# Introduction to Ga CF P30 Proposal

Major advances in the management of pulmonary manifestations of cystic fibrosis (CF) have led to a needed redirection toward non-pulmonary comorbidities that significantly impair quality of life and reduce long-term survival. Such emerging comorbidities include chronic endocrine complications such as CF-related diabetes (CFRD), CF bone disease, gastrointestinal (GI) and hepatic manifestations, and nutrition. Furthermore, the majority of research on endocrine, GI, and nutritional outcomes was conducted before the advent of CFTR modulator therapies; therefore, new research is critically needed to address how these now-available treatments affect non-pulmonary outcomes. In addition, with increased longevity there is an additional focus on the quality of these extra years of life and in particular, modifiable factors such as exercise, diet, and other lifestyle choices, and how these behaviors impact the pulmonary complications of CF.

This application to establish the ***Georgia CF Research and Translation Core Center*** at Emory University, Georgia Tech, and Augusta University proposes to leverage the research activities of investigators across these three institutions in order to enhance the quality and length of life for the ~900 CF patients in our care programs. Four research Cores are proposed, as described below. These Cores will be supported by an Administrative Core and a Pilot & Feasibility Program. Investigators that join this effort as members of the Center will have access to the following Core Services at subsidized rates.

# Core 1: Diabetes, GI, and Nutrition Translational Core

The **overall goal** of the DGNT Core is to support the research and training of clinical, basic, and translational scientists on extra-pulmonary CF comorbidities, manifestations, and outcomes related to diabetes and other endocrinopathies, the GI/hepatic system, and nutritional status in children and adults with CF.

**Endocrine services:**

- Annual Oral Glucose Tolerance Test (OGTT) diagnostics
- Continuous glucose monitoring and interpretation
- Specialized diabetes research methodologies (euglycemic and hyperglycemic clamps, intravenous glucose tolerance tests)
- Sex steroid analysis, including estradiol, testosterone, and sex hormone binding globulin
- Vitamin D, parathyroid and calcium mineral analysis
- Bone turnover biomarker analysis
- Bone mineral density and fracture risk assessment
- Dynamic endocrine testing including ACTH stimulation and growth hormone stimulation

**Liver services**:

- HepaFat Scan®: Measure hepatic steatosis as well as may have role in essential fatty acid def analysis.
- FibroScan®: Noninvasive and quick measure of liver stiffness and steatosis. Some very interesting data about to come out from our group
- Secretin enhance MRI: superior pancreatic imaging with validated (in adults) measure of pancreatic function. Pediatric validation of pancreatic function in the works
- Emory Cholestasis Panel: Determine liver related genetic modifiers of disease

**GI services**:

- Endoscopy: Obtain biopsies for organoid development, aspiration samples to study dysbiosis or SIBO, perform pill endoscopy and perform direct pancreatic function testing
- Impedance probes: Provide information on number of reflux events, acidic vs. non-acidic and provide symptoms association with respiratory events such as cough, wheeze, etc.
- Microbiome assessment: 16S rRNA and other methods to determine gut microbiome changes
- Breath hydrogen testing: assessment of small intestinal bacterial overgrowth (SIBO)
- Electronic Patient Reported Outcome Measures (ePROMs): electronic patient reported outcomes through Medidata (using for the GALAXY study)

- Intestinal permeability/barrier function/inflammation assessments (sugar permeability studies, circulating lipopolysaccharide (LPS), immunoglobulins against LPS and flagellin, lipocalin-2, calprotectin assays, stool calprotectin, lipocalin-2 and short-chain fatty acid assays)

**Nutrition:**

- Body composition and fat distribution assessment via anthropometrics, skinfolds, DEXA, bioelectrical impedance analysis, ultrasound, air displacement plethysmography (BodPod), MRI, CT, and doubly-labeled water
- Nutrient absorption assessment via classical nutrient balance studies
- Energy expenditure and substrate (fat, CHO, protein) oxidation assessment via indirect calorimetry
- Micronutrient plasma assessment and clinical interpretation and treatment/research strategies [including fat-soluble and water-soluble vitamins (e.g. Vitamins A, D, E, K, C, B12), trace elements (e.g. zinc and copper), and minerals (e.g. magnesium and phosphorus)]
- Essential fatty acid and metabolic lipid panel (e.g, cholesterol, free fatty acids) assessment and interpretation

## Core 2: Molecular & Microbial Multi-Omics Core

The **overall goal** of the MMM Core is to provide advanced analytical capabilities for investigators engaged in CF-related research, primarily those performing studies in Core 1 or Core 3, to develop a comprehensive omics foundation for next-generation management of people with CF. Services provided by this Core will emphasize high-content analyses of samples from subjects under study via Core 1 or Core 3, along with bioinformatics approaches to analyze these results which then will be put into context of disease progression by collaboration with Core 4, the Clinical Informatics Core.

