subphenotypes, and also potentially identify novel, mechanistically-driven biomarkers that better predict a beneficial treatment response to one statin versus another.
Modeling sources of human heterogeneity

Introducing heterogeneity, inherent in human ARDS, into preclinical models may contribute to understanding of downstream biological consequences and identify potentially novel nodes for therapeutic targeting. This strategy can take many forms, including but not limited to modifying host susceptibility, varying insult type or intensity, and altering environmental or supportive care factors.

Cross-breeding mice to introduce genetic diversity may inform understanding of genetically regulated complex traits ranging from inflammation to wound repair. The Collaborative Cross model for complex trait analysis is one such example, a collection of roughly 200 distinct recombinant inbred strains of mice created by reciprocal inter-cross breeding of eight founder strains. The Collaborative Cross model has been used to decipher genetic factors influencing host susceptibility to various infectious pathogens, mapping phenotypic variation to gene loci to elucidate the genetic basis for variation in infection potency, severity, and pathogenesis. This model could be integrated with human genome-wide association studies to dissect a genetic basis for ARDS heterogeneity.

Adding variation to mechanism and intensity of the lung injury stimulus also may help elucidate differential activation of mechanistic pathways and resulting effects on treatment responsiveness. For example, in the cecal ligation and puncture (CLP) model of experimental sepsis, cecal puncture of random severity can be performed in outbred mice to yield a heterogeneous insult in genetically heterogeneous animals, facilitating interrogation of biological pathways that might influence heterogeneity of host response and treatment effect. A recent study using a variable CLP severity model in outbred mice identified two distinct sepsis phenotypes, a high-mortality variant characterized by early onset of cardiogenic shock and a low-mortality
variant with intact cardiac function, which exhibited differential response to treatment with hydrocortisone, ascorbic acid, and thiamine.65

**Multisystem crosstalk and modifiable risk**

Acute and long-term extrapulmonary morbidity, including physical, cognitive, and psychiatric disability, are common in ARDS.4,5 Bidirectional pathogenic interactions of the lungs with the kidneys, brain, and other vital organ systems have been discovered. For example, acute kidney injury may predispose the lungs to a secondary inflammatory insult,66 precipitating lung injury that in turn may exacerbate renal injury.67 Similarly, endothelial activation and neuroinflammatory signaling from brain injury may predispose to lung injury,68 which in turn may exacerbate brain injury.69 Many pathways of multiorgan crosstalk are similar across critical illness syndromes and thus might be considered clinically in terms of “treatable traits” rather than unique to any one particular diagnosis.58 Deciphering mechanisms of multisystem interactions, with preclinical models and human data, may aid development of interventions that attenuate such multiorgan positive feedback crosstalk loops and associated morbidity in a variety of critical illness syndromes, including ARDS.

**Human “models”**

Human experimental models of lung injury may have a unique role for understanding ARDS pathophysiology.70 Ex-vivo human lung models, using organs declined for transplant, allow experimental manipulation and serial evaluation of distal lung tissue that otherwise is typically inaccessible in human ARDS.71 In-vivo human models range from subclinical lung inflammation in healthy volunteers induced by inhaled lipopolysaccharide to surgeries such as cardiopulmonary
bypass or intra-operative single-lung ventilation that induce lung inflammation or ischemia reperfusion injury in a more regulated setting. As an example of potential relevance to ARDS heterogeneity, differential inflammatory responses observed to lipopolysaccharide have been linked to genetic polymorphisms modulating innate immunity in healthy volunteers. However, human models have important limitations. For instance, ex-vivo models fail to capture multisystem crosstalk and are technically difficult. In-vivo models yield low-level regulated inflammation, which may be informative but is in contrast to the dysregulated inflammation, physiological derangements, and severity of lung injury characteristic of ARDS.

