Request for Biorepository Proposals (RFP)
Prepared by Northwestern University Data Analysis and Coordinating Center (NUDACC)

Application Deadline: August 5, 2022

Northwestern University Data Analysis and Coordinating Center (NUDACC)
Northwestern University Feinberg School of Medicine
Department of Preventive Medicine, Division of Biostatistics
680 N Lake Shore Drive Suite 1400
Chicago, IL 60611
lcn@northwestern.edu

1.0 INTRODUCTION

The Liver Cirrhosis Network (LCN) is seeking a Biorepository to assist the Scientific and Data Coordination Center (SDCC) in collecting biosamples from **10 participating study sites** for the duration of the LCN studies. This document introduces the background and rationale for the LCN studies, as well as the general LCN study objectives, study populations and designs. LCN Biorepository responsibilities, application instructions and evaluation criteria are also outlined.

The LCN study protocols are developed by recipients of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Liver Cirrhosis Network Clinical Research Centers (RFA-DK-20-003) and Scientific and Data Coordination Center (RFA-DK-20-004) cooperative agreement awards. The primary aims of the LCN are to 1) perform a **randomized controlled trial** to test the efficacy of 'statins' to mitigate the progression of liver cirrhosis, and 2) **create a prospective observational cohort** to understand progression of disease. The protocols for both studies are being finalized. The current **request for a central biorepository** is being issued to **collect and store all study samples i**n order to accomplish current and future study aims.

Responses to this Request for Biorepository Center are due by July 25, 2022 and are expected to follow the application instructions detailed in this document. Biorepository Center selection will be performed according to the evaluation criteria outlined in this document. Support for the selected Biorepository Center will be administered as subcontracts from the LCN SDCC.

2.0 BACKGROUND AND RATIONALE

Cirrhosis represents not a single disease, but rather the consequence and major serious outcome of many chronic liver diseases, caused by a wide range of conditions (e.g., hepatitis C, alcohol use disorder, nonalcoholic steatohepatitis). Clinical complications of cirrhosis include various symptoms such as fatigue, weakness, weight loss, itching and jaundice, but also more significantly, complications such as gastrointestinal bleeding from varices, ascites, renal dysfunction, and hepatic encephalopathy. A dreaded complication of cirrhosis is hepatocellular carcinoma, a highly fatal cancer that arises in 1 to 3% of persons with cirrhosis yearly. Once cirrhosis is present, treatment of the underlying liver disease can impede further disease progression and deterioration, but it does not eliminate all risk of complications and cirrhosis-related death.

Mortality due to liver disease remains a significant public health burden in the United States, currently ranked 11th overall and ranking 6th in persons below the age of 65 years. Median survival among compensated patients with cirrhosis is 12 years, but expected survival drops to 1.8 years among decompensated patients (e.g., ascites). Cirrhosis appears to be rising in some populations such as persons living with HIV infection and cystic fibrosis. Hepatocellular carcinoma incidence is also rising in the United States and is a surrogate for the prevalence of cirrhosis.

Treatment of underlying causes of chronic liver disease such as antivirals for chronic hepatitis B and C; therapeutic phlebotomy for genetic hemochromatosis; ursodiol for primary biliary cirrhosis; and cessation of alcohol consumption for alcoholic liver disease, all underpin the overarching clinical approach to prevent the development of cirrhosis by early abrogation of ongoing injury to the still noncirrhotic liver. Neutralization of the liver disease etiology may allow the injured liver to invoke endogenous mechanisms to reverse the consequences of chronic inflammation and the accumulation of mild or even modest amounts of liver fibrosis. However, once cirrhosis has been established, neutralization of the causes of liver disease generally will not reverse the cirrhosis.

Liver transplantation is currently the only medically viable avenue for patients with end-stage liver disease that will extend their longevity. On an annual basis, despite treatment success rates for chronic hepatitis C and other liver diseases, the national wait list for liver transplantation in the United States remains essentially unchanged at approximately 13,000 patients, likely less than 1% of those afflicted by the disease. Only 9,000 liver transplantations are performed annually. However, the majority of patients with end-stage liver disease are not even placed on liver transplantation lists for a variety of reasons such as lack of access, co-morbididities or psychosocial issues.