**Services provided include assays for:**

- Targeted metabolomics and lipidomics
- Glycoproteomics
- Redox biology
- Seahorse-based metabolic studies
- Insulin measurements
- Microbial metabolism
- Metatranscriptomics of host and pathogens

## Core 3: Lifestyle & Behaviors Core

The **overall goal** of the L&B Core is to bring advanced research methodologies to diet and exercise focused CF research and to accelerate translational, bio-behavioral research comprised of exercise, physical activity, diet, and sleep outcomes in people with CF. The LBC will fill a critical knowledge gap by increasing the awareness, educating and disseminating, and supporting the integration of important lifestyle and behavioral measurements and outcomes into clinical investigations of both children and adults with CF.

**Exercise and Physical Activity Services**

1. Cardio-pulmonary exercise testing in children and adults
    a. Godfrey protocol – The testing protocol used in people with CF
    b. Exercise capacity – Gold standard assessment that uses a metabolic cart
        i. $VO_2$ max
        ii. $VO_2$ peak
    c. Ventilatory equivalents – Additional indices of exercise efficiency that can provided independent prognostic value
        i. $VE/VO_2$
        ii. VE/VCO2

   d. Anaerobic threshold – The point during testing where aerobic metabolism shifts to anaerobic metabolism
   e. Oxygen uptake kinetics – Additional indices of exercise efficiency that are effort independent
      i. $VO_2$ response time
      ii. Functional $VO_2$ gain ($\Delta VO_2/\Delta WR$)
2. Daily Physical Activity – Free living assessment of the individuals physical activity patterns
   a. Actigraphy – the method for collecting daily physical activity
      i. Tri-Axial accelerometry – multi-plane assessments
      ii. Moderate to vigorous physical activity –assessment of intensity dependent physical activity
      iii. Sedentary time – Quantification of physical inactivity
3. Handgrip Strength – Shown to correlate with whole body muscle strength and correlates with clinical outcomes and overall health.
4. Standardized submaximal exercise testing
   a. Six minute walk test (6MWT)
   b. 5x Sit to Stand
   c. Timed wall squat test
   d. Step test
5. Analysis and interpretation of Exercise and physical activity data
6. Study design integrating exercise and physical activity outcomes
7. Assistance with disseminating findings

**Diet related services:**

1. Dietary assessment (data collection and nutrient analysis)
   a. Triple pass 24-hour recalls (gold standard) to precisely measure recent intake and estimate nutrient intake using the *National Data System for Research (NDSR)*
   b. Food frequency questionnaires/screener to assess longer term usual intake
      i. *Block diet questionnaires and screeners* for adults and children
   c. Observations to assess diet in children of all ages and cognitive abilities
   d. Diet quality scoring (diet quality scores, Alternate Healthy Eating Index (aHEI), Dietary Approach to Stop Hypertension (DASH), and Alternate Mediterranean Diet Score (MDS) calculated from FFQ output.
   e. Beverage intake assessments
      i. *BevQ15*- Rapid assessment of beverage intake among adults

**Behavior Related Services**

1. Other lifestyle/behavior assessments
   a. *Graphs for Recalling Activity Time (GReAT),* a physical activity self-report recall instrument developed for school-aged children.
2. Home environment assessments
   a. *Home Self-Administered Tool for Environmental Assessment of Activity and Diet Family Food Practices Survey.*
   b. *Home Environment Survey (HES*) to assess availability, accessibility, parental role modelling, and parental policies related to PA resources, fruits and vegetables (F&V), and sugar sweetened drinks and snacks (SS).
3. Research updates on diet behavior modification best practices
4. Diet intervention study design consulting
5. Guidance on behavior change messaging and related interventions
6. Analysis of dietary data
   a. Primary data from research projects

b. Secondary data from existing datasets

**Sleep Services**

1. Actigraphy – Validated method to determine sleep outcomes that correlate with sleep studies.
    a. Sleep efficiency – The quality of sleep
    b. Awake time – The amount of time spent awake during the night
    c. Wake after sleep onset -
    c.