**Clinical Cohorts to Advance Precision Medicine**

*Need for large observational studies*

Rigorous cohort studies are essential to understanding the entire spectrum of ARDS pathogenesis and recovery in usual care. These natural history experiments serve a crucial link in the translational science continuum, informing research directions in preclinical studies and clinical trials (Table 2). Key content foci for ARDS cohort studies include (i) to identify, validate, and refine clusters of heterogeneity (subphenotypes) and factors associated with treatment responsiveness; (ii) to develop rapid diagnostics in support of such subphenotyping; (iii) to explore underlying mechanisms and potential drivers of biological heterogeneity; (iv) to identify populations at greater risk of ARDS-attributable outcomes for clinical trial prognostic enrichment; (v) to evaluate generalizability of clinical trial findings to less selective populations; and (vi) to identify novel interventions for testing in preclinical models and clinical trials. Cohort
studies also might enroll patients at risk of ARDS to determine why some patients progress to severe lung injury while others do not.

The many sources of clinically overt heterogeneity in ARDS necessitate harmonized clinical data and biospecimen collection and sufficiently large sample sizes to ensure statistical power for dissecting clinically occult heterogeneity. A recent international period prevalence study\(^1\) suggests the typical 12-bed ICU may see approximately 65 ARDS patients per year (5.5 cases per bed per year). Multicenter cohort studies are best suited to ensure timely accrual and diversity (ethnic, phenotypic, and biological) representative of the total population of patients with ARDS, as required for discovery and validation of subphenotypes. Encouraging broader patient participation in clinical research studies, with the involvement of patient advocates, may further enhance development of these larger datasets.

**Harmonizing data and specimen collection**

Observational research networks in other fields provide a template for building synergistic research teams and comprehensive cohorts to advance precision medicine. For example, the NHLBI Severe Asthma Research Program (SARP) was a uniquely structured multicenter collaborative network of investigators who led independently funded mechanistic studies but were required to recruit patients and obtain samples that were shared across the network.\(^{13}\) The result – a rigorously phenotyped cohort of more than 700 patients with pulmonary function, imaging, and multiple biological samples – enabled identification of several asthma subphenotypes and key mechanistic nodes\(^{74,75}\) now being targeted in clinical trials.

SARP offers several lessons learned relevant to ARDS.\(^{13}\) The funding mechanism explicitly mandated a team science approach, wherein multiple investigators contributed to a
shared cohort with individual mechanistic studies championed by a specific investigator and embedded within the cohort. This shared cohort model required that all investigations have a common longitudinal protocol, with uniform data acquisition and analysis procedures, while allowing some highly specialized studies to involve only a subset of sites.

Development of Rapid Diagnostics

Since ARDS develops and evolves quickly, the development of rapid diagnostics that can be deployed on-site (i.e. at bedside or in the hospital clinical laboratory) will be critical for timely biological phenotyping.54 Assay platforms will need to generate actionable data within minutes to a few hours, rather than days, in order to be implemented in precision trials. Given current technologies and the existing body of evidence, protein-based enrichment strategies appear closest to clinical application, when compared to gene expression (mRNA) based enrichment strategies. The development of these assay platforms will be most efficient via collaborations with industry and early involvement of regulatory agencies.

Clinical Trials to Advance Precision Medicine

Predictive and Prognostic Enrichment

Enrichment strategies are essential to enabling precision trials among critically ill patients.76 Enrichment broadly refers to the selection of a patient cohort in whom an experimental intervention is more likely to be of benefit, when compared to an unselected cohort. Prognostic enrichment entails selecting patients more likely to have a disease-related event—for example, those at higher risk of ARDS-related death. Prognostic enrichment decreases the sample size
required to detect relative differences in a trial endpoint for a given desired power. However, it does not address treatment response heterogeneity.

*Predictive* enrichment entails selecting patients in whom an intervention is anticipated more likely to be effective, based on clinical and/or biological characteristics and mechanism of action of the intervention. The challenge for predictive enrichment is that it is difficult to prospectively identify subgroups most likely to benefit from specific therapies. When treatment response heterogeneity is plausible, trials should be designed to allow for that possibility.