Given the discrepancy between the need and the availability of liver organs for patients on liver transplant waiting lists and the even more numerous patients who are unable to be considered for listing for liver transplantation, there is a significant need to improve our understanding of clinical and translational scientific aspects of liver fibrosis and cirrhosis. In addition, there is a need for furthering fundamental understanding of both the underlying pro- and anti-fibrotic mechanisms as well as risk factors and mechanisms that accentuate pro- and anti-fibrotic processes.

There has been a growing body of literature regarding the use of statins for advanced liver fibrosis and cirrhosis. Statins have been reported to have pleomorphic effects that have encompassed anti-inflammatory, anti-proliferative, and diminished stellate cell activation. Clinically, statins have been suggested to reduce portal venous pressure, reduced risk of hepatocellular carcinoma, and improved survival. The Liver Cirrhosis Network (LCN) is poised to further investigate the effects of statins in the liver cirrhosis population, and if beneficial, findings may translate into improved care of patients afflicted with this condition and a lessening of the cirrhosis disease complication burden.

3.0 STUDY OBJECTIVES

The purpose of the biorepository is to provide a central storage location for biosamples (blood, urine, saliva, and stool) that are collected at LCN study sites, and to retrieve and ship selected samples to secondary study sites for analyses.

Through the establishment of the LCN, the NIDDK is proposing two broad approaches to be undertaken. First is the **establishment of a Longitudinal Cohort of patients with compensated cirrhosis**. Second is the **development and implementation of an intervention trial using an HMG-coenzyme A reductase inhibitor ("statin").** All studies undertaken by the LCN will be performed in adult participants. The findings and results emanating from these two approaches should advance the understanding about the pathophysiological mechanistic aspects of liver fibrosis from both pro- and anti-fibrotic processes; improve the assessment of clinical risk factors associated with advancement or recession of liver fibrosis; provide an opportunity to assess noninvasive measures of liver fibrosis and cirrhosis in conjunction with clinical measures; and determine the safety and efficacy of statin therapy in preventing disease progression and adverse clinical outcomes of cirrhosis.

3.1 Primary Objectives of the Liver Cirrhosis Network

Primary objective of the longitudinal cohort study:

To evaluate improvements in predictive accuracy for risk of decompensation using a composite risk score that includes non-modifiable and modifiable clinical, pathophysiological and behavioral risk factors compared to a composite risk score that includes clinical risk factors alone in a large, multi-center cohort of patients with

cirrhosis.

Primary objective of the statin trial:

To evaluate the safety and efficacy of rosuvastatin 10-20 mg compared to placebo in patients with compensated cirrhosis in changing disease progression as measured by liver stiffness.

3.2 Additional and Exploratory Measures

Key Components of primary, secondary and exploratory objectives of the LCN studies:

1. Behavioral and Psychosocial measures
2. Pathophysiological measures
3. Non-invasive testing imaging procedures
4. Microbiome
5. Metabolome
6. Genetic variants and ancestry
7. Biorepository: biological samples will be collected throughout the course of the LCN studies; some of these samples may be evaluated as part of the overall LCN goals and some samples will be used for future investigation of potential biomarkers or signatures of cirrhosis.

4.0 STUDY POPULATION

The study population includes adults diagnosed with compensated liver cirrhosis.

