Extracorporeal life support (ECLS) refers to a group of techniques that provide extracorporeal gas exchange or circulatory support for patients with respiratory or cardiac failure. The use of ECLS in adults has grown exponentially in the last decade, fueled both by technological advances in cardiopulmonary bypass equipment, from which ECLS was principally derived, and by several specific events. The perceived need for advanced respiratory support in patients with influenza A(H1N1)-associated ARDS during the 2009 pandemic, along with the publication of the Conventional Ventilation or ECMO for Severe Adult Respiratory Failure (CESAR) trial that same year, generated considerable interest in ECLS for adult respiratory failure. Although use of cardiac ECLS was already growing, its use increased dramatically in some countries after the publication of the Intraaortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) trial. The current growth of ECLS is outpacing the evidence base supporting its use. For example, in the last decade, only one large randomized clinical trial assessing the efficacy of ECLS for respiratory failure has been published; none has been published for cardiac failure. This lack of data leaves us without definitive answers to a number of important questions, including the most fundamental: When is ECLS indicated? Also, is it superior to the best current standard of care?
The paucity of data in support of ECLS is in part due to a number of challenges in performing clinical trials in this field. First, ECLS practices are very heterogeneous across centers. Sources of this heterogeneity include the equipment used, circuit configurations, methods of weaning, protocols for anticoagulation, the use of retrieval from other hospitals, and the range of underlying diseases for which it is used. Second, the patients are often very ill, with short time-windows for study enrollment. Third, there may be questionable equipoise for clinicians who believe ECLS is the only thing standing between possible life and certain death. Fourth, research funding, particularly from public institutions, is often not easy to access for ECLS studies, perhaps due in part to the aforementioned challenges. Finally, there are external factors, such as institutional prestige, industry influence, and family requests, that drive the use of ECLS and compete with research for influence over the direction of the field. Given these challenges, it is essential that we develop a strategy to strengthen the evidence base in ECLS.

Evidence is required because ECLS is complex, expensive, high risk, and resource intense.\textsuperscript{10} We need to clarify whether ECLS should be applied at all and, if so, how early in the clinical course it should be initiated; which patients benefit most; and exactly what complications to expect with different devices or techniques, informing the risk-to-benefit ratio of using ECLS in various clinical settings. Importantly, in the setting of clinical trials, we must take care to protocolize the ECLS practices. If efficacy is established, we will then be able to coalesce around those elements of the protocol most closely linked to the benefits seen. In doing so, we can begin to illuminate a set of best practices for clinical care in ECLS.

Until such information is available, clinicians should consider restricting the use of ECLS to cases of refractory cardiopulmonary failure and, even then, only after applying conventional evidence-based practices, as appropriate. The use of extracorporeal carbon dioxide removal for COPD or less-than-severe cases of ARDS, for instance, should be restricted to the research setting until we understand the risk-to-benefit ratio and can show the value of this therapeutic approach.\textsuperscript{11}

Successful research in ECLS will require collaboration among centers, across regions, countries, and continents (Table 1). It will also require collaboration across medical disciplines. The ECLS community must come together to decide on research priorities and collaborate on high-quality research.\textsuperscript{10} A recent article by a group of experts in the field set out in this direction by trying to prioritize just such a research agenda for ECLS.\textsuperscript{12} The article reviews the evolving literature in several key areas of ECLS and goes on to recommend the top 10 studies or trials that should be conducted in the next decade. To successfully examine these and other clinical, physiological, and basic science questions, we believe that research in ECLS must be conducted with the following three points in mind.

First, we will need the involvement of centers capable of both participating in research and having the expertise and experience to be able to perform high-quality ECLS.\textsuperscript{10,13} Second, we need research networks of these high-quality centers to address many of the key research questions in ECLS, because even high-volume ECLS centers may not treat sufficient numbers of such patients to conduct large observational studies or well-powered randomized controlled trials within a single center. The use of existing research networks and medical societies to design and conduct research will be important, as will the creation of research networks dedicated specifically to the study of ECLS, which facilitate such collaboration within the field. The International ECMO Network\textsuperscript{14} is one such organization. In conjunction with major organizations in the field, such as the Extracorporeal Life Support Organization,\textsuperscript{15} these networks would be helpful in bringing consensus to definitions and nomenclature, as well as defining clinical standards for ECLS delivery. This approach in turn could drive the