**Lessons from Other Fields: Innovative Trial Designs**

Innovative trial designs may help accelerate precision therapeutic discovery, in part by embracing disease heterogeneity and uncertainty around matching the right therapy to the right patient. Platform trials evaluate multiple therapies simultaneously for a disease against a single control group.\(^77\) Platform trials typically are designed to permit the addition and removal of therapies without stopping the trial, according to predefined rules regarding efficacy and futility in the overall trial population or particular subgroups. The I-SPY2 and PrecISE trials are examples of adaptive platform trials (*Table 3*). I-SPY2 evaluates neoadjuvant therapies for high-risk, early stage breast cancer,\(^12\) while PrecISE evaluates therapies for severe and/or exacerbation-prone asthma.\(^78\) Both are signal-finding phase 2 trials that aim to rapidly evaluate multiple candidate therapies for their probability of success in phase 3 trials.

I-SPY2 and PrecISE offer several lessons that may be relevant to ARDS. As platform trials, they enroll continuously on a single master protocol and evaluate multiple treatments simultaneously.\(^77,79\) A given therapy may be eliminated from the trial and replaced by a new candidate therapy without interrupting enrollment, so that more therapies are tested in a time- and
cost-efficient manner. Both trials embrace a team science approach and engaged key collaborators and stakeholders early in trial formulation, including sponsors, regulatory agencies, pharmaceutical and biotechnology industries, academia, patient advocates, and the broader medical community.

Both I-SPY2 and PrecISE leverage the inherent biological heterogeneity of their respective targeted phenotypes. The main outcome of I-SPY2 is the predictive probability of success in a confirmatory phase 3 trial within each of ten prespecified biomarker signatures; a therapy is deemed sufficiently promising to “graduate” if there is an 85% Bayesian predicted probability of success in a 300-patient, 1:1 randomization, confirmatory neoadjuvant phase 3 trial for any of the prespecified biomarker signatures. The trial design includes the use of standard (FDA-approved), qualifying (highly promising, and pre-specified for FDA validation), and exploratory (hypothesis generating) biomarkers, and uses incoming data to identify the best biomarkers for stratifying patients for each of the therapies under investigation. Over a decade, more than 20 agents from multiple pharmaceutical companies have been evaluated in I-SPY2; several agents have graduated and been validated, spanning a range of biomarker signatures. In addition, the prognostic importance of an early endpoint — pathologic complete response to therapy regardless of subtype or treatment delivered — has been established, and new tumor classifiers have been identified that improve the ability to target therapies and improve outcomes.

In PrecISE, novel candidate therapies are chosen that are hypothesized to be effective for biological subtypes of severe asthma based on a priori beliefs about underlying mechanisms. A crossover design allows each patient to serve as his/her own control and, through repeated randomizations, receive multiple therapies during the study. Randomization at every step is weighted (initially in a 2:1 ratio) so that patients in the biomarker subgroup targeted by a particular
intervention are more likely to receive that intervention, and definitions of the biomarker-defined subgroups are updated over time as trial data accumulate. This approach allows for detection of drug effect in subgroups not anticipated to benefit from the drug, as well as confirmation of “non-responders” essential for targeted treatments. At the conclusion of this phase 2 signal-finding trial, novel therapies demonstrating efficacy across three dimensions of asthma severity (lung function, symptom control, and exacerbations), and the optimally defined disease subtype each therapy should target, will be identified for further study in a phase 3 confirmatory trial.

Although I-SPY2 and PreclISE are phase 2 trials, platform trials similarly might improve efficiency when multiple candidate therapies amenable to the same platform are ready for confirmatory phase 3 testing.

*Early Lessons from COVID-19*

After this October 2019 workshop, the SARS-CoV-2 virus, which causes the clinical syndrome of COVID-19 with severe ARDS, has spread across the globe. Spurred by the urgent need for novel therapies, many clinical trials groups have embraced platform trials to accelerate scientific discovery. The RECOVERY platform trial, run through the UK’s National Health Service, was the first to demonstrate a survival benefit with corticosteroids for severe COVID-19, a finding since replicated in several subsequent trials. In addition, the RECOVERY platform design rapidly evaluated and discarded several other repurposed therapies (e.g. hydroxychloroquine, lopinavir-ritonavir) as ineffective in the population studied.

