

A Research Agenda for Precision Medicine in Sepsis and Acute Respiratory Distress Syndrome: An Official American Thoracic Society Research Statement.

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30 3 2021 15 10 2021 204 8 392352 891 901 30 03 2021 25 10 2021 21 02 2026 Copyright © 2021 by the American Thoracic Society 2021 <https://creativecommons.org/licenses/by-nc-nd/4.0/> You may print one copy of this document at no charge. However, if you require more than one copy, you must place a reprint order. Domestic reprint orders: amy.schriver@sheridan.com ; international reprint orders: louisa.mott@springer.com . Background: Precision medicine focuses on the identification of therapeutic strategies that are effective for a group of patients based on similar unifying characteristics. The recent success of precision medicine in non-critical care settings has resulted from the confluence of large clinical and biospecimen repositories, innovative bioinformatics, and novel trial designs. Similar advances for precision medicine in sepsis and in the acute respiratory distress syndrome (ARDS) are possible but will require further investigation and significant investment in infrastructure.

Methods: This project was funded by the American Thoracic Society Board of Directors. A multidisciplinary and diverse working group reviewed the available literature, established a

conceptual framework, and iteratively developed recommendations for the Precision Medicine Research Agenda for Sepsis and ARDS.

Results: The following six priority recommendations were developed by the working group: 1) the creation of large richly phenotyped and harmonized knowledge networks of clinical, imaging, and multianalyte molecular data for sepsis and ARDS; 2) the implementation of novel trial designs, including adaptive designs, and embedding trial procedures in the electronic health record; 3) continued innovation in the data science and engineering methods required to identify heterogeneity of treatment effect; 4) further development of the tools necessary for the real-time application of precision medicine approaches; 5) work to ensure that precision medicine strategies are applicable and available to a broad range of patients varying across differing racial, ethnic, socioeconomic, and demographic groups; and 6) the securement and maintenance of adequate and sustainable funding for precision medicine efforts.

Conclusions: Precision medicine approaches that incorporate variability in genomic, biologic, and environmental factors may provide a path forward for better individualizing the delivery of therapies and improving care for patients with sepsis and ARDS.

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Sepsis and acute respiratory distress syndrome (ARDS) are well-described clinical syndromes (1 , 2) that constitute a substantial portion of ICU admissions and hospital deaths (3 , 4) with few therapies demonstrating consistent benefit in clinical trials (5 – 9). A major impediment to identifying new therapies is unrecognized heterogeneity that may influence patients' susceptibility to these syndromes and their response to specific treatments (10 – 12). Precision medicine approaches that incorporate variability in genomic, biologic, environmental, and lifestyle factors into the optimal therapeutic strategy may provide a path forward for sepsis and ARDS management (13 , 14).

For this research statement, we convened a workshop to discuss the challenges for implementing precision medicine in the ICU and to suggest a research agenda in precision medicine that could spur advances for sepsis and ARDS. Key recommendations include the following: 1. Creating large richly phenotyped and harmonized knowledge networks of clinical, imaging, and multianalyte molecular data for sepsis and ARDS.

Implementing novel trial designs that facilitate precision medicine approaches.

Continuing to innovate in the data science and engineering methods required to identify heterogeneity of treatment effect.

Further developing the tools necessary for the real-time application of precision medicine in the ICU.

Ensuring that precision medicine strategies are applicable and available to a broad range of patients varying across differing racial, ethnic, socioeconomic, and demographic groups.

Securing and maintaining adequate and sustainable funding for precision medicine efforts.

The terms “precision medicine” and “personalized (or individualized) medicine” are sometimes used interchangeably. In precision medicine, the focus is on identifying which approaches will be effective for a group of patients based on similar unifying characteristics. Although the eventual goal

is to tailor care for each individual (personalized medicine), most current efforts are focused on precision medicine because predicting treatment response at an individual patient level is challenging (15).

Significant breakthroughs have been made in precision medicine in non-critical care settings, including oncology, asthma, and chronic obstructive pulmonary disease, by leveraging extensive clinical data and molecular phenotyping to uncover subgroups that share dysregulation of specific pathways (16 – 21). These advancements have engendered a hope that we could rapidly apply similar techniques for sepsis and ARDS, but there are key differences (13). The molecular landscapes of sepsis and ARDS are complex and evolve rapidly, and clinicians often make therapeutic decisions within hours in contrast to days or weeks for outpatient decisions. Although “omics” platforms may improve molecular characterization of diseases, rapid turnaround times for complex assays are currently not readily available. Thus, initial steps toward precision medicine for patients with sepsis and ARDS include using clinical markers or easy-to-measure biomarkers. Importantly, clinical benefits of future precision medicine approaches in sepsis and ARDS, if any, will need to be tested and confirmed in rigorous well-conducted prospective clinical trials.

This project was proposed by members as an American Thoracic Society (ATS) project and approved for funding by the ATS Board of Directors. Participants included the project proposers and an invited diverse group of individuals with 1) expertise in managing critically ill pediatric or adult patients; 2) experience in patient-oriented research from mechanistic, clinical, translational, or bioinformatic perspectives; and 3) representation from different geographic regions (e.g., North America, South America, Europe, Africa, and Australia) and federal funding agencies (e.g., National Institute of Health), and reflecting different perspectives based on sex, seniority, and race/ethnicity.

A small working group met initially to review the available literature, develop a conceptual framework, agree on definitions for key terms, and determine the goals of the document. Members of the panel met in person at the Critical Care Canada Forum in November 2018 and the ATS International Conference in May 2019 to develop and prioritize recommendations. The chairs and a small working group prepared an initial draft of the document on the basis of the in-person meetings and circulated it to the panel for iterative feedback. Members of the committee were asked to vote on the prioritization of recommendations. The revised document was shared electronically and iteratively refined until all authors approved the work.

Although the current definitions of sepsis and ARDS are useful for assessing epidemiology and providing supportive care, they select a heterogeneous group of patients and may exclude some patients who could be part of a subgroup identified with alternate definitions and approaches. We use the term “subgroups” to generally include several commonly used terms, including phenotypes, subphenotypes, and endotypes (22 , 23). Prior work has identified subgroups of patients with sepsis and ARDS who are more or less likely to have poor clinical outcome on the basis of clinical or biologic biomarkers (prognostic markers). The efficacy (relative or absolute benefit or harm) of a treatment may vary across patient subgroups, such that the benefit (or harm) is concentrated in one or more subgroups—a variability referred to as heterogeneity of treatment effect (HTE) (24). Understanding HTE and identifying biomarkers based on genomic, biologic, environmental, and lifestyle factors that predict benefit or harm from a treatment (predictive markers) is key to advancing precision medicine strategies (14 , 25).

Prognostic markers have an established discovery pipeline and can be identified in any observational cohort by testing for association with outcome. In contrast, predictive markers are most readily determined through the interrogation of a dataset in which patients are randomly assigned to a treatment, such as a randomized controlled trial (RCT). Without random allocation, causal inference that patients with a set of observed variables are more or less responsive to therapy is limited by potential confounding. Confounding variables may be measured or unmeasured (residual confounding). A common example is confounding due to indication, in which a treatment is more or less likely to be administered on the basis of illness severity, comprising both inadequate adjustment of measured confounders and residual unmeasured confounding (26 , 27).

We propose a conceptual framework to develop precision medicine strategies for sepsis and ARDS through the creation of knowledge networks as recommended by the National Academy of Sciences (28). A knowledge network can include both observational studies and RCTs to integrate layers of clinical, lifestyle, environmental, and biological data about a disease (similar to a geographic information system map), allowing us to understand the connections within and across layers. Depending on the research questions and treatments being studied, knowledge networks could be small (and potentially include observational studies only) or large (including multiple large observational studies and RCTs). These knowledge networks will enable the identification of subgroups and the elucidation of complex pathways using a combination of observational studies and RCTs, and the discovery of HTE using RCTs. The confidence in subgroups identified as “likely to benefit” may vary, and, on the basis of the certainty of subgroup identification, trial designs could employ traditional (enroll only the subgroup that is most likely to benefit under settings of a very high level of certainty) or novel (e.g., adaptive platform trial design) methods to identify and validate precision medicine strategies (Figure 1). The financial investment required for the advancement of precision medicine in sepsis and ARDS will be substantial, but it ultimately could reduce costs through improved targeting of treatments and patient outcomes.

Conceptual model of the path forward for precision medicine in sepsis and the acute respiratory distress syndrome. EHR = electronic health record.

Create large richly phenotyped harmonized knowledge networks of clinical, imaging, and multianalyte molecular data from patients with sepsis and ARDS.

Discovery of prognostic and predictive biomarkers in complex heterogeneous disorders, including cancer, asthma, and cardiovascular disease, have occurred through the coordinated establishment and harmonization of knowledge networks. Similar collaborative efforts for sepsis and ARDS are necessary to advance precision medicine efforts. Observational studies, both already completed and future studies, recruit a broad group of patients unlike those enrolled in RCTs and can provide platforms for the discovery of phenotypes using clinical, imaging, and multianalyte molecular data (e.g., DNA, RNA, proteomics, microbiome, and metabolomics) from whole blood, plasma/serum, sputum/tracheal aspirate, BAL, or urine samples, as well as facilitate deep phenotyping (precise and comprehensive analysis of phenotypic abnormalities). Previously completed RCTs contribute to knowledge networks as venues for validation of phenotypes and HTE hypotheses. Multiple RCTs, if available for the same treatment, will enable the identification of HTE in subgroups of patients and for validation of observations identified in a single trial. The variables defining HTE may not be known or measured (or the technologies to uncover these variables may not be readily accessible) at the time of enrollment in observational studies and RCTs and may potentially be identified retrospectively as new knowledge becomes available without the need to conduct new studies.

Despite the increased financial cost of collecting and storing a variety of biospecimens in clinical studies, such efforts are necessary for the advancement of precision medicine in sepsis and ARDS. Successful harmonization of data will be essential to reduce and account for variability between studies and to facilitate validation of promising findings. Recent examples include efforts by the International Severe Acute Respiratory Infection Consortium and the Discovery Viral Infection and Respiratory Illness Universal Study research registries for coronavirus disease (COVID-19) (Table 1). Measures that can support the creation of these large collaborative knowledge networks include the following:

Current Knowledge Networks and Efforts to Harmonize Data across Observational Studies or Randomized Controlled Trials

Definition of abbreviations : ARDS = acute respiratory distress syndrome; BBMRI-ERIC = Biobanking and Biomolecular Resources Research Infrastructure–European Research

Infrastructure Consortium; BLUE CORAL = Biology and Longitudinal Epidemiology of COVID-19 Observational Study; COLOBILI = COVID-19 Longitudinal Biomarkers in Lung Injury; COVID-19 = coronavirus disease; CSCC = Center for Sepsis Control and Care; IBBJ = Integrated Biobank Jena; ISARIC = International Severe Acute Respiratory and Emerging Infection Consortium; NHLBI BioLINCC = NHLBI Biologic Specimen and Data Repository Information Coordinating Center; PHENOMS = Biomarker Phenotyping of Pediatric Sepsis and Multiple Organ Failure Study; RCT = randomized controlled trial; SEPNET = German Competence Network Sepsis; VIRUS = Viral Infection and Respiratory Illness Universal Study.

Making greater global efforts to organize and catalog extant data and biospecimens from already completed clinical studies of sepsis and ARDS, such as the NHLBI Biologic Specimen and Data Repository Information Coordinating Center repository (29 , 30) (Table 1). No similar publicly available biobanks currently exist for sepsis in the United States, but these are actively encouraged by the National Institute of General Medical Sciences (31), and none exist to organize studies globally.

Including biospecimen collection, both before randomization and longitudinally, in future observational studies and RCTs and modifying consent processes to ensure that data and biologic samples may be widely shared with additional investigators for collaborative efforts. Using approaches that are less resource intense, such as collecting samples at a single time point before administering the treatment, using leftover samples in the clinical laboratory (32), and collecting samples from a subset of sites rather than in all patients enrolled in large RCTs, should be considered.

Cultivating a harmonized global infrastructure that can recruit patients, measure molecular markers consistently and rapidly, integrate data, and regularly report results to help maintain the networks. For clinical data, adopting a common set of minimum data elements, employing consensus definitions for outcomes, covariates, and interventions, and developing standardized protocols for clinical data collection (33). For molecular data, developing uniform protocols for sample collection, processing, storage, and assay selection as well as encouraging the use of consistent imaging and biochemical platforms, similar to clinical minimal data elements.

Prioritizing funding for sepsis and ARDS studies with discrete and transparent data sharing plans (e.g., requiring submission of data to a common online data repository) and by allocating funds specifically for the creation and maintenance of data harmonization initiatives because the expense and effort required for harmonization can be substantial and are often not budgeted in initial study designs.

Implement novel trial designs to identify precision medicine strategies for sepsis and ARDS.

The RCT is a valuable tool to test efficacy, avoid confounding, and establish causal effect of an intervention. Traditional RCTs are conducted in a broad group of patients anticipating that the average treatment effect across trial participants will demonstrate benefit.

Adaptive designs allow prospective modifications of one or more aspects of the study on the basis of interim analyses of participants already enrolled in the study (34). These designs may be more efficient than traditional trial designs for identifying patients who benefit in settings in which HTE exists within the study population. Frequentist or Bayesian statistical approaches may be used in these designs depending on the complexity of potential modifications (35 , 36). The additional interim analyses and modifications potentially increase the risk of false positive results. Defining all modifications a priori and building strong partnerships with statisticians are essential to reduce bias. Examples of designs that may identify precision medicine approaches are included in Table 2 (37).

Trial Design Strategies for Precision Medicine in Sepsis and Acute Respiratory Distress Syndrome

Additional considerations include embedding trial procedures in the electronic health records (EHRs) and using response adaptive randomization strategies to increase trial efficiency, participant enrollment, and generalizability of results (32 , 38). These aspects of trial design allow the integration of research and clinical care (e.g., REMAP-CAP) and the creation of a “learning health system” (39).

Advance data science and engineering approaches to facilitate precision medicine strategies for sepsis and ARDS.

Continued innovations in data science and engineering methods are essential to identify HTE and advance the use of novel trial designs. Both applying approaches developed for other conditions to sepsis and ARDS and developing novel approaches will be necessary. Potential areas for advancement include methods to identify patients who benefit by incorporating combinations of clinical and molecular markers across multiple omics platforms (combining deep phenotyping with HTE identification), as has recently been explored in other non-critical care disorders (40 , 41), to modify treatment approaches in response to the rapid changes in the host immune response over time, and to use causal modeling when RCT data are sparse and only results of observational studies are available (42) (Table 3).

Potential Statistical Approaches to Improve Use of Knowledge Networks

Definition of abbreviations : ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease.

Develop the tools necessary for the real-time application of precision medicine approaches.

Precision medicine for sepsis and ARDS will require rapid assessment of patient phenotype and subgroups that benefit, in contrast to other disorders, such as cancer or asthma, in which precision medicine decisions can be made days or weeks after initial assessment. Potential strategies to facilitate the rapid deployment of precision medicine strategies include leveraging EHRs and novel technologies to ensure rapid turnaround of biomarker results. 1. Observational studies can be partially or completely nested within EHRs. Linking EHRs with claims data from health insurance providers may be preferred because patients may receive care at multiple sites, many of which may not share EHRs. Opportunities to embed RCTs in EHRs include using real-time clinical and laboratory data to identify patients with sepsis and ARD, identifying of subgroups that may benefit from the intervention using machine learning and artificial intelligence algorithms, randomizing within the EHR, and using live decision support (e.g., using edge computing to reduce latency) to provide treatment options to providers at the bedside (43 – 46). Finally, these approaches will have to be incorporated across multiple EHRs for multicenter RCTs. Recent trials, such as the REMAP-CAP (Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-acquired Pneumonia): COVID adaptive clinical trial, have successfully used some of these approaches (39).

Treatment response to a particular therapy in sepsis and ARDS may depend on molecular signatures that need to be determined quickly, preferably using point-of-care assays. Recent advances in diagnostic testing have enabled the prompt identification of such signatures (e.g., detection of infectious versus noninfectious transcriptomic signatures and for the detection of antimicrobial resistant bacterial pathogens in hours) (47 – 49). However, there are important challenges to develop these molecular signatures. First, it is logistically challenging to conduct RCTs to test molecular signatures to tailor therapies because these tests are not Food and Drug Administration approved and are often validated in Clinical Laboratory Improvement Amendment–certified laboratories across multiple sites as laboratory-derived tests. This is an expensive endeavor that may not be efficiently completed in a single RCT. This situation creates a regulatory and development paradox in that the major investment needed to develop a diagnostic test is not attractive to pharmaceutical companies until the diagnostic's market has been confirmed,

yet the therapeutic's utility may be uncertain without the diagnostic test to identify patients who will benefit. In the United States, the Food and Drug Administration has mechanisms to codevelop a diagnostic assay with a therapeutic agent during the approval process (50). Second, these efforts may require partnerships between academic investigators and pharmaceutical companies. It would be important to ensure that the intellectual property rights of the various stakeholders are maintained.

Ensure that precision medicine advances be applicable to a broad range of patients across different healthcare delivery systems; resource-rich and resource-limited settings; racial, ethnic, socioeconomic, and demographic groups; and social and environmental practices.

Precision medicine should improve care for patients with sepsis and ARDS globally and not worsen healthcare inequalities. A threat to this goal is to solely focus on molecular substratification, which may require complex assays and apply only to highly resourced quaternary medical centers. More than 80% of the world's population resides in resource-limited or developing countries, and patients in these countries account for >85% of the global sepsis burden (51). However, these patients may not have access to results of complex assays to target treatments precisely and rapidly. Similarly, critical care outcomes vary significantly by race, ethnicity, and sex, and clinical trials have often underrepresented minoritized and socioeconomically disadvantaged groups (52 , 53). Differences in lifestyle factors such as diet, physical activity, and tobacco and alcohol exposure among groups warrant consideration in precision medicine approaches, as they potentially may be of equal if not greater importance compared with biologic markers in explaining differences in prognosis and treatment response (54 , 55). Potential strategies to enact an equitable and just global deployment of precision medicine include: 1. Consciously including diverse stakeholders from different geographic, economic, cultural, racial/ethnic, and sex backgrounds on advisory panels and peer review committees. Specifically, patient advocates, funding agencies (both federal and nonfederal), medical foundations, public health entities, and pharmaceutical companies should each have a voice in articulating the precision medicine priorities for these conditions and how they might be achieved. Enhanced efforts to promote the inclusion of ethnically and racially diverse populations in observational studies and clinical trials will allow broader applicability of precision medicine.

Using approaches tailored for low-resource settings. These include 1) partnerships with industry to develop cost-effective and rapid diagnostic tests, which can be stored and performed easily and used in any healthcare setting; 2) simplifying predictor and classifier models by reducing data redundancy and using surrogate models that are reliant on readily available clinical data instead of complex biological data; 3) using the "Fast-Second Winner model" (51), which leverages large-scale discovery efforts elsewhere to develop more site-specific public health strategies to accelerate investment in promising biomarker and diagnostic candidates based on local health burdens and needs in low-resource settings; and 4) artificial intelligence applications that leverage high dimensional clinical data with relatively low local technological investment (56), preferably using electronic data feeds if available.

Secure and maintain adequate and sustainable funding.

Funding for precision medicine initiatives will require a shared financial investment by academic institutions, federal and nonfederal funding agencies, pharmaceutical and biotechnology companies, philanthropic societies, and healthcare systems. No single agency funding precision medicine in isolation will be able to advance quickly enough to meaningfully impact the field. Sustainable funding is required to build and maintain collaborative networks that allow multiple agents to be tested sequentially or in parallel, ensure data and biospecimen harmonization, develop novel trial design and informatic approaches, and enroll patients in new precision medicine studies. The success of precision medicine efforts in breast cancer has come in no small part because of the multiple stakeholders that have provided funding, including academic institutions, pharmaceutical companies, not-for-profit organizations, and food and drug retailers, in addition to the substantial investment from federal sources that ensured stability. However, efforts across

multiple stakeholders will have to be coordinated. Recent examples include the REMAP-CAP, RECOVERY (Randomised Evaluation of COVID-19 Therapy), and iSPY-COVID trials, which quickly engaged multiple stakeholders and sponsors (including various pharmaceutical companies whose products were tested, academic healthcare centers, and federal agencies such as the NIH in the United States and the National Health Service in the United Kingdom) to develop the infrastructure, technology, and resources necessary to rapidly and flexibly test multiple therapeutic interventions in the midst of the COVID-19 pandemic.

Specific recommendations include increased funding by federal and nonfederal agencies for proposals that advance precision medicine for sepsis and ARDS and improved efforts to coordinate activities across multiple stakeholders.

Developing precision medicine approaches will require reexamination of the conduct of observational studies and RCTs for sepsis and ARDS. In particular, the equitable sharing of data and biospecimens and the creation and maintenance of large knowledge networks to identify HTE and subgroups that benefit from a treatment will be imperative. Although observational studies are important, conducting RCTs remains critical to making inferences about causality and validate findings. These steps will require significant investment up front by multiple stakeholders, and, ultimately, successful precision medicine approaches will have several economic advantages. Pharmaceutical and biotechnology companies, trial investigators, and funding agencies will benefit from infrastructures that allow for different treatments to be tested within established precision medicine trial networks, which may reduce costs and improve chances for a successful trial. Healthcare systems and insurance companies will benefit from creating learning healthcare systems by potentially decreasing low-value care. Most importantly, patients will benefit from the ability to receive therapies that have a higher likelihood of success.

This official research statement was prepared by an ad hoc subcommittee of the ATS Assembly on Critical Care.

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