Executive Summary

The Sepsis Human Biospecimens Investigators' Meeting gathered National Institute of General Medical Sciences (NIGMS) grantees through funding opportunity announcement (FOA) PAR-21-077. The purpose of this FOA is to support the efficient collection, biobanking, and sharing of biospecimens and associated clinical data from critically ill and sepsis patients for use in future mechanistic research. It grew from the need to accelerate fundamental discoveries that provide novel insights into the heterogeneity of the pathogenesis and resolution of human sepsis, which has not been achieved by studies overly reliant on murine models of sepsis.

Throughout the meeting, investigators presented ongoing research funded by PAR-21-077; and discussed ideas, data, methods, and best practices for biorepository creation and use. Their advice to the sepsis research community is as follows:

1. There are strong benefits to using **remnant samples** including cost, feasibility, and consent. Areas to improve include reporting and normalization of the sample processing, and defined quality metrics specific for assays and scientific questions. Testing of new ways to analyze remnant samples (e.g., detecting microbial information) is a promising area to expand.
2. Novel sample storage approaches that are amenable to **emerging and future technologies** (e.g., whole-blood cryo, redox, dried blood) should be tested and incorporated into the biobanking process whenever possible. Assays for testing sample deterioration during storage would be helpful.
3. State-of-the-art technologies enabling advanced analysis using **small sample volumes** (e.g., microfluidics) will reduce the need for remnant samples and are useful for answering specific scientific questions. It is also useful to test the limits for certain advanced assays (e.g., scRNA seq, airway samples, metabolic assays) to inform the field.
4. **Clearly defined** ontology for biobanking and data repositories is the first step toward a standardized sample and data collection and processing protocol fitting specific analysis and scientific questions, which will ultimately improve resource sharing.
5. Broad biobanking with **thoughtful clinical annotation** (e.g., subgroups, timing of key events) is imperative for the effective utilization of biospecimens linked to clinical data.
6. It is important to set a reference for the **ground truth** (e.g., pre-analytic variability) before getting into the biological reality of the disease, which could be due to sample processing variability but more due to patient variability.
7. A combination of **automatic EHR screening** of patients and **retrospective syndrome adjudication** is found to be an effective workflow for prompt enrollment of critically ill patients at different disease stages without losing much fidelity.
8. It is important to identify the **proper control** groups (e.g., non-critically ill controls, non-infection controls, infection but non-septic controls) for every study and enroll those patients alongside study patients**.**
9. It is recommended to use **broad inclusion criteria** (e.g., all acutely and critically ill patients) to avoid excluding patients who do not fit neatly within the clinical definition of sepsis and who can also serve as controls. The analysis could start with the more defined patient group to serve as an anchor point and a reference.

10. **Paired samples** before and after treatment and **longitudinal specimen collection** may be good ways to overcome the vast heterogeneity that exists in the sepsis disease course. Time zero samples would be highly valuable for finding sepsis signatures and diagnostic tools. It is of note that patient subgroups may change during longitudinal sampling and in future sepsis definitions.
11. **Pairing biospecimens with clinical metadata** should be a fundamental element when building a sepsis biorepository. The ultimate goal is to pair comprehensive longitudinal biospecimens with deep clinical phenotyping. It may be helpful to start by compiling a list of EHR elements and bedside assessments that provide high clinical value but do not add a significant burden to clinical care. Patient privacy must be adequately protected in this process.
12. There are opportunities to study **novel economic sample types** such as HME filters and urine because they are easily accessible and offer a wealth of information that may complement traditional sampling.
13. Quality assurance and data model standardization are important for the wide **sharing of EHR data** across institutions. A consensus on the types of variables to be standardized is helpful.
14. A wide range of consenting methods such as waivered consent and delayed consent are used, but local Institutional Review Board (IRB) committees have divergent interpretations of policies. It would be helpful to **publish more studies on consenting methods** to aid with the regulatory approval process. Studies to improve the rate of consent are also useful.
15. There should be a healthy balance between **open-ended discovery studies** and **hypothesis-driven studies** using a broad heterogenous biorepository or a well-defined cohort, as both are valuable to move the field forward in different ways. A top-down approach to finding the **biological signatures of clinical subgroups** or a bottom-up approach to identifying **shared underlying biological phenotypes** that explain the clinical heterogeneity both have values. A strategic way to pursue the **"biological truth**" could be layered to different depths of patient stratification.
16. There may be value in **a centralized approach** such as a structured database to deposit datasets from various sources and high-capacity computational tools, as well as biorepository centers that have the capacity and expertise in multicenter patient recruitment. It may also be beneficial to establish a searchable data and biorepository registry so investigators know about available resources for possible collaborations.

This meeting report summarizes investigators' presentations and the discussions surrounding **the current challenges in biobanking and sample utilization** facing sepsis researchers, and the **suggestions for overcoming them**