Principal Investigator: Michael Rickels, MD., MS., Andrea Kelly, MD., MSCE.

Study Title: Emergence and Progression of Abnormal Glucose Tolerance in Cystic Fibrosis (Aim 1)

Purpose:
This is a matched prospective longitudinal observational study evaluating insulin secretion and glucose excursion. We hope to better understand the emergence and progression of abnormal glucose tolerance in pancreatic insufficient cystic fibrosis and to test a potential strategy of restoring β-cell function.

The primary objective of this study is to examine the association of change in β-cell secretory capacity with emergence and progression of abnormal glucose tolerance over 7 years in Pancreatic Insufficient Cystic Fibrosis (PI-CF) youth and adults without baseline Cystic Fibrosis Related Diabetes (CFRD).

Brief Description
This Longitudinal research study is being done to test how high blood sugar develops and worsens over time in some people with cystic fibrosis. Participants must have Pancreatic Insufficient Cystic Fibrosis, and must not have Diabetes.

About 70 participants from the Children’s Hospital of Philadelphia (CHOP), the Hospital of the University of Pennsylvania (HUP), and the local region will participate in the study. Participation can last for up to 7 years.

VISIT SCHEDULE:
The attached table provides a description of the proposed study long-term visit schedule.

Actual study visit scheduling may vary slightly depending on participant availability, lab availability, and the availability of procedure results in a participant’s electronic medical record. There will be a “Year 7” visit offered to participants who only completed 2 of the 4 visits within the first 5 years, so that every subject has at least 3 completed visits.

DESCRIPTIONS:
Mixed Meal Tolerance Test (MMTT): This test will look at a body’s response to food. After the participant has eaten a breakfast made up of a specific combination of calories, protein, and carbohydrates. Samples will be drawn from an IV at specific time-points over a 4 hour period.

Whole body DXA: A special x-ray of the body
Glucose Potentiated Arginine Test (GPA): This test will measure the insulin and other glucose controlling hormones, which will assist in evaluating pancreas cell function. Arginine is a naturally occurring amino acid (substance in our bodies). In the study it is given in an IV to make the cells of the participants’ pancreas secrete the hormone insulin. This test takes about 6 hours to complete.

Eligibility
MAIN INCLUSION CRITERIA
- Male and female subjects age ≥6 and ≤50 years on date of consent.
- Subjects able to provide written informed consent, and, as applicable child assent and/or parental/guardian permission.
- Confirmed diagnosis of CF, defined by positive sweat test or CFTR mutation analysis according to CFF diagnostic criteria.
- Pancreatic insufficiency defined by clinical requirement for pancreatic enzyme replacement.
- OGTT consistent with Normal Glucose Tolerance (NGT), Early Glucose Intolerance (EGI), or Impaired Glucose Tolerance (IGT) within the previous 6 months.

MAIN EXCLUSION CRITERIA
- Established diagnosis of non-CF diabetes (e.g. type 1 diabetes) or CFRD.
- New diagnosis of CFRD based on a 2-hour OGTT glucose ≥200 mg/dL at baseline; individuals who develop CFRD
during study participation are of particular interest and will not be excluded

- Prior lung or liver transplant.
- Severe CF liver disease, as defined by portal hypertension.
- Fundoplication-related dumping syndrome.
- History of any illness or condition that, in the opinion of the investigator might confound the results of the study or pose an additional risk to the subject.
- Pulmonary exacerbation requiring IV antibiotics or systemic glucocorticoids within 4 weeks prior to study procedures.
- Hemoglobin < 10g/dL, most recent within 180 days of study procedures or at screening.
- Abnormal renal function, most recent within 180 days of study procedures or at screening; defined as creatinine > 2x upper limit of normal (ULN) or potassium > 5.5mEq/L on non-hemolyzed specimen.
- Inability to perform study specific procedures (MMTT, GPA).
- Parents/guardians or subjects who, in study team opinion, may be non-compliant with study procedures.
- For female subjects, a positive urine pregnancy test performed prior to DXA scan, at which point a positive test will result in withdrawal from the study.

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<th>Compensation (if applicable)</th>
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<td>Participants will be compensated as follows:</td>
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<td>$75 for the screening visits involving an Oral Glucose Tolerance Test (OGTT)</td>
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<tr>
<td>$200 for visits involving a Mixed Meal Tolerance Test (MMTT,)</td>
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<tr>
<td>$200 for visits involving Glucose Potentiated Arginine Test (GPA).</td>
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At the University of Pennsylvania, you will receive payment using a visa gift card. The gift card will be given to you by the study team at your first visit and will be loaded in an ongoing manner throughout the study at the completion of your visits.

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<tr>
<th>Name</th>
<th>Kathryn Gallagher</th>
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<tbody>
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