## Core 4: Clinical Informatics Core

The **overall goal** of the CI Core is to provide a comprehensive, multi-disciplinary resource for the design and analysis of CF-related clinical and translational research studies focused on diabetes, other endocrine disorders, digestive and hepatic disorders, nutrition, and lifestyle choices. This will be accomplished by utilizing appropriate and innovative statistical methodology and through the development and maintenance of a high-quality relational research database. The CI Core will allow CF investigators to have a formalized, ongoing, and collaborative relationship with an outstanding team of biostatisticians, data scientists, clinician experts in CF care, and database engineers.

**Service 1**

***Goal:*** To provide clinical and statistical consulting and collaboration on the design and conduct of all project research studies and cores.

***Rationale:*** By providing our CF researchers access to clinical experts, biostatisticians, and data scientists during the planning stages of a study, we will improve the design and conduct of the study, while increasing efficiency and scientific rigor.

***Services:***

- Sample size/power calculations
- Methods for randomization and study implementation
- Study design
- Clinical input on cohort selection
- Review the integrity and statistical soundness of all studies involving human subjects
- Provide statistical plans for interim reviews and final analysis
- Provide support for data safety monitoring plans and boards
- Work with the administration core and clinical investigators on recruitment and retention plans
- Collaborate with each investigative team on the development of a manual of procedures for each research study to help ensure compliance with a scientifically sound protocol
- Evaluation of specimens and materials available within the CFBR and clinical phenotyping of subjects at specimen collection

**Service 2**

***Goal:*** Provide oversight of all human-subject CF research through the Scientific Advisory Council (SAC).

***Rationale:*** We are a large-scale diverse research network with several projects that may have competing interest and/or overlapping patient populations. The goal the SAC is to maximize information gather from patients involved in research protocols will encouraging multi-disciplinary collaboration among investigators.

***Services:***

- Ensure the feasibility and scientific merit of all new prospective human-subjects research studies being conducted in our CF research network
- Approve and allocate resources to CF projects including use of other core services and research coordinators within the network
- Assist researchers with regulatory research components including IRB submission, data use agreements, material transfer agreements

**Service 3**

***Goal:*** To facilitate, direct, and participate in statistical analysis between fellow cores and across our diverse CF research network.

***Rationale:*** Providing comprehensive statistical support to CF researchers is an indispensable resource needed for clinical and translation research studies.

***Services:***

- Coordinate and manage statistical activities in the projects to ensure that investigators have ready access to statistical consultation and support
- Provide timely statistical analysis support to ensure the completion of the primary results paper from each project by the time of study completion
- Assist with the writing of statistical components of manuscripts and creation of publication-ready tables and figures

**Service 4**

***Goal:*** To provide, manage and maintain a high-quality research database that supports the research projects and cores and ancillary studies, while preserving the confidentiality of all subject data.

**Rationale:** A centralized, relational database is need to ensure the quality and validity of research data collected across an extensive CF research network.

**Services:**

- Provide computer-based tools that facilitate the efficient and secure collection, storage and retrieval of the data generated in the proposed research, thereby creating and maintaining a centralized relational database that provides access to common resources and information
- Ensure the accuracy of the data maintained in the database by software based data consistency and quality control systems.
- Organize and maintain the database to maximize accuracy and accessibility, while maintaining strict confidentiality.
- Provide detailed descriptions of the available populations and resources for current and future investigators
- Provide high-quality electronic data capture (EDC) systems and CRF design.
- Generate monthly reports to help the investigative team monitor and maintain data completeness during follow-up and achieve high data capture performance standards by minimizing missed scheduled clinical visits, preventing missing data and maintaining high cohort retention rates

## Other Cores: Administrative Core, Pilot & Feasibility Program

**If you are interested in joining this research team, please send a brief note to Ms. Nicole Crowell, Grant Proposal Development Associate, Department of Pediatrics, at: nicole.lee.crowell@emory.edu. Other questions can be sent to Dr. Nael McCarty at namccar@emory.edu.**