### Table 1. Major Recommendations for Research in ECLS

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Details</th>
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<tbody>
<tr>
<td>Defining top research priorities</td>
<td>Establishing whether ECLS should be applied and, if so, how early it should be initiated.</td>
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<tr>
<td>Collaborating among existing ECLS centers</td>
<td>Ensuring that research networks can adequately address key research questions.</td>
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<tr>
<td>Utilizing research networks</td>
<td>Standardizing practices across centers.</td>
</tr>
<tr>
<td>Defining core datasets and core outcome sets</td>
<td>Assessing complications and their impact.</td>
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<tr>
<td>Creating a robust research registry</td>
<td>Developing appropriate end points for studies.</td>
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<tr>
<td>Establishing efficacy for various potential indications</td>
<td>Using predictive enrichment strategies specific to ECLS.</td>
</tr>
<tr>
<td>Using predictive enrichment strategies specific to ECLS</td>
<td>Optimally targeting the appropriate patient population.</td>
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<tr>
<td>Assessing prehospital practices</td>
<td>Considering organ donation as an outcome in some cases.</td>
</tr>
<tr>
<td>Looking beyond randomized controlled trials</td>
<td>Standardizing practices across centers.</td>
</tr>
<tr>
<td>Considering organ donation as an outcome in some cases</td>
<td>Analysing the impact of organ donation on patient outcomes.</td>
</tr>
<tr>
<td>Standardizing of practices across centers</td>
<td>Coordinating practices across different locations.</td>
</tr>
</tbody>
</table>

ECLS = extracorporeal life support.
creation of a commonly accepted dataset for the field, including core outcomes, allowing comparisons across studies and individual patient data meta-analyses to be conducted. The development and use of common research databases and registries should be considered obligatory for centers using ECLS for participation in research or, at a minimum, for quality assurance. A high-quality research database could be used to further research in numerous ways, not least by facilitating registry randomized controlled trials. Drawing on the experience of the Interagency Registry for Mechanically Assisted Circulatory Support database in patients with heart failure, the field of ECLS could benefit greatly from a similar collaboration among funding bodies, governmental agencies, academia, and clinicians, as well as industry, to create a powerful tool for both research and quality; this database could perhaps be an extension of the current Extracorporeal Life Support Organization registry. We strongly advocate the creation of just such a database.

The third key point emphasizes the outcomes these studies should target. Although mortality is clearly an important outcome to consider and account for, it does not have to be the primary outcome for every study. The right outcome should depend on the specific research question being addressed and could include physiological data, organ function, safety outcomes, resource utilization, ethical questions, and quality of life. In some cases of respiratory failure, extracorporeal systems may alleviate the need for endotracheal intubation, with significant potential impact on survival. In selected cases of profound brain damage, organ procurement may be increased. Other outcomes of importance for the patient, including long-term outcomes, should be explored with meaningful input from patients and families. It will also be important to use control groups treated with the highest current standards of care for the disease in question. Novel forms of enrichment strategies, including a recently developed model in ECLS, may identify those patients most likely to respond to any specific application of ECLS and might enhance statistical power. This strategy uses physiological variables to enrich the population enrolled, thereby targeting the intervention to the appropriate patient population and optimizing sample size. This approach is particularly important in ECLS due to the limited number of patients with any given potential indication.

Research strategies will also need to address the common use of ECLS as a “rescue” strategy. The dire nature of many clinical situations in which ECLS may be applied, and the lack of personal equipoise many clinicians feel in such situations, may require reaching beyond traditional randomized controlled trials. Consideration should be given to well-designed propensity matching studies, as well as adaptive randomization, as was done in the early trials of neonatal ECLS using, for instance, a “play-the-winner” strategy as alternative methods to assess questions of efficacy. However, it must be noted that each of these strategies has its own significant limitations in this setting, with no way to fully escape the ethical and methodologic challenges to the design of such trials.

If and when we are conducting randomized controlled trials of ECLS, it is essential to bear in mind that what we are studying is not simply ECLS vs the current standard of care (without ECLS). Because the device itself provides organ support but not treatment for the underlying pathophysiology, the ECLS arm in such a trial is fundamentally a strategy for treating the heart or lung disease, which is in turn made possible by the physiological support provided by ECLS. We therefore need to focus carefully on the non-ECLS management within the ECLS arm. Just as there is a lack of consensus on the optimal management of the circuit itself, it is not at all clear that we understand the optimal strategies for managing various forms of heart or lung failure during ECLS support.

Importantly, once efficacy has been established for a given indication, it would be wise to assess cost-effectiveness to inform policymaking by health-care and governmental organizations. Finally, there is a cost to forgoing rigorous research to inform best practices; inappropriate use of ECLS could well harm the appropriate long-term penetration of the technology into routine practice.

The field of ECLS is growing and will continue to evolve along with the technology. The need for rigorous research in ECLS is only increasing. Momentum is gathering for conducting scientific research to create a stronger evidence-based foundation for the use of ECLS. We believe that meaningful collaboration among centers throughout the world through research networks will be key to driving this important agenda.

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