4.1 Participant Inclusion Criteria

Study participants will be adults (age > 18 years) from one of the 10 participating LCN sites who are

1) Able to consent
2) Willing to provide samples
3) Diagnosed with Cirrhosis of any etiology and

4.2 Participant Exclusion Criteria

Study participants are excluded for reasons outlined in the LCN study protocols. Some key exclusion criteria according to the current protocol versions include:

1) Known prior or current hepatocellular carcinoma (HCC) or cholangiocarcinoma
2) Known transjugular intrahepatic portosystemic shunt (TIPS), balloon retrograde transvenous obliteration (BRTO) or porto-systemic shunt surgery regardless of time of occurrence
3) Known prior solid organ transplant or bone marrow transplant
4) Current participation in active medication treatment trials
5) Current liver-unrelated end-stage organ failures, current chronic obstructive pulmonary disease (COPD) on home oxygen, current known active malignancy besides non-melanomatous skin cancer or carcinoma in situ
6) Documented history of alcohol-associated hepatitis in the 6 months prior to consent
7) Known recent (within 1 year prior to consent) or present hepatic decompensation with ascites/hydrothorac, hepatic encephalopathy or variceal bleeding
8) Current known Hepatitis C Virus (HCV) without sustained virologic response (SVR)

5.0 BIOREPOSITORY

5.1 Description

The two LCN studies (cohort and trial) will involve **an anticipated 1,750 participants (1,200 cohort, 550 statin)** over four years (anticipated enrollment start 9/2022-8/2026). Biosamples will be collected as outlined by the LCN protocols at different time points during the participant enrollment. The SDCC will generate barcoded labels for the 10 LCN sites to label the biosamples (blood, urine, saliva, stool) and at predetermined intervals (likely every 3 months) will send them to the Biorepository. The LCN sites will be responsible for aliquoting, labeling, and temporary storage of the samples at the appropriate temperature (mostly -80C, but will depend on the sample type), and they will batch shipments of the collected biosamples every 3 months to the biorepository (centers will cover the cost of their boxes and shipping). The Biorepository will be responsible for receiving biospecimens, logging the samples into the study-specific specimen management database (i.e., REDCap database), and long-term storage at the appropriate temperature until the agreed upon time frame after study completion. (Within a few years after the the end of the terminal funding period, the samples will be transferred to the repository specified by the National Institute of Digestive and Kidney Diseases [NIDDK]). Upon request from the SDCC, shipment of selected samples to outside investigators for additional analyses will be completed by the Biorepository. The Biorepository will also be responsible to be in daily contact with the SDCC to optimize the alignment of participant information and samples in the biorepository and the sample databases. After completion of the study period and in coordination with the National Institutes of Health (NIH), the samples will be sent to a biorepository within NIDDK.

The estimated breakdown of estimates by study and sample type are outlined below (estimates of aliquots over the study period are also provided in Exhibit A):

Study #1: Cohort: (**maximum** total aliquots per participant: 69)

Study collection time points are: baseline, Year 1, Year 2, Year 3 (4 time points)

Sample Type	N time points	Aliquots (amount per)	Total Aliquots
Serum – baseline	1	8 (100-250 ul)	8
Serum – follow-up	3	4 (100-500 ul)	12
Plasma	4	4 (100-500 ul)	16
Whole blood (DNA)	1	1	1
PBMC	4	1	4
Urine	4	4	16
Saliva	4	2 (1ml cryovials each)	8
Stool	4	1 kit	4
All Samples			**69**

The anticipated 69 individual aliquots (blood, urine, stool, saliva, serum, plasma combined) per participant x 1,200 participants total across the 10 LCN sites equates to an **estimated 82,800 over the course** of roughly 6 years (24 quarters) or about **3,500 aliquots per quarter (i.e., every 3 months) that the LCN Biorepository would be expected to receive.** If we anticipate just a proportion of participants agreeing to optional sample collection (e.g., stool, whole blood for DNA), then a reasonable lower bound of aliquots the biorepository may expect on a quarterly basis is about **2,500 aliquots per quarter for this study alone**.