In the US, the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) and Collaborating Network of Networks for Evaluating COVID-19 and Therapeutic Strategies (CONNECTS) public-private partnerships with government, academia, and industry aim to rapidly
assess promising candidate therapies for COVID-19 in a series of federally-funded master protocols and platform trials that utilize NIH-supported research networks to test prioritized agents from immune-modulators, monoclonal antibodies, anti-thrombotics, or other domains.86,87 Growing out of this NHLBI workshop, the I-SPY COVID phase 2 platform trial has fostered novel collaborations, pairing the precision medicine expertise of oncologists with the content expertise of ARDS clinical trialists, with repurposed and investigational agents under evaluation that target several mechanistic pathways in severe COVID-19.88

Worldwide trial efforts have been coordinated by the World Health Organization (WHO) Solidarity Trial Consortium89 and the REMAP-CAP Trial investigators.90 REMAP-CAP was planned before the COVID-19 pandemic as a perpetual enrollment adaptive platform trial studying treatments for community-acquired pneumonia. Its unique platform design was intended for rapid adaptation to respiratory pandemics and illustrates successful implementation of such trial design principles on a global scale.91

Although COVID-19 developments post-dated this workshop, they demonstrate the potential for rethinking trial design to accelerate therapeutic discovery for conditions where few evidence-based treatments exist. They also illustrate the importance of public-private partnerships with broad stakeholder engagement to achieve this vision. COVID-19 exhibits substantial phenotypic heterogeneity despite being precipitated by a single causative organism,92 highlighting the need for deeper understanding to support a precision medicine approach.

Potential application of platform trial design to ARDS

Therapeutic discovery for ARDS, from COVID-19 or otherwise, could be accelerated through platform trials. Building efficient trial machinery with perpetual enrollment to test
multiple agents could help establish a cost-effective drug development pipeline. Efficiency of the
platform design, access to existing trial infrastructure, and input from academic physician-
scientists could incentivize pharmaceutical industry collaboration to develop and test new and
repurposed drug candidates.93

The inherent heterogeneity of ARDS could be leveraged by designing trials to differentiate
treatment responsiveness by biomarker signature, potentially to inform predictive enrichment for
a subsequent phase 3 trial (Figure 1). Key hurdles include uncertainty about temporal stability of
biomarker signatures over time and lack of rapid diagnostics for molecular biomarkers, which
would need to be developed and validated before or in parallel with any such trial. An adaptive
design may improve efficiency by using data from the ongoing trial to refine subgroup-intervention
pairings and/or eliminate biomarker-defined subgroups from consideration for a particular therapy.
Whether response-adaptive randomization might boost efficiency further depends on the particular
construct of the trial.94 For example, response-adaptive randomization may improve both statistical
efficiency and effectiveness of therapies within the trial when (i) there exist at least three arms
available for allocation (including, typically, a standard-of-care control arm), (ii) it is not
implemented until there is sufficient early data (e.g., “burn in”) to provide reasonably stable
preliminary estimates of treatment effect, and (iii) when a sufficient fraction of patients are
allocated to the control in an ongoing manner to mitigate risks of bias from secular changes.94

While the efficiencies of platform trials are appealing, some challenges remain. The
eligibility criteria for a platform trial may be broad to capture the range of patients affected by
ARDS. Careful consideration should then be given to whether all treatment arms should be made
available to the full range of enrolled subjects. Narrower eligibility criteria can be applied for
particular candidate therapies within the trial to address specific contraindications, provided that a
subgroup of the trial population qualifies for at least two arms so randomization can be used. Although best practices may change over time, platform trials can be designed to permit updates to the standard of care across treatment groups as the evidence evolves, and concurrent controls can be used in analyses to reflect the contemporary standard of care. Having multiple interventions in the trial poses challenges for safety monitoring and blinding, which can be mitigated by separating group assignment into a two-step process: (1) unblinded randomization to one potential intervention in the trial while (2) blinding the assignment to active or placebo for that intervention.95 This approach preserves the advantages of blinding and allows multiple routes of drug administration to be included in the same master protocol. In some settings such as more pragmatic trials, placebo may not be available or blinding may not be possible for other reasons; best practices for preserving study integrity with unblinded treatment administration should still be followed. Sustained funding sources are needed to develop and maintain the infrastructure needed to test a series of therapies at multiple sites. These challenges will need to be considered carefully in designing ARDS platform trials.

