Title:	**Feasibility and Acceptability of Home Use of Continuous Glucose Monitors for Type 2 Diabetes Risk Evaluation in Youth**
Short Title	**CGM for T2D Risk Evaluation**
Drug or Device Name(s):	N/A
FDA IND	N/A
Regulatory Sponsor:	N/A
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ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
CAYAH	Center for Adolescent and Young Adult Health
BMI	Body mass index
CGM	Continuous glucose monitor
PCTRC	Pediatric Clinical and Translational Research Center
PHI	Protected Health Information
SAE	Serious adverse event
T2D	Type 2 Diabetes
OGTT	Oral glucose tolerance test
HbA1c	Hemoglobin A1c

ABSTRACT

Context: Youth-onset type 2 diabetes (T2D), an increasingly common and aggressive disease that disproportionately impacts racial and ethnic minorities, presents several diagnostic challenges.The screening tests currently used in practice, including hemoglobin A1c (HbA1c), fasting glucose, and 2-hour oral glucose tolerance test (OGTT), have significant drawbacks. Real-time continuous glucose monitors (CGM) are promising new tools for risk stratification in individuals with dysglycemia, but whether use of CGMs to evaluate type 2 diabetes risk in free-living youth is feasible and acceptable to patients and families is unknown.

Objectives: The primary objective is to determine the feasibility of CGM-based type 2 diabetes risk evaluation in youth, as measured by adequacy of CGM data capture and nutrition logging quality and completion during at-home glucose challenge. Secondary objectives are to determine the test performance characteristics of at-home, CGM-measured glucose challenge as compared to a gold-standard laboratory-based 2-hour OGTT; and to determine the acceptability of use of CGM for at-home dysglycemia evaluation as an alternative to clinical 2-hour OGTT.

Study Design: prospective observational study

Setting/Participants: Pubertal or post-pubertal 8-18 year-old children and adolescents with overweight/obesity (BMI≥85th percentile for age/sex, or ≥25 kg/m2 if =18 years old), who have or are at risk for prediabetes or type 2 diabetes, and attend the Endocrinology or Adolescent Medicine outpatient clinic at the Children's Hospital of Pittsburgh; 40 participants will be recruited.

Study Interventions and Measures: Vitals, body size measurement, pubertal status, medical history, and laboratory assessments including oral glucose tolerance test and hemoglobin A1c will be assessed at one in-person study visit after overnight fast. Participants will wear continuous glucose monitor and wrist-worn actigraphy device for physical activity and sleep measurement for 10 days beginning on the day of the study visit, then return the monitors by mail. During the 10 day wear period, participants will respond to text message-based surveys to document food intake, physical activity, and sleep times and will complete two at-home challenges: 1) glucose challenge using study-provided glucose beverage that is identical to that they consume during clinical oral glucose tolerance test; and 2) food challenge with mixed carbohydrate/fat/protein-containing food of their choice. Glucose trends during these at-home challenges will be compared with oral glucose tolerance test obtained during the study visit. Individual interviews will be conducted upon completion of CGM wear to assess acceptability of the use of at-home glucose challenge and CGM wear as a strategy to evaluate diabetes risk in youth.

PROTOCOL SYNOPSIS

Study Title	Feasibility and Acceptability of Home Use of Continuous Glucose Monitors for Type 2 Diabetes Risk Evaluation in Youth
Funder	Institutional funds
Study Rationale	Youth-onset type 2 diabetes (T2D), an increasingly common and aggressive disease that disproportionately impacts racial and ethnic minorities, presents several diagnostic challenges. The rapid loss of glycemic control soon after T2D diagnosis makes early identification an important goal in pediatrics, and risk-based screening has been recommended for children for over two decades. However, the screening tests currently used in practice, including hemoglobin A1c (HbA1c), fasting glucose, and 2-hour oral glucose tolerance test (OGTT), have significant drawbacks. Real-time continuous glucose monitors (CGM) are promising new tools for risk stratification in individuals with dysglycemia. These patient-worn medical devices measure interstitial glucose every 5 minutes and offer glimpses into an individual's everyday life, which may include consumption of carbohydrates in amounts larger than that assessed in an OGTT, enhancing test sensitivity. Whether use of CGMs to evaluate type 2 diabetes risk in free-living youth is feasible and acceptable to patients and families is unknown. Assessment of CGM with standardized, but practical, home-based glucose and mixed-meal challenges is needed to determine facilitators and barriers to use of this technology-driven approach in clinical practice. Without advancement in the approach to screening for youth-onset T2D, there is ongoing risk of failure to understand which individuals are at highest risk for complications and could benefit the most from intervention early in the disease process.
Study Objective(s)	**Primary**: to determine the feasibility of CGM-based type 2 diabetes risk evaluation in youth, as measured by adequacy of CGM data capture and nutrition logging quality and completion during at-home glucose challenge. **Secondary**: to determine the test performance characteristics of at-home, CGM-measured glucose challenge as compared to a gold-standard laboratory-based 2-hour OGTT; to determine the acceptability of

	use of CGM for at-home dysglycemia evaluation as an alternative to clinical 2-hour OGTT
Study Design	Prospective observational study
Subject Population **Key criteria for Inclusion and Exclusion:**	**Inclusion Criteria** 1. Any gender, age 8-18 years 2. Tanner 2 or higher pubertal development 3. Overweight or obese (BMI ≥85th percentile for age/sex, or ≥25 kg/m^2 for participants =18 years) 4. A) No previously documented abnormal HbA1c or glucose but at higher risk for T2D based on race/ethnicity (Black, Hispanic, Asian, Native American, Pacific Islander), diagnosis with dyslipidemia, hypertension, polycystic ovary syndrome, presence of acanthosis nigricans, or first degree relative with T2D (n = 15); *or* B) previously documented (within 6 months) HbA1c 5.7-7.0%, fasting glucose ≥100 mg/dL, or 2-hour plasma glucose on OGTT of ≥140 mg/dL (n = 25) 5. Consent (adult subjects), parental/guardian permission (if applicable), assent (if applicable) 6. Willingness to wear ActiGraph watch and CGM continuously for 10 day study duration **Exclusion Criteria** 1. Current or recent (within 1 month) use of diabetes-related medication 2. Current use of hydroxyurea (due to interference with CGM) 3. Known type 1, cystic fibrosis-related, or medication-induced diabetes 4. Potential subject unable to speak or read in English 5. Severe cognitive impairment 6. Current or previous pregnancy
Number Of Subjects	40 total, all at Children's Hospital of Pittsburgh
Study Duration	Each participant will attend 1 in-person study visits that will last 2.5-3 hours, followed by 10 days of continuous CGM wear at home. The entire study is expected to last approximately 1 year, from July 1, 2022 – June 30, 2023.