Study #2: Trial: (**maximum** total aliquots per participant: 70)

Study collection time points are: baseline, Month 6, Year 1, Month 18, Year 2 (5 time points)

Sample Type	N time points	Aliquots (amount per)	Total Aliquots
Serum – baseline	1	8 (100-250 ul)	8
Serum – follow-up	4	4 (100-500 ul)	16
Plasma	5	4 (100-500 ul)	20
Whole blood (DNA)	1	1	1
PBMC	5	1	5
Urine	5	4	20
All Samples			**70**

The anticipated 70 individual aliquots (blood, urine, serum, plasma) per participant x 550 participants total across the 10 LCN sites equates to about **38,500 aliquots over the course** of roughly 5 years.
Thus, the Biorepository would need to be equipped to receive approximately **1,900** aliquots for the LCN clinical trial every 3 months. Factoring in the possibility that some study participants may not agree or be able to provide all samples for this study, a reasonable lower bound of aliquots the biorepository may expect on a quarterly basis is about **1,300 aliquots per quarter for this study alone**.

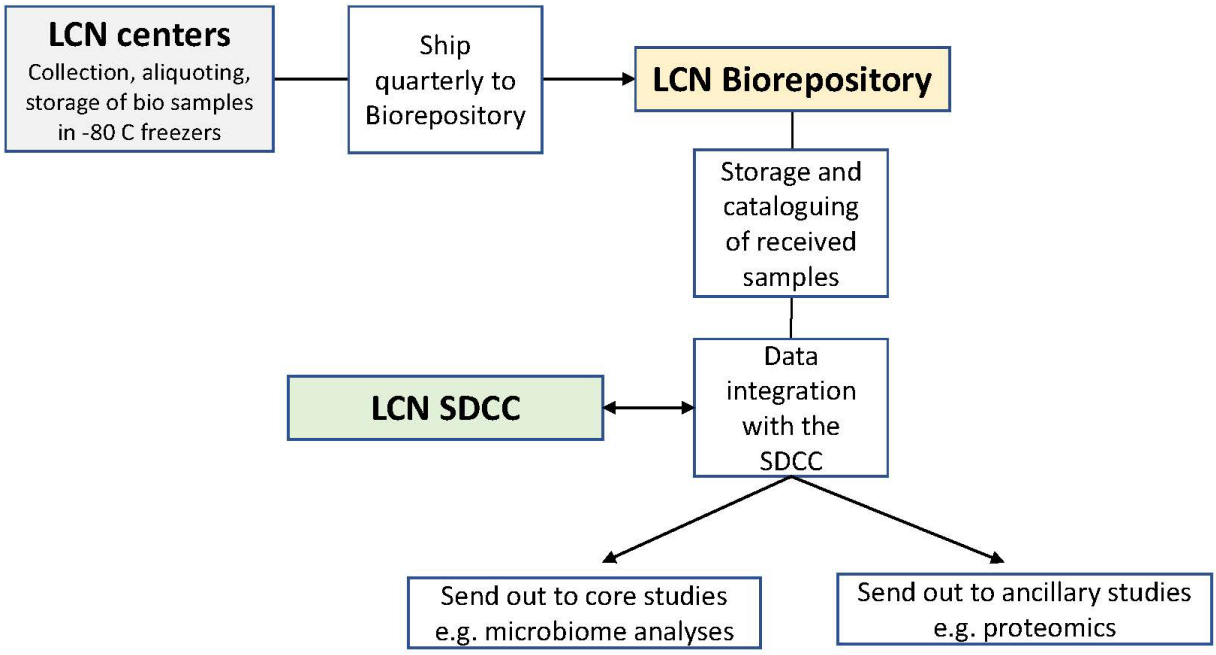
In total – between Cohort & Trial, the Biorepository is expected to receive ~ **3,800-5,100 aliquots every 3 months, on average**, and about **92,000 – 122,000 over the course of entire study periods**.

It is recommended to have **2** full-time equivalent (FTEs) staff members at the biorepository dedicated solely to the effort of handling, storing, and pulling samples for shipment, and another for quality control, oversight, and communication with the SDCC. All samples should be entered into a specimen management database (e.g., Freezerpro, OpenSpecimen, etc.) that can be integrated with REDCap. REDCap is the open-source software used by the SDCC to capture participant information from the 10 participating LCN centers, including data related to sample collection.

The Biorepository, together with the SDCC, will schedule sample collection and protocol specific timelines. It is expected of the Biorepository to communicate with individual LCN sites 1-2 times per month for data review and to ensure operations are running smoothly.

A quarterly status report will be generated detailing the samples that have been received and stored from the various sites. This report will also include participant-level information, including the total number of aliquots available for each sample type for each participant. The Biorepository is also expected to pull samples from each site on a semiannual basis and send to a central laboratory for quality control analysis.

5.2 Biorepository organizational Schema



5.3 Study Schedule

Sample Collection

Prospective Cohort Study:
The following samples will be collected from approximately 1,200 participants:
1. Whole blood (DNA) at baseline only
2. Plasma at baseline, Month 12, Month 24, Month 36 (4 aliquots at all study time points)
3. Serum at baseline, Month 12, Month 24, Month 36 (8 aliquots at baseline, 4 at all others)
4. Urine at baseline
5. Saliva at baseline

The following will likely be collected for a subset of participants; the proportion of participants providing at each time point will vary by site:
6. Stool at baseline, Month 12, Month 24, Month 36
7. Urine at Month 12, Month 24, Month 36
8. Saliva at Month 12, Month 24, Month 36
9. PBMC at baseline, Month 12, Month 24, Month 36

Statin Trial Study:
The following samples will be collected from approximately 550 participants:
1. Whole blood (DNA) at baseline only
2. Plasma at baseline, Month 6, Month 12, Month 18, Month 24 (4 aliquots at all study time points)
3. Serum at baseline, Month 6, Month 12, Month 18, Month 24 (8 aliquots at baseline, 4 at all others)
4. Urine at baseline

The following will likely be collected for a subset of participants; the proportion of participants providing at each time point will vary by site:
5. PBMC at baseline, Month 12, Month 24
6. Urine at Month 6, Month 12, Month 18, Month 24

5.4 Biorepository Schedule

Before receiving shipments:
1. All specimen and shipping labels will be generated by the SDCC
2. Individual LCN centers process, aliquot, and temporarily store samples in -80ºC freezer (as appropriate, depending on sample type)
3. Each center will ship samples to Biorepository on a **quarterly** basis (a staggered approach can be discussed)

Upon receiving shipments:
4. **Month 1:** Receive and organize incoming shipments from the most recent quarter using barcode scanner
5. **Month 2-3:** Pull and organize samples to send to secondary laboratories for analysis
    a. SDCC will communicate samples pull/shipment lists to Biorepository
6. **End of quarter:** Create a biorepository status report for the SDCC
7. **Month 4:** Receive next shipment

…

Twice a year: Pull 1-2 aliquots from each site for quality control analysis, to be shipped to central lab.

6.0 CLINICAL CENTER VS. BIOREPOSITORY RESPONSIBILITIES

The Clinical Centers for the Liver Cirrhosis Network studies will be expected to:
1. Implement all research study procedures as described in the LCN study protocol(s) and manual(s) of operations
2. Collect, process, and ship all LCN laboratory samples on a quarterly basis to Biorepository
3. Perform timely and accurate data collection using LCN case report forms
4. Conduct study training and certification to ensure protocol compliance
5. Maintain participant confidentiality and abide by data security procedures

6. Participate collaboratively in LCN study group meetings, including attendance at semimonthly Steering Committee meetings of Clinical Center PI/MPIs and participation on standing LCN committees and writing groups
7. Comply with all study, institutional and federal requirements for study conduct and all study activities

The Biorepository for the Liver Cirrhosis Network studies will be expected to:

1. Engage in daily communication with the SDCC
2. Receive, organize, store, and record location of sample aliquots
3. Retrieve and ship samples to secondary laboratories for additional analyses as directed by the SDCC (expected turnaround time 3 weeks from request to shipment to ancillary study destinations)
4. Enter data into the LCN REDCap database and respond efficiently to data quality checks and queries
5. Conduct sample processing training and certification to ensure protocol compliance at collection sites
6. Maintain participant confidentiality and abide by data security procedures
7. Participate collaboratively in LCN study group meetings, including attendance at Steering Committee meetings as appropriate or as invited by the LCN Executive Committee
8. Comply with all study, institutional and federal requirements for study conduct and all study activities
9. Maintain biorepository accreditation by the College of American Pathologists (CAP) or similar accreditation and utilize Standard of Procedures (SOPs) and processes that comply with the Biospecimen Repository Best Practices as defined by the International Society of Biological and Experimental Repositories-ISBER
10. Retrieve aliquots for semiannual quality control from each LCN site and send to central lab for quality control testing
11. Store and maintain samples until transfer to NIDDK after end of terminal funding period until transfer to repository specified by NIDDK

7.0 APPLICATION INSTRUCTIONS

7.1 General Instructions

Applications for Repository Proposals to join the existing Liver Cirrhosis Network should include the sections and content described in what follows. Applications should not exceed 8 pages (11pt font, 0.5" margins, single spaced), not including the cover letter and requested biosketches. Applications should be submitted electronically in .pdf format to lcn@northwestern.edu and must be received by 5pm central time on **July 25, 2022**.

All questions, including technical or budgetary/fiscal questions, should be directed via email to lcn@northwestern.edu.

It is anticipated that an incrementally funded cost-reimbursement sub-agreement will be awarded to Biorepository selected through this solicitation. The instructions below establish the minimum acceptable requirements for the format and content of the application. Northwestern University reserves the right to reject any and all applications not meeting the following minimum acceptable requirements for the format and content of the application. The application shall be signed by an individual authorized to bind the applicant organization.

7.2 Proposal Organization and Content

Please adhere to the following instructions when preparing the submission. Content covered in 7.2.2.-7.2.6 should not exceed 8 pages total.

7.2.1 Cover Letter

A cover letter should be included and signed by a person authorized to commit the applicant organization to performance of the project. The cover letter should include the following statement:

'If our site is selected as the Liver Cirrhosis Network (LCN) Biorepository, we will abide by the LCN study protocols and the study procedures.'

The LCN utilizes Advarra as the sIRB of record. All study sites have a reliance agreement in place with the Advarra. In addition, the PI and an authorized Institutional Official must provide a letter of support stating that the institution is willing to sign a standard agreement to rely on the single IRB being utilized for this study. This is in accordance with the HHS policy on the use of a single IRB for multi-site research.

7.2.2 Executive Summary
Prepare an executive summary that succinctly describes the distinguishing factors of the proposed biorepository team and personnel for serving as a LCN Biorepository.

7.2.3 Facilities and Resources
Describe the relevant facilities and resources for the organization that would support successful implementation of all aspects of the LCN studies.

7.2.4 Study Team Qualifications
Describe study team personnel qualifications, including research experience for key personnel and study team leadership, as well as research experience for all planned staff.

7.2.5 Biosketches
Provide NIH-style biosketches for all key personnel. Each biosketch is limited to 5 pages.

7.3 Budget Organization and Content
Please submit a proposed budget for the conduct of the study protocol as described in the RFP for the biorepository. A detailed budget justification should be included with the application. The proposed budget may not exceed $500,000 total per year and should span 5 years with and progressive enrollment and an anticipated start date of December 1, 2022. Budget documents will not count toward the 8-page application limit.

8.0 Evaluation Criteria
All applications will be reviewed by the LCN Executive Committee (SDCC MPIs, the LCN Study Chair and Vice-Chair, and the NIDDK Project Scientist and Program Officer, and representatives from NCI and NIAAA). Applications will be reviewed according to the content categories described above. Final selections of the Biorepository from the top-rated applicants will be made after discussion with the Ancillary Studies Committee and the Steering Committee with the LCN. Formal written critiques of submitted applications will not be returned to the applicants.