Endpoint selection

ARDS lacks a well-validated, patient-centered, disease-specific endpoint. Mortality remains the most widely accepted endpoint for ARDS trials.96 Still, ARDS-attributable risk of death can differ considerably between patients and cohorts,97 an important factor influencing statistical power of trials and a potential cause of heterogeneity of treatment effect.98 No validated surrogate endpoint exists for ARDS mortality. Physiologic endpoints, such as change in oxygenation or extravascular lung water, have not consistently correlated with treatment effects
on mortality and in some instances have suggested improved lung function for interventions subsequently found to increase mortality.\textsuperscript{2,16,99}

Endpoints other than mortality must address death as a competing risk. Ventilator-free days, a composite outcome that includes death and time from successful ventilator liberation to day 28, is not clearly patient centered and as originally defined equates death as equivalent to 28 days of ventilator dependence. To overcome this limitation, ventilator free survival is a ranked composite score that compares each patient to every other first by vital status and then, only if both subjects in a pair survive, by duration of ventilation.\textsuperscript{100,101} Alternatively, the World Health Organization proposed an ordinal scale for COVID-19 trials that incorporates post-extubation level of respiratory support,\textsuperscript{102} and some COVID-19 trials have used the scale to evaluate time to recovery as the main trial endpoint.\textsuperscript{88}

Long-term follow-up of ARDS survivors has revealed protracted physical, cognitive, and psychological morbidity,\textsuperscript{4,5} and core outcomes measures have been proposed for studies of ARDS survivorship.\textsuperscript{103} These core outcomes were developed with input from both survivors of ARDS and their families, emphasize many domains contributing to quality of life, and have been integrated into recent trials.\textsuperscript{53,104,105} Measuring long-term outcomes is essential to understand the totality of patient-centered treatment effects and spectrum of survivorship within trials.\textsuperscript{96} To be suitable for consideration as a primary endpoint for trials, long-term outcomes must account for the competing risk of death to retain face validity and should be supported by evidence suggesting these measures can be modified by candidate interventions. The preferred outcome, or family of outcomes, for a given trial may depend on the particular population enrolled and intervention that is studied.
Response Indicators

Response indicators are early markers of therapeutic target engagement and are distinct from trial endpoints. For example, in oncology, tumor shrinkage or change in tumor biomarker serum levels after initial cycles of chemotherapy could indicate drug target engagement but would not itself be an appropriate trial outcome until unambiguously linked to patient-centered clinical outcomes. The ideal response indicator would be useful early in the treatment course to determine whether the prescribed therapy is likely to be effective for a given patient and thus should be continued in that patient. Response indicators also may be useful to guide dose adjustment for titratable therapies. No universal response indicator exists for ARDS, but intervention-specific response indicators could be tested within trials as they become available.

Candidate Interventions

Discovery and development of new drugs is expensive and time-consuming, costing $1-2 billion or more, and often taking 10-15 years from discovery to regulatory approval. Testing approved drugs and known drug candidates for new indications takes advantage of their established mechanisms of action and known safety and pharmacokinetic profiles, reducing cost and time. Large databases of clinically approved drugs have been established, such as the National Center for Advancing Translational Sciences (NCATS) Pharmaceutical Collection, and efforts have been made to profile these moieties for activity over a wide range of pathways and disease models. Cross-referencing known drug activities with appropriate targets in ARDS could lead to development of new drugs at reduced cost and time than required for entirely new compounds, an approach embraced by the scientific community to fight the COVID pandemic.
Repurposing drugs has had successes in other pulmonary diseases including pulmonary arterial hypertension (PDE5 inhibitors) and asthma, in which recognition of the Th-2 paradigm provided a pathophysiological basis for new drugs inhibiting the IL-5 and IL-4/13 pathways.\textsuperscript{109} Drug discovery efforts for ARDS also should consider whether several different pathways need to be manipulated simultaneously to maximize therapeutic effect, as in cancer chemotherapy.

Conclusions

Therapeutic discovery for ARDS requires new approaches that bring phenotypic and biological heterogeneity to the fore to match candidate therapies to resulting subgroups. Concerted coordination across the research community will be required to achieve this precision medicine vision. Mechanistic preclinical studies, translational clinical cohort studies, and randomized trials fulfill intertwined roles in understanding mechanisms, prognostic relevance, and therapeutic implications of ARDS heterogeneity. Clinical trials must be reimagined to build the discovery pipeline, leveraging the efficiencies of novel designs to test multiple candidate therapies simultaneously and match them to the right patient subgroups. Partnership between academia, industry, regulatory agencies, sponsors, and patients must be nurtured.

Several areas of uncertainty remain regarding the best path forward to advance precision medicine in ARDS. These key unanswered questions form a foundation for future areas of research (Table 4). With broad recognition that ARDS heterogeneity modifies therapeutic efficacy, the impetus to develop and advance precision medicine strategies is clear. Deeper understanding of key nodes in mechanistic pathways established through rigorous preclinical studies and well-designed observational cohorts, paired with innovative trials designed to test for sources of
heterogeneity that influence treatment responsiveness, will accelerate discovery of targeted therapy to reduce morbidity and mortality for patients with ARDS.

**Search Strategy and Selection Criteria**

We searched PubMed for the terms “acute respiratory distress syndrome” OR “acute lung injury” and “precision medicine” without date or language restriction to identify potentially relevant publications. This search was supplemented by the authors’ own topical literature reviews addressing the themes developed in the workshop as reflected in this manuscript. When publications with overlapping content were identified, the references deemed most immediately relevant were included in the final citation list.

**Acknowledgments**

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**Contributors**

BTT, NRA, and CSC conceived of and planned the workshop. All authors attended and contributed important intellectual content to the workshop. JRB, BTT, NRA, and CSC wrote the first draft of the manuscript. All authors critically reviewed the manuscript and approved the final version.
Declaration of Interest

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ARDS; outside the submitted work. NJM reports grants from NIH, grants from Athersys, Inc, grants from Marcus Foundation, grants from BioMarck, Inc, and grants from Quantum Leap Healthcare Collaborative outside the submitted work. MM reports grants from NIH outside the submitted work. LAR reports nothing to disclose. ER reports other support from ARDS Foundation, outside the submitted work. EPS reports grants from NIH and other support from IHP Therapeutics, outside the submitted work. TJS reports nothing to disclose. LBW reports personal fees from Merck, personal fees from Bayer, Boehringer Ingelheim, CSL Behring, Quark, Foresee Pharmaceuticals, and Citius; and grants from CSL Behring and Genentech, all outside the submitted work. HRW reports grants from NIH, and holds a patent for Sepsis Biomarkers for Prognostic and Predictive Enrichment. NRA reports nothing to disclose. CSC reports grants from NIH, grants and personal fees from Roche/Genentech, grants and personal fees from Bayer, personal fees from Quark Pharmaceuticals, personal fees from Prometic, personal fees from Gen1e Life Sciences, personal fees from Vasomune, and grants from Quantum Leap Healthcare Collaborative outside the submitted work.
FIGURE CAPTIONS

Figure 1: Proposed Research Schema to Advance Precision Medicine Pharmacotherapy in ARDS.
Table 1: Summary Statements among Workshop Participants: Rationale for Precision Medicine in ARDS

1. Phenotypic heterogeneity (clinical and biological) is inherent in ARDS and likely to influence response to therapy, yet remains poorly understood. Better understanding of heterogeneity is essential for identifying treatments and minimizing harm.

2. Mortality and morbidity from ARDS remain high. Current proven treatments involve lung-protective ventilation and better supportive care. Pathways involved in pathogenesis, resolution, and repair include multiple potential targets for therapeutic development.

3. ARDS is a clinical diagnosis. Clinical features alone may not distinguish biological heterogeneity with sufficient precision to match targeted therapies to patients in whom the relevant pathway is most active.
Table 2: Summary Statements among Workshop Participants: Designing Research to Advance Precision Medicine in ARDS

<table>
<thead>
<tr>
<th>Preclinical Research to Advance Precision Medicine</th>
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<tbody>
<tr>
<td>1. Preclinical models cannot fully replicate ARDS heterogeneity, yet remain useful to advance precision medicine for ARDS by: understanding specific biologic processes, identifying key nodes in pro-injury and pro-resolution pathways, introducing controlled heterogeneity to elucidate differential activation in mechanistic pathways, and using reverse translation of clinical findings to help identify key biological drivers for therapeutic targeting.</td>
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<tr>
<th>Clinical Cohorts to Advance Precision Medicine (Also Relevant to Clinical Trials)</th>
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<tbody>
<tr>
<td>1. Cultivating and sustaining multicenter observational cohorts that collect clinical, physiological, radiological, and biological data and samples in harmonized fashion will facilitate deep phenotyping of patients and identify pathways for reverse translation. Biological specimens that are lung-specific should be particularly prioritized, recognizing challenges exist that limit the feasibility of obtaining time-sensitive specimens, particularly in critically ill patients.</td>
</tr>
<tr>
<td>2. Cohort studies should encourage adherence across participating sites to best clinical practices that are strongly supported by evidence (e.g. daily evaluation for spontaneous awakening and breathing trials), and prioritize standardized measurement and collection of biospecimens for known and hypothesized sources of clinically overt and occult (sub)phenotypic heterogeneity.</td>
</tr>
</tbody>
</table>
3. Development of rapid, locally practical diagnostic assays will be a prerequisite for molecular signature-guided therapy in trials or clinical practice. Collaboration with industry and the FDA will be critical.

Clinical Trials to Advance Precision Medicine

1. Predictive and prognostic enrichment approaches should be considered, though the optimal method of enrichment for each therapeutic approach will vary. At a minimum, all clinical trials in ARDS should collect biospecimens to enable future subtype analyses.

2. Establishing and maintaining collaborative clinical trial networks that adapt and learn from previous iterations is critical to decrease the time, effort, and resources consumed from serially rebuilding trial machinery with successive trials.

3. Platform trials with a master protocol may facilitate efficient simultaneous and/or sequential testing of multiple candidate therapies versus a common control and create a discovery pipeline for ARDS pharmacotherapies.

4. Adaptive clinical trial designs should be strongly considered as they may increase efficiency.

5. Structural factors such as a central institutional review board (IRB) and integrated data capture from the electronic health record would improve efficiency of trial operations.

6. Clinical trials should not only evaluate a given therapy’s overall efficacy but also evaluate differential treatment effect according to prespecified subphenotypes.

7. Testing the repurposing of existing drugs and drug candidates with sound biological plausibility may accelerate pharmacotherapeutic discovery by leveraging existing data on safety, side-effects, and on- and off-target mechanisms of action. Collaboration with
the pharmaceutical industry and regulatory bodies is crucial to identifying and testing candidate drugs.

Table 3: Key Principles Shaping Precision Medicine Trials in Breast Cancer and Severe Asthma

<table>
<thead>
<tr>
<th>Key Principle</th>
<th>I-SPY2 Trial for Breast Cancer</th>
<th>PrecISE Trial for Severe Asthma</th>
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<tbody>
<tr>
<td><strong>Leverage disease heterogeneity in the trial design</strong></td>
<td>Evaluate drug effect in each of ten prespecified biomarker signatures.</td>
<td>Six novel drug candidates hypothesized to benefit a biological subtype of severe asthma were selected, with some overlap among subtypes, and randomization is weighted so patients are more likely to receive the drug(s) targeting their subtype.</td>
</tr>
<tr>
<td><strong>Analyses that incorporate biologic subtypes</strong></td>
<td>Main outcome is Bayesian probability of success in a subsequent confirmatory phase 3 trial for each prespecified biomarker signature.</td>
<td>Primary analysis determines the refined target biological subgroup definition for each therapy demonstrating efficacy compared to placebo with respect to three dimensions of asthma severity (lung function, symptom control,</td>
</tr>
<tr>
<td><strong>Utilize efficiency of the platform trial design</strong></td>
<td>Master protocol with continuous patient enrollment that can evaluate up to five candidate therapies at once. Therapies can be added to or removed from the protocol without interrupting enrollment.</td>
<td>Master protocol with continuous patient enrollment and crossover design so that each patient serves as his/her own control and potentially receives more than one study drug. New therapies can be added to the protocol without interrupting enrollment, and therapies demonstrating futility can be discontinued, preserving resources for remaining therapies.</td>
</tr>
<tr>
<td><strong>Personalize therapy within trial to maximize benefit to each patient</strong></td>
<td>Therapy can be escalated or deescalated based on each individual’s response to therapy, assessed by pathologic complete response (pCR).</td>
<td>As trial data accumulate, definition of biomarker-defined subgroups and treatment assignment probabilities are updated so each patient likeliest to get most promising drug for his/her subtype</td>
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<tr>
<td><strong>Collaborate early and transparently with multiple drug</strong></td>
<td>Investigators determine most promising drug candidates and work with nonprofit collaborative</td>
<td>Investigators independently propose and rank drug candidates based on their feasibility, innovation, safety, phenotype match, predictive</td>
</tr>
<tr>
<td>companies in a single platform trial</td>
<td>to secure drugs from multiple companies.</td>
<td>biomarker, and prior data. Top-ranked agents obtained from companies.</td>
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Table 4: Unresolved Key Questions for Advancing Precision Medicine in ARDS

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
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<tr>
<td>What is the biological overlap between critical illness syndromes like ARDS and sepsis? When should trials consider enrolling patients according to “treatable traits” that may span conventional diagnostic labels?</td>
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<tr>
<td>Who are the patients at highest risk for ARDS-attributable mortality, and how can they be identified early in the disease course? Should ARDS trials restrict enrollment to this subset of patients, and what is the impact on generalizability of results—benefits and risks?</td>
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<tr>
<td>What are useful surrogate outcome measures for ARDS clinical trials? Should clinical trials focus primarily on mortality, or is there a more ARDS-specific endpoint with favorable performance characteristics?</td>
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<td>What is the stability of molecular subphenotypes of ARDS over time, and what implications does this stability have for clinical trials?</td>
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<tr>
<td>What are the key mechanistic drivers (“nodes”) of molecular subphenotypes of ARDS? What are the contributions of variations in genetics and the microbiome?</td>
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<tr>
<td>What assays should be prioritized for development into rapid diagnostics to enable future trials?</td>
<td></td>
</tr>
<tr>
<td>What are the highest priority therapeutic candidates for testing in precision medicine trials?</td>
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</tbody>
</table>
References


Identify drug candidates (new or repurposed) to target key nodes & explore plausibility in preclinical models & existing cohorts

Review/conduct basic & translational studies to identify possible key nodes in pathways (reverse translation)

Evaluate reproducibility & refine distinct signatures in independent cohorts

Develop & validate rapid diagnostics for biomarker signatures

Test most promising drugs in phase 2 platform trial* that simultaneously evaluates potential efficacy among distinct biophysiological signatures

Discover distinct biophysiological signatures in cohort studies and secondary analyses of trials

Phase 1 trial for safety if unknown

Platform Trial with 3 Biomarker Signatures

Parallel usual care observational cohort for patients not enrolled in trial

* Phase 2 and phase 3 trials might employ platform design if multiple candidate therapies are deemed ready for testing and amenable to a platform. Other trial designs may also be considered. The number of simultaneous arms need not be constant and may depend on resources, enrollment rate, and number and priority of candidate treatments, among other factors.