Study Phases	**Screening and recruitment**: Potential subjects will be identified via review of Endocrinology clinic schedules weekly and by using the Research Interest Form distributed by Adolescent medicine. After potential subjects are identified, they will be contacted along with their parents/guardians (as applicable), to screen for eligibility. Subjects will be consented and will be scheduled for a morning study visit at the Pediatric Clinical and Translational Research Center (PCTRC). They will be instructed to complete an overnight 10 hour fast at home prior to the study visit. **Study Visit 1:** Participants will undergo physical examination by a pediatric endocrinologist, anthropometrics, vital signs measurement, questionnaires (medical, family, social history), and 2-hour oral glucose tolerance test (OGTT). Dexcom G6 Pro (blinded, no data visible to participant) CGM will be placed on the participant's abdomen by trained study staff. Participants (or their parent) will be registered for text message-based surveys and will be instructed on nutrition, activity, and sleep logging to be completed during the 10-day CGM wear period. Participants will be provided with a wrist-worn actigraphy device (ActiGraph GT9X Link) to wear continuously during the 10-day period for collection. **10-day Observation Period**: Participants will be instructed to participate in their typical daily routines, with the exception of two at-home challenges: 1) glucose, and 2) mixed-meal. The ***at-home glucose challenge*** will serve as the primary comparison to the laboratory-measured OGTT. For this challenge, participants will be asked to drink the same glucose solution (Trutol) consumed as part of the OGTT at PCTRC and provided with the appropriate weight-based amount. They will be instructed to choose a day between days 3 and 9 of the study period during which they will be able to fast for at least 10 hours, drink the glucose beverage over the course of 5 minutes, and then be inactive for 2 hours. They will log the date and time of glucose ingestion. For the ***at-home mixed-meal challenge***, participants will be asked to choose a day between study days 3 and 9, separate from the glucose challenge day, during which they will be able to fast for at least 10 hours, eat a snack or meal with at least 50 grams of carbohydrate as well as fat and protein content, and then be inactive for 2 hours. All participants and families will be instructed on

	determination of carbohydrate content using example foods that they typically consume. *Text message-based surveys*: Participants will be sent surveys 3 times daily via text message, inquiring about food and drink intake, physical activity, and time in bed (start/stop times). *Study completion*: On day 10 of CGM wear (or earlier in case of discomfort), participants will remove the sensor and transmitter at home by simply peeling off the device. Transmitter and ActiGraph will be returned to the study team by participants using prepaid shipping envelopes or in-person if preferred. Upon receipt of the transmitter and ActiGraph, participants will receive compensation for participation in the study ($100). *Individual interview and disordered eating questionnaire*: Upon completion of CGM wear, participants, with or without their parents at the discretion of the research team, will be invited to participate in a 20-minute semi-structured interview via phone or videoconferencing platform to assess the acceptability of CGM use as an alternative to clinical OGTT for diabetes risk assessment. Interviews will be conducted by study staff and will be audio-recorded and professionally transcribed. After completion of the interview, participants will be asked to complete a brief, 12-item questionnaire related to disordered eating behaviors in the past 28 days. This will be completed via REDCap. Participants will be allowed to skip questions if they are uncomfortable answering. Participants will be compensated $15 for completion of the interview.
Efficacy Evaluations	Feasibility and acceptability of CGM with at-home glucose challenge as compared to clinical OGTT
Safety Evaluations	Adverse events are not anticipated. Ingestion of the glucose beverage uncommonly leads to nausea/vomiting. Mild skin irritation may result from use of adhesives for CGM placement. OGTT evaluation may result in recognition and diagnosis of previously unknown diabetes; results will be shared with participants. Any AEs and SAEs will be reported to IRB within the allotted timeframe.

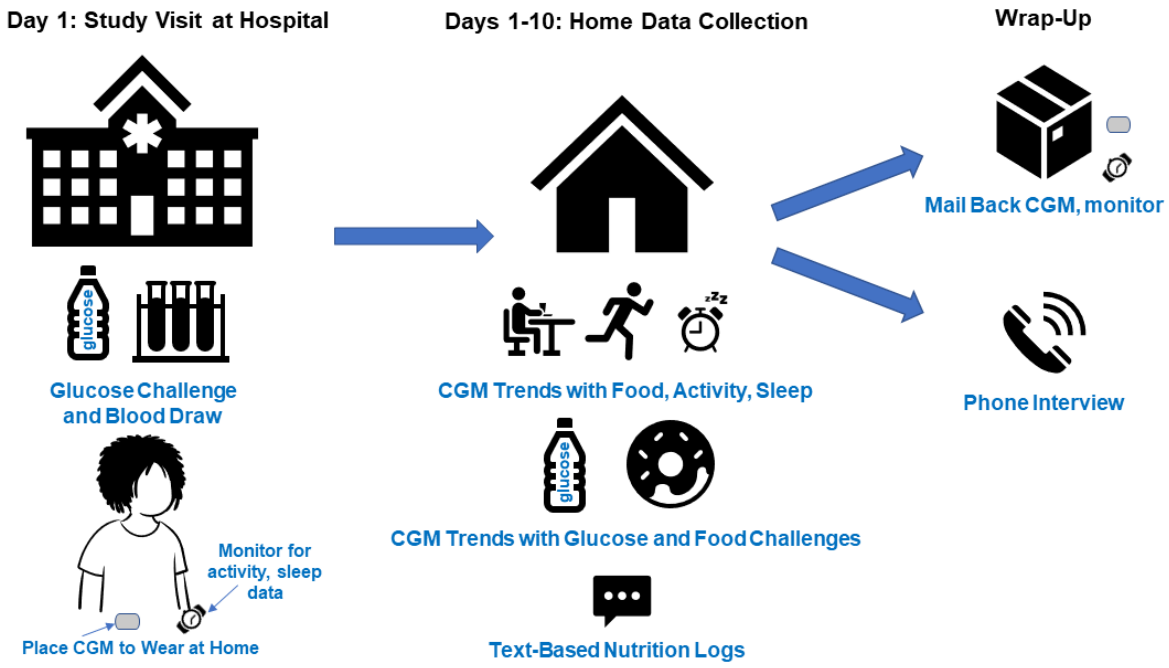
Statistical And Analytic Plan	Demographic and clinical characteristics will be described using summary statistics, including means, standard deviations, medians, and ranges for continuous variables, and frequencies for categorical variables. Analyses will be conducted using Stata 17 (StataCorp, College Station, TX). Raw actigraphy data will be processed using GGIR, a package in R: A language and environment for statistical computing (R Corp Team, Vienna, Austria). The significance level for two-sided hypothesis testing will be set at 0.05. To assess completeness of CGM data, the number of days with adequate CGM data will be divided by 9, omitting the first 24 hours due to possible inconsistent measurements after initial placement. Feasibility will be defined as ≥ 80% (7.2) of days with data. To assess completeness of glucose and mixed-meal challenge documentation, the number of participants who document the date and time of glucose and mixed-meal ingestion (including mixed-meal content) will be determined and divided by the total number of participants (40). Feasibility will be defined as ≥80% of participants documenting date and time of either the glucose challenge, mixed-meal challenge, or both. To evaluate test performance characteristics, sensitivity, specificity, and positive and negative predictive values of glucose on CGM 2 hours after at-home glucose beverage ingestion (CGM-2h) to predict OGTT-2h≥140 mg/dL will be assessed for various thresholds of CGM-2h. Area under the receiver operating characteristic curve (AUC) will be determined. An AUC threshold of ≥0.7 will be used to define adequate discrimination. Acceptability will be rated on a Likert scale (1: completely unacceptable, 2: mostly unacceptable, 3: neutral, 4: mostly acceptable, 5: completely acceptable). Acceptability will be defined as a mean score for all participants of ≥3. Interview transcripts will be reviewed by study staff trained in qualitative analysis. Content analysis will be used to identify themes and sub-themes.
DATA AND SAFETY MONITORING PLAN	The study team will be responsible for data management and collection and are responsible for the accuracy and completeness. Only investigators and study team members that have completed appropriate IRB training/approval are eligible to collect and work on information collected from this study. Data will be entered directly into REDCap by the study team or by

	participants when responding to surveys. In order to guard against disclosure of PHI, each study participant will be assigned a unique identification code. The code will be kept in a password-protected file on the PI's UPMC-managed secure server.

TABLE 1: SCHEDULE OF STUDY PROCEDURES

Study Phase	**Screening (Phone or in-person)**	**Study Visit (PCTRC)**	**Observation Period (Home)**	**Interview (Phone)**	**Return of CGM and ActiGraph (mail)**
Study Days		1	1-10	Within 4 weeks after Study Visit	Upon completion of CGM wear
Review Inclusion/Exclusion Criteria	X	X		X	
Written Documentation of Consent/Assent	X	(X if not obtained prior)			
Demographics/Medical History		X			
Physical Examination		X			
Vital Signs: BP, HR, RR		X			
Anthropometry		X			
Urine Pregnancy Test		X			
Prior/Concomitant Medications		X			
2-hour OGTT, HbA1c		X			
Place CGM, give ActiGraph to wear		X			
Wear CGM, ActiGraph			X		
Respond to surveys			X		
Individual interview,questionnaire				X	
Adverse Event Assessment			X	X	
Return CGM, ActiGraph					X
Upload CGM, Actigraphy data					X

FIGURE 1: STUDY DIAGRAM



2 BACKGROUND INFORMATION AND RATIONALE

2.1 Introduction

Youth-onset type 2 diabetes (T2D), an increasingly common and aggressive disease that disproportionately impacts racial and ethnic minorities, presents several diagnostic challenges. Unlike type 1 diabetes, type 2 diabetes may occur asymptomatically while still contributing to complications including nerve damage, blindness, and kidney failure. Early identification and targeted lifestyle intervention for those at risk for T2D has proven effective in adults.(Knowler, Barrett-Connor et al. 2002) Although similar efficacy data is lacking in youth, the rapid loss of glycemic control soon after T2D diagnosis(Group, Zeitler et al. 2012) makes early identification an important goal in pediatrics, and risk-based screening has been recommended for children for over two decades.(American Diabetes Association Professional Practice, American Diabetes Association Professional Practice et al. 2022) However, the screening tests currently used in practice, including hemoglobin A1c (HbA1c), fasting glucose, and 2-hour oral glucose tolerance test (OGTT), have notable drawbacks. Fasting tests, particularly the time-intensive 2-hour OGTT, are often impractical to complete, while the non-fasting HbA1c is an indirect measure of glycemia that is unreliable in the setting of abnormal hemoglobin or atypical blood cell turnover.

Real-time continuous glucose monitors (CGM) are promising new tools for risk stratification in individuals with dysglycemia. These patient-worn medical devices measure interstitial glucose every 5 minutes and are increasingly used in clinical practice for diabetes management, particularly for type 1 diabetes. This technology offers glimpses into an individual's everyday life, which may include consumption of carbohydrates in amounts larger than that assessed in an OGTT, enhancing test sensitivity. Whether use of CGMs to evaluate type 2 diabetes risk in free-living youth is feasible and acceptable to patients and families is unknown. Assessment of CGM with standardized, but practical, home-based glucose and mixed-meal challenges is needed to determine facilitators and barriers to use of this technology-driven approach in clinical practice. Without advancement in the approach to screening for youth-onset T2D, there is ongoing risk of failure to understand which individuals are at highest risk for complications and could benefit the most from intervention early in the disease process.

The overall objective for this study is to determine whether CGM paired with technology-driven health behavior data collection is a feasible and acceptable approach to T2D screening for youth and their caregivers. The central hypothesis is that CGM, text message-based surveys, and home-based glucose challenge will allow for accurate classification of diabetes risk while providing an acceptable alternative to clinical OGTT for families. Previous research has demonstrated the strong correlation between several CGM indices and HbA1c or 2-hour glucose on OGTT in youth with obesity and dysglycemia,(Chan, Pyle et al. 2015) and home-based glucose challenge with CGM appears promising for use in adults across the glycemia spectrum.(Dehghani Zahedani, Shariat Torbaghan et al. 2021) Determination of the feasibility and acceptability of CGM with home-based glucose challenge in youth at risk for T2D will pave the way for a new screening method that minimizes family burden while maximizing data quality and ability to accurately risk-stratify.

2.2 Name and Description of Intervention

This study will compare laboratory-measured glucose after oral glucose tolerance test to CGM-measured glucose after at-home glucose challenge, as well as assess the feasibility and acceptability of this approach to T2D risk assessment in youth.

2.3 Relevant Literature and Data

Type 2 diabetes (T2D), an obesity-related disease once limited to adults, has become increasingly common in youth over the past two decades.(Divers 2020, Lawrence, Divers et al. 2021) Prevalence of youth-onset T2D is highest among racial and ethnic minorities, a disparity that will widen due to a more rapidly rising incidence in minority youth as compared with non-Hispanic white youth.(Mayer-Davis, Lawrence et al. 2017) Youth-onset T2D is associated with numerous severe health outcomes, including an 80% cumulative incidence of microvascular comorbidities such as kidney, retinal, and nerve disease within 15 years of diagnosis.(Group, Bjornstad et al. 2021) Pregnancy outcomes for adolescent and young adult women with T2D are incredibly poor, with a 25% rate of pregnancy loss and 33% rate of preterm birth.(Group 2021) Due to the severe complications of youth-onset T2D, the American Diabetes Association recommends a risk-based screening approach, targeting youth ages 10 and older (or earlier if pubertal) with overweight or obesity who have at least one additional risk factor including race/ethnicity (African American, Native American, Latino, Asian American, Pacific Islander), maternal history of gestational diabetes, family history of T2D in a first- or second-degree relative, or signs of insulin resistance or associated condition (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight).(American Diabetes Association Professional Practice, American Diabetes Association Professional Practice et al. 2022) However, the screening tests currently used in practice, including hemoglobin A1c (HbA1c), fasting glucose, and 2-hour oral glucose tolerance test (OGTT), have notable drawbacks. Fasting tests, particularly the time-intensive 2-hour OGTT, are often impractical to complete, while the non-fasting HbA1c is convenient (Lee, Eason et al. 2014) but is an indirect measure of glycemia that is unreliable in the setting of abnormal hemoglobin or atypical blood cell turnover and is a more expensive test than plasma glucose.(Wu, Kazzi et al. 2013, Vajravelu and Lee 2018)

Real-time continuous glucose monitors (CGM) are a promising new tool for risk stratification in individuals with dysglycemia. These patient-worn medical devices measure interstitial glucose every 5 minutes and are increasingly used in clinical practice for diabetes management. This technology offers glimpses into an individual's everyday life, which may include consumption of carbohydrates in amounts larger than that assessed in an OGTT, enhancing test sensitivity. In an observational study of 98 youth with obesity, prediabetes, or T2D who wore CGM for 48 hours, free-living glycemia was highly correlated (r=0.5) with both HbA1c and OGTT.(Chan, Pyle et al. 2015) Although this study demonstrated strong correlations between CGM indices and traditional testing strategies, it consisted of only 2 days of data, without standardized home glucose or mixed-meal challenge. A study in adults across the glucose and dysglycemia spectrum, including non-insulin treated T2D, prediabetes, and normal glucose, did evaluate home glucose and mixed-meal challenges during 10-day CGM wear and demonstrated diabetes-range glucose excursions even in participants with self-reported prediabetes.(Dehghani Zahedani, Shariat Torbaghan et al. 2021) This study did not directly compare home glucose challenge results with laboratory-measured OGTT, however.

The potential acceptability and safety of use of CGM among adolescents with obesity as a behavior modification tool has been shown in a pilot study evaluating time-limited eating and CGM use.(Vidmar, Naguib et al. 2021) To our knowledge, no studies have evaluated home-based glucose challenges using CGM in adolescents at risk for T2D. If feasible and acceptable, this strategy could improve access to critical health evaluations, minimizing patient and family burden while providing rich glycemic data to guide treatment decisions. Whether use of CGMs to evaluate T2D risk in free-living youth is feasible and acceptable to patients and families is unknown. Without advancement in the approach to screening for youth-onset T2D, it will remain challenging to accurately determine which individuals are at highest risk for complications and could benefit the most from targeted, intensive lifestyle interventions.

An additional important research question relates to the impact of disordered eating, most notably loss-of-control (LOC) eating, on glycemia. Disordered eating, including the consumption of objectively large amounts of food in one sitting, is common among youth with obesity and type 2 diabetes (TODAY Study Group 2011). The amount of carbohydrate and other nutrients consumed in a real-life, non-lab setting may be significantly larger than that provided in a standard oral glucose tolerance test, potentially leading to greater discrepancy between at-home and lab-based measures of glycemia in youth with disordered (LOC) eating than those without this tendency.

2.4 Compliance Statement

This study will be conducted in full accordance all applicable Children's Hospital of Pittsburgh and University of Pittsburgh Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46. All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent, and will report unanticipated problems involving risks to subjects or others in accordance with institutional Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

3 STUDY OBJECTIVES

The purpose of the study is to determine the feasibility and acceptability of CGM-based at-home glucose challenge as an alternative to clinical OGTT for T2D risk assessment in youth.

3.1 Primary Objective

The primary objective is to determine the feasibility of at-home CGM-based glycemia evaluation as measured by adequacy of CGM data capture and nutrition logging quality and completion.

3.2 Secondary Objectives

The secondary objectives are to:

- determine the test performance characteristics of at-home, CGM-measured glucose challenge as compared to a gold-standard laboratory-based 2-hour OGTT
- to determine the acceptability of use of CGM for at-home dysglycemia evaluation as an alternative to clinical 2-hour OGTT

4 INVESTIGATIONAL PLAN

4.1 General Schema of Study Design

This prospective observational study will include screening by phone or in-person, completion of one in-person study visit, completion of 10 days of CGM wear and survey completion at home, one at-home glucose challenge and one at-home mixed meal challenge, and one phone interview.

4.1.1 Screening Phase

Potential subjects will be identified through weekly review of Pediatric Endocrinology and Diabetes clinic schedules. In addition, a list of potentially eligible patients will be generated via review of a list of patients with diagnosis of prediabetes or obesity and insulin resistance from current and previous research conducted by the PI or the PI's mentor, Dr. Silva Arlsanian. The Wellness and Obesity Registry, monitored by Dr. Silva Arslanian, will be used to screen for potential subjects as well.The CAYAH RESEARCH INTEREST FORM will also be used for recruitment purposes. This is a REDCap form with a survey link that will contain questions for adolescents to answer self-screen questions which are non-sensitive. Center for Adolescent and Young Adult Health (CAYAH) clinical staff will manage and distribute this survey. CAYAH clinical research staff will advertise the study to the teen. If the teen (age 13 or older) indicates interest in the study by viewing the study advertisement within the CAYAH RESEARCH INTEREST FORM, they will provide their contact information to the CAYAH clinical research staff who will then share it with the study team. Medical records of potential subjects will be screened by the study team using the protocol inclusion and exclusion criteria. Those who appear to meet the criteria will be approached by a member of the study team by phone, email, or in-person and asked if they would like to hear about the study. Subjects and/or their parent/guardian will provide demographic, social, and medical information about themselves, their child, or family (as applicable) to confirm eligibility.

4.1.2 Study Visit

After study procedures are reviewed and questions answered, written informed consent and assent (participants<18) will be obtained if not already obtained electronically via REDCap. Participants will arrive after overnight fast (minimum 10 hours) and will undergo physical examination by a pediatric endocrinologist as well as anthropometrics, vital sign measurement, questionnaires (medical, family, social history), and 2-hour OGTT performed according to American Diabetes Association criteria.(American Diabetes Association Professional Practice, American Diabetes Association Professional Practice et al. 2022) After baseline (time 0) venous blood sample, participants will ingest glucose solution (1.75 g/kg body weight, max 75g) within 5 minutes or less. Additional venous blood samples will be obtained at timed intervals after ingestion to determine plasma glucose, insulin, and c-peptide

(30, 60, 90, 120 min) . HbA1c will also be measured (one venous blood sample). During OGTT, Dexcom G6 Pro (blinded, no data visible to participant) CGM will be placed on the participant's abdomen by study staff trained in CGM placement. Participants will be assigned a unique study ID for use with Dexcom and survey collection. Participants (or their parent if the participant does not have a phone with text messaging capability) will also be registered for text message-based surveys via Mosio, a text messaging platform for clinical research, and will be instructed on nutrition, activity, and sleep logging to be completed during the 10-day CGM wear period. Paper logbooks will be provided for use in case of technical difficulties with texts. Participants will be provided with a wrist-worn actigraphy device (ActiGraph GT9X Link) to wear continuously during the 10-day period for collection of objectively measured activity and sleep data to define periods of eating, overnight fasting, and exercise.

4.1.3 Observation Period

Participants will be instructed to participate in their typical daily routines, with the exception of two at-home challenges: 1) glucose, and 2) mixed-meal. The ***at-home glucose challenge*** will serve as the primary comparison to the laboratory-measured OGTT. For this challenge, participants will be asked to drink the same glucose solution (Trutol) consumed as part of the OGTT at PCTRC and provided with the appropriate weight-based amount. They will be instructed to choose a day between days 3 and 9 of the study period during which they will be able to fast for at least 10 hours, drink the glucose beverage, and then be inactive for 2 hours. They will log the date and time of glucose ingestion. For the ***at-home mixed-meal challenge***, participants will be asked to choose a day between study days 3 and 9, separate from the glucose challenge day, during which they will be able to fast for at least 10 hours, eat a snack or meal with at least 50 grams of carbohydrate as well as fat and protein content, and then be inactive for 2 hours. All participants and families will be instructed on determination of carbohydrate content using example foods that they typically consume. Participants will receive $20 for travel to the study visit, loaded onto a university payment card.

Text message-based surveys and actigraphy: Participants will be sent surveys 3 times daily via text message, inquiring about food and drink intake, physical activity, and time in bed (start/stop times). Survey responses will be collected via Mosio and entered in Research Electronic Data Capture (REDCap), a secure, web-based application for clinical research data collection. Branching logic will be used in REDCap so that participants will only need to provide detail for relevant activities each time. As an incentive for ActiGraph wear, participants will earn an additional $20 if the ActiGraph device is worn for at least 8/10 days.

Study completion: On day 10 of CGM wear (or earlier in case of discomfort), participants will remove the sensor and transmitter at home by simply peeling off the device. Transmitter and ActiGraph will be returned to the study team by participants using prepaid shipping envelopes or in-person if preferred. Upon receipt of the transmitter and ActiGraph, participants will receive compensation for participation in the study ($100).

4.1.4 Individual Interview and Disordered Eating Questionnaire

Upon completion of CGM wear, youth participants, with or without their parents at the discretion of the research team, will be invited to participate in a 20-minute semi-structured interview via phone or videoconferencing platform to assess the acceptability of CGM use as an alternative to clinical OGTT for diabetes risk assessment. Interviews will also be used

to elicit barriers and facilitators to diabetes evaluation and follow up for diabetes risk. Interviews will be conducted by study staff and will be audio-recorded and professionally transcribed.

After completion of the interview, participants will be asked to complete a brief, 12-item questionnaire related to disordered eating behaviors in the past 28 days. This will be completed via REDCap. Participants will be allowed to skip questions if they are uncomfortable answering.

Participants will be compensated $15 for completion of the interview.

4.1.5 Data Collection

CGM data extraction: Upon receipt of a participant transmitter, study staff will use a Dexcom G6 Pro receiver to upload the data to Clarity, a cloud-based software for data visualization and extraction. Glucose values and timestamps will be downloaded via CSV file to the principal investigator's secure UPMC shared drive for analysis.

Actigraphy data extraction: ActiLife 6 desktop software will be used to extract actigraphy data from returned ActiGraph GT9X Link devices. Automatically-detected sleep periods will be cross-checked with participant-reported start/end times in bed.

4.2 Study Duration, Enrollment and Number of Sites

4.2.1 Duration of Subject Study Participation

The study visit is expected to take approximately 2.5-3 hours. CGM will be worn for 10 days, beginning the day of the study visit. The phone interview is expected to take approximately 30 minutes. The phone call will take place no more than 4 weeks after the study visit.

4.2.2 Total Number of Study Sites/Total Number of Subjects Projected

This study will be conducted at the Children's Hospital of Pittsburgh. A maximum of 40 subjects will be included.

4.3 Study Population

We will not restrict enrollment based on gender or age within the eligible age group.

We plan to enroll only English-speaking patients.

4.3.1 Inclusion Criteria

1. Any gender, age 8-18 years
2. Tanner 2 or higher pubertal development
3. Overweight or obese (BMI $\geq 85^{th}$ percentile for age/sex, or ≥ 25 kg/m^2 for participants =18 years)
4. A) No previously documented abnormal HbA1c or glucose but at higher risk for T2D based on race/ethnicity (Black, Hispanic, Asian, Native American, Pacific Islander),

diagnosis with dyslipidemia, hypertension, polycystic ovary syndrome, presence of acanthosis nigricans, or first degree relative with T2D (n = 15); *or* B) previously documented (within 6 months) HbA1c 5.7-7.0%, fasting glucose ≥100 mg/dL, or 2-hour plasma glucose on OGTT of ≥140 mg/dL (n = 25)

5. Consent (adult subjects), parental/guardian permission (if applicable), assent (if applicable)
6. Willingness to wear ActiGraph watch and CGM continuously for 10 day study duration

4.3.2 Exclusion Criteria

1. Current or recent (within 1 month) use of diabetes- or obesity-related medication
2. Current use of hydroxyurea (due to interference with CGM)
3. Known type 1, cystic fibrosis-related, or medication-induced diabetes
4. Potential subject unable to speak or read in English
5. Severe cognitive impairment
6. Current or previous pregnancy

Subjects that do not meet all of the enrollment criteria may not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

5 STUDY PROCEDURES

5.1 Phone screening

- Medical Record Review
- Brief study overview: 5 minutes
  - Consent/HIPAA Authorization: 5-10 minutes/as long as needed for full comprehension of study involvement (if not already obtained electronically via REDCap)
  - Screening questionnaire: 5 minutes
  - Overview of 12-hour overnight fast and upcoming study visit: 5 minutes

5.2 Study Visit

- Vital signs (heart rate, blood pressure): 5 minutes
- Urine pregnancy test (all females): 3 minutes

- Height, weight, waist and hip circumference: 5 minutes
- Focused physical exam, including pubertal status: 5 minutes
- Fasting 2-hour oral glucose tolerance test: 120 minutes
    - Medical, surgical, family, social history: 10 minutes (during OGTT)
    - Provide ActiGraph device, instruct on use: 5 minutes (during OGTT)
    - Place CGM on abdomen, instruct on use: 5 minutes (during OGTT)
    - Review instructions for glucose and mixed meal challenge, including food label interpretation for carbohydrate content: 10 minutes (during OGTT)
    - Enroll in text messaging platform, instruct about survey completion: 5 minutes (during OGTT)
- Provide addressed, pre-paid shipping envelope to return CGM, ActiGraph

5.3 Observation Period, Days 1-10

5.3.1 Non-Challenge Days:

- Participant wears CGM, ActiGraph continuously
- Text messages sent 3 times daily (10 AM, 2 PM, 8 PM) to collect nutrition, physical activity, sleep records
- No changes to routine diet or activity

5.3.2 Glucose Challenge: day of participant's choice between Days 3 and 9

- Participant wears CGM, ActiGraph continuously
- After minimum 10 hours of fasting overnight, participant drinks study-provided glucose beverage without any additional food or drink and remains as inactive as possible for 2 hours
- Text messages sent 3 times daily (10 AM, 2 PM, 8 PM) to collect nutrition, physical activity, sleep records
    - At next available survey time, participant indicates time that glucose beverage was consumed (start and finish times)

5.3.3 Mixed Meal Challenge: day of participant's choice between Days 3 and 9

- Participant wears CGM, ActiGraph continuously
- After minimum 10 hours of fasting overnight, participant eats food item of their choice that contains at least 50 grams carbohydrate as well as fat and protein, without any additional food or drink, and remains as inactive as possible for 2 hours
- Text messages sent 3 times daily (10 AM, 2 PM, 8 PM) to collect nutrition, physical activity, sleep records

- At next available survey time, participant indicates time that mixed meal challenge was completed, as well as food item chosen and nutritional content (amount, and carbohydrates, fat, protein per serving)

5.3.4 Removal and Return of CGM and ActiGraph: Day 10

- Midday on the 10th day of CGM wear, participants will remove CGM by painlessly peeling off the adhesive and device
- Sensor and transmitter will be placed in a Ziploc bag and placed in the prepaid, addressed envelope for return
- ActiGraph will be removed from wrist and placed with CGM in envelope
- Envelope will be sent to study team by participant
- Compensation will be provided to participants upon receipt of the CGM and ActiGraph

5.4 Individual Interview and Disordered Eating Questionnaire: any time between Day 10 of Observation Period and 1 month after Study Visit

- Participants (ages 15-18) or their parents (for participants ages 8-14) will be invited to participate in a 30-minute semi-structured individual interview via phone or videoconferencing platform to assess the acceptability of CGM use as an alternative to clinical OGTT for diabetes risk assessment.
- Participants will be asked to complete a brief, 12-item questionnaire related to disordered eating behaviors in the past 28 days. This will be completed via REDCap. Participants will be allowed to skip questions if they are uncomfortable answering
- Participants will be compensated $15 for completion of the interview.

5.5 CGM, ActiGraph Data Extraction

- Dexcom G6 Pro receiver will be used to transfer CGM sensor data to Dexcom Clarity (https://clarity.dexcom.com/professional/)
- ActiGraph data will be uploaded from the device using ActiLife software on the PI's UPMC desktop computer

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5.6 Subject Completion/Withdrawal

Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to study treatment or visit schedules, AEs, or due to adherence to study treatment or visit schedules. The Investigator may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded in the source documents and on the case report form (CRF) on REDCap.

CGM, ActiGraph, questionnaire, and clinical data obtained prior to subject withdrawal will be retained.

5.6.1 Early Termination Procedures

Subjects who withdraw from the study will be asked to complete the interview to assess reasons for early termination and will be asked to return the CGM and ActiGraph device via the prepaid envelope. Full compensation will still be provided upon receipt of the devices.

6 STUDY EVALUATIONS AND MEASUREMENTS

6.1 Screening and Monitoring Evaluations and Measurements

6.1.1 Medical Record Review

Participants will be interviewed regarding their medical history. To ensure that no major items are missed and to clarify interview answers, the study team will review participant electronic medical records prior to and after the participant interview to confirm the following:

- Date of birth
- Birth history (gestational age, birth weight, complications during pregnancy)
- Anthropometrics (weight, height, BMI)
- Medications
- List of medical problems, especially as they relate to inclusion and exclusion criteria
- Demographic data including race, ethnicity, gender, and insurance type
- Endocrine-related diagnoses, including: insulin resistance, prediabetes, impaired glucose tolerance, impaired fasting glucose, elevated hemoglobin A1c, diabetes mellitus, and polycystic ovary syndrome
- History of attendance at an obesity clinic
- History of bariatric surgery
- Diabetes-related labs, including: plasma and point-of-care glucose, hemoglobin A1c, and insulin
- History of non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, elevated ALT or AST, or other known liver disease

6.1.2 Physical Examination

A study physician (pediatric endocrinologist) will review with the parent and child the child's current and past medical history, a review of systems, and family history (with particular attention to cardiovascular disease and diabetes). A focused physical examination will be conducted, including measurement of height, weight, waist circumference, hip circumference, pubertal staging, and pertinent physical findings associated with insulin resistance, including the presence of acanthosis nigricans, which will be recorded on a standardized form. Investigators will verify that the patient has been fasting for a minimum of 10 hours.

6.1.3 Vital Signs

- Blood pressure (BP) will be recorded while the subject is sitting down by the nursing staff. BP will be measured by auscultation three times, after a five minute rest in a quiet area with the subject in a seated position; the average of the 2nd and 3rd measurements will be used.
- Pulse and respiratory rate will be measured by nursing staff

6.1.4 Laboratory Evaluations

6.1.4.1 Table: Clinical Laboratory Tests

Category	Tests
Biomarkers of glucose metabolism	Hemoglobin A1c, plasma glucose, insulin, c-peptide

6.1.4.2 Pregnancy Testing

A urine pregnancy test will be performed for all female subjects at baseline. A positive pregnancy result will be disclosed to the participant only. Pregnancy results will be disclosed to the parent/guardian if the subject gives the investigators permission. Subjects found to be pregnant during the visit will not be able to enroll in this study. The investigators will counsel the subject and guide them to seek the appropriate care.

6.1.5 Medical History, Family History, Social History Questionnaire

Will include past medical history, 1st and 2nd degree family history of diabetes, dyslipidemia, cardiovascular disease, and socioeconomic status questions. Social history will include questions to understand predictors of acceptability of the intervention, including parent/guardian's employment (hours worked, flexibility of hours), household income, approximate travel time to UPMC Children's Hospital of Pittsburgh from their home, child's school start time, number of missed days of school this year related to medical appointments or assessments, child's school performance (excellent, average, below average, failing), household size (number of adults, number of children), insurance type (commercial/government), and use of government assistance (e.g. SNAP, WIC, public housing).

6.1.6 Interview and Disordered Eating Questionnaire

Semi-structured individual interviews will be conducted by study staff after the observation period to evaluate acceptability of use of CGM for diabetes risk assessment, including barriers and facilitators to this approach. Interviews will be audiorecorded and then professionally transcribed for qualitative analysis using NVivo software.

The disordered eating questionnaire includes 12 questions that inquire about the feeling of "loss of control" when eating. This questionnaire does not have a validated threshold for normal versus abnormal and is not in clinical use in its form in this study.

6.2 Efficacy Evaluations

CGM data completeness (data available for >=80% requested days worn), nutrition logging quality and completion (>=80% of participants documenting date and time of glucose challenge, mixed meal challenge, or both), and acceptability (mean score >=3, or "neutral" for all participants) will be used to determine feasibility and acceptability of this approach.

6.3 Safety Evaluations

Participants will be fasting for a minimum of 10 hours prior to the study visit. This may cause hunger pangs, upset stomach, headache, or light-headedness. If the participant shows any signs of clinical instability or definitively decides to discontinue participation, the study visit will be ended.

The patient will be notified of any clinically relevant abnormal test result(s) performed. It will be recommended that results, especially abnormal results, be discussed by the guardian with the participant's primary care physician.

7 STATISTICAL CONSIDERATIONS

7.1 Primary Endpoint

We will determine the completeness of CGM data capture and adequacy of nutrition logs for evaluation of at-home glucose challenge.

7.2 Secondary Endpoints

Secondary endpoints include test performance characteristics of at-home CGM-measured glucose challenge as compared with gold-standard laboratory-based 2-hour OGTT; acceptability of use of CGM for at-home dysglycemia evaluation as an alternative to 2-hour lab-based OGTT.

7.3 Control of Bias and Confounding

Potentially eligible subjects will be stratified by sex and age (8-14, 15-18), and an equal number of participants will be contacted per group until recruitment goals are reached or all potentially eligible subjects in a category are enrolled or decline to participate.

Multivariable models will adjust for covariates including age, sex, race, ethnicity, and anthropometrics (e.g. BMI-Z).

7.4 Statistical Methods

7.4.1 Analysis of Primary and Secondary Outcomes of Interest

Primary objective: Determine the feasibility of at-home, CGM-based glycemia evaluation as measured by adequacy of CGM data capture and nutrition logging quality and completion on days of at-home glucose and mixed-meal challenge.

H1a: Complete CGM data will be available for ≥ 80% of requested days worn: The number of days with adequate CGM data will be divided by 9, omitting the first 24 hours due to possible inconsistent measurements after initial placement. Feasibility will be defined as ≥ 80% (7.2) of days with data.

H1b: Documentation of glucose and mixed-meal challenge will be complete and adequate for analysis for ≥80% of participants: The number of participants who document the date and time of glucose and mixed-meal ingestion (including mixed-meal content) will be determined and divided by the total number of participants. Feasibility will be defined as ≥80% of participants documenting date and time of either the glucose challenge, mixed-meal challenge, or both.

Secondary objective: Determine the test performance characteristics of at-home, CGM-measured glucose challenge with laboratory-based 2-hour OGTT.

H2: CGM-measured glucose 2 hours and 5 minutes after standardized glucose ingestion will have adequate discrimination of normal (<140 mg/dL) versus dysglycemic (≥140 mg/dL) 2-hour OGTT glucose, as assessed by area under the receiver operating characteristic curve ≥ 0.7: Using participant logs via text message survey or paper-based logs, date and time of home glucose challenge will be determined and labeled in CGM data. A time point 2 hours and 5

minutes later (accounting for lag due to interstitial measurement)(Wadwa, Laffel et al. 2018) (CGM-2h) will serve as the comparison to the 2-hour glucose during OGTT obtained at the study visit (OGTT-2h). Sensitivity, specificity, and positive and negative predictive values of CGM-2h to predict OGTT-2h≥140 mg/dL will be assessed for various thresholds of CGM-2h. Area under the receiver operating characteristic curve (AUC) will be determined. An AUC threshold of ≥0.7 will be used to define adequate discrimination. The same analysis will be repeated for the comparison of baseline CGM glucose (at time of glucose ingestion) to fasting glucose on OGTT, using a fasting glucose threshold of ≥100 mg/dL to define dysglycemia. Finally, correlation analyses (Spearman or Pearson depending on distribution) will be performed to further explore the relationship between CGM indices obtained during at-home glucose challenge (e.g., baseline, peak, mean glucose) and both laboratory-measured HbA1c and plasma glucose during OGTT. Correlations will be examined across subgroups such as lower versus higher ActiGraph-measured physical activity level and self-reported carbohydrate intake on the day prior to at-home glucose challenge, age, pubertal stage, and body mass index.

7.4.2 Qualitative analysis

After the completion of individual interviews, recordings will be transcribed. Transcripts will be analyzed in NVivo software, using directed content analysis techniques (Merriam and Tisdell 2016) to identify and organize relevant themes. Codes and coding rules for a codebook will be established by the PI and study staff based on the interview guide and transcripts. When the codebook is established, at least two study staff will independently code transcripts to identify themes and sub-themes, resolving disagreements in coding through discussion. Themes will be summarized and compared across demographic groups (e.g. sex, age, race/ethnicity), activity level (high/low), and sleep duration (longer/shorter). Acceptability of the use of CGM for T2D risk evaluation at home will be rated on a Likert scale (1: completely unacceptable, 2: mostly unacceptable, 3: neutral, 4: mostly acceptable, 5: completely acceptable). Acceptability will be defined as a mean score for all participants of ≥3.

7.4.3 Exploratory analyses

The analyses for at-home glucose challenge described above will be repeated to evaluate the test performance of at-home mixed-meal challenge in comparison to 2-hour OGTT. In addition, CGM metrics such as average, area under the curve, and peak glucose as well as coefficient of variation will be compared for days of CGM wear without glucose or mixed-meal challenge versus challenge days to assess the difference in glucose trends of typical daily life versus those artificially imposed by testing.

An additional exploratory analysis will use responses from the disordered eating questionnaire to assess whether correlations between OGTT and CGM-measured glycemia differ between youth with higher versus lower self-report of loss-of-control eating.

7.4.4 Missing Data

The CGM measures interstitial glucose every 5 minutes, but glucose data may be missing due to signal disruption or mechanical dislodgment. Periods of missing data for more than

20 minutes will not be replaced. For data gaps of up to 20 minutes, the two glucose values preceding and following the missing period will be averaged and used to replace the missing data.

7.5 Sample Size and Power

The sample size for this pilot study balances feasibility with the likelihood of obtaining meaningful results for future studies. Assuming 20% drop-out or incomplete data, a sample size of 40 should lead to 32 evaluable subjects. This will allow for subgroup analyses, including by sex and physical activity strata (high versus low). This study will include nearly twice as many participants with known dysglycemia (or more if previously undiagnosed) as those without in order to maximize the ability to compare impaired glucose tolerance and abnormal CGM-measured glucose trends.

8 SAFETY MANAGEMENT

8.1 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study.

8.2 Adverse Event Reporting

Since the study procedures are not greater than minimal risk, serious adverse events (SAEs) are not expected. If any unanticipated problems related to the research involving risks to subjects or others happen during the course of this study (including SAEs) they will be reported to the IRB in accordance with institutional guidelines. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

The relationship of each SAE to the study intervention will be characterized using one of the following terms in accordance with IRB Guidelines: definitely, probably, possibly, unlikely or unrelated.

8.3 IRB/IEC Notification of SAEs and Other Unanticipated Problems

The Investigator will promptly notify the IRB of all on-site unanticipated, serious Adverse Events that are related to the research activity. Other unanticipated problems related to the research involving risk to subjects or others will also be reported promptly. Written reports will be filed using the electronic IRB system and in accordance with the timeline below. External SAEs that are both unexpected and related to the study intervention will be reported promptly after the investigator receives the report.

Type of Unanticipated Problem	Initial Notification (Phone, Email, Fax)	Written Report
Internal (on-site) SAEs Death or Life Threatening	24 hours	Within 2 calendar days
Internal (on-site) SAEs All other SAEs	7 days	Within 7 business days
Unanticipated Problems Related to Research	7 days	Within 7 business days
All other AEs	N/A	Brief Summary of important AEs may be reported at time of continuing review

8.3.1 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) will be submitted to the IRB. The investigator will be responsible for ensuring that all SAE are followed until either resolved or stable.

8.4 Investigator Reporting of a Serious Adverse Event to Sponsor

Reporting will be consistent with National Institutes of Health requirements.

8.5 Medical Emergencies

Medical emergencies that might develop during the course of the study at PCTRC will be referred to the CHP emergency room. Medical emergencies that might develop during the course of the study during the at-home intervention will be referred to local emergency medical services.

9 STUDY ADMINISTRATION

9.1 Data Collection and Management

The PI is responsible for the accuracy and completeness of data collection and management. The PI may designate qualified individual(s) to collect data and manage data. Only investigators and research staff that have completed appropriate IRB training and approval and are listed on the IRB approved protocol are eligible to collect and work on information from the study. Future studies that may use patients or data collected from this study must have separate approved IRB protocols and consent forms, if applicable.

REDCap Case Report Forms (CRF): REDCap CRFs will be created by the study team for data capture. REDCap is a secure web-based data management software designed by Vanderbilt University investigators. Study data will be entered through intelligent REDCap forms that adapt to data content, and include built-in eror checks to trap out-of-range or inconsistent entries into the central database. Original data will be recorded directly into CRFs by the study coordinator or a study investigator after consent is documented. Copies of laboratory, physical exam, anthropometric, and questionnaire responses will be received through the electronic medical record or through secured email. This information also will be recorded into CRFs in REDCap. The password to log into REDCap will be unique to each member of the study team. REDCap will also be used to collect disordered eating questionnaire responses.

Dexcom G6 Pro Data: Dexcom Clarity for Health (https://clarity.dexcom.com/professional/) will be used to upload CGM data. Only study IDs will be used, without identifiable patient information. A separate "clinic" will be created for this research project on the website, with a separate login created for each study team member. The PI and primary research coordinator will have Administrator privileges for data access and uploads; additional study staff will be added for view or upload only, without editing priviliges.

ActiGraph GT9X Link Data: ActiLife 6 software will be used to upload and analyze anonymized actigraphy data. This software will be on the PI's UPMC desktop computer, and uploaded data will be saved to the PI's UPMC secure shared drive.

Text Message-Based Survey Data: Following enrollment, study staff will obtain the phone number for the participant or participant parent's text message-enabled cellphone in order to send and receive text message based nutrition, activity, and sleep surveys. No PHI will be shared with the text message platform Mosio.

Interview Data: Written data collected during the interview will be stored in a secure file cabinet in the PI's office. Only the research team will have access to interview notes, which will be destroyed after a minimum of 7 years after completion of the study. Interviews will also be audio-recorded. Audio recordings will be kept as digital files and kept on the PI's password-protected institutional shared drive. Recordings will be destroyed after the recordings are transcribed and qualitative analysis is complete.

Participant Recruitment Log: This password-protected Microsoft Excel file, saved on the PI's institutional shared drive will include patient identifying information necessary for registration, enrollment, and follow-up. Following enrollment, this document will be used to maintain a log of enrolled patients. For patients who are not enrolled, patient-identifying information will be destroyed. A non-identifiable list of patients that were not enrolled will be retained for the purpose of calculating response rate.

Consent Forms: Electronic copies of the consent forms will be stored in a password-protected folder on the PI's shared drive. Participants will be emailed their signed consent form. If a participant turns 18 during the study, consent will be re-obtained electronically via REDCap.

Anonymization: Data will be extracted from REDCap, Dexcom Clarity, and ActiLife software and downloaded onto the PI's secure UPMC shared drive. Datasets will be stripped of all identifiers and individuals will be referred to by their study ID. The study ID will also be used on all analytical files.

9.2 Confidentiality

All data and records generated during this study will be kept confidential in accordance with institutional policies and on HIPPA subject privacy. The investigators/study team members/site personnel will not use such data and records for any purpose other than for conducting the study.

As a way to minimize the chance of PHI (protected health information) from being disclosed, a unique identification code will be used for each participant. Specific keys will be saved in an encrypted format on the PI's secure institutional shared drive.

Participants will not be identified by name/PHI on any publications that result from this research.

The information collected as part of this study will be kept for 7 years after study completion. At that time, the information collected will be destroyed or all identifiable information will be removed. All keys will be destroyed at this time, as well. No identifiable data will be used for future studies without first obtaining IRB approval.

9.3 Regulatory and Ethical Considerations

9.3.1 Data and Safety Monitoring Plan

Due to the minimal risk involved in the investigation, a Data and Safety Monitoring Board (DSMB) is not applicable. Study data will be carefully monitored by the PI. The PI will provide weekly supervision to a trained clinical research coordinator who will be involved in data collection. The study team will monitor and track collection of all study data. The team will additionally track all protocol deviations and adverse events and will report these to the IRB, in accordance with reporting guidelines.

9.3.2 Risk Assessment

Study participation poses no more than minimal risk. Expected risks by procedure are as follows:

Phlebotomy and IV insertion: The blood volume collected will be approximately 18 mL. The blood volume removal is much less than the maximum blood volume removal per 8-week period recommended by OHRP (children < 7 ml/kg over 6 weeks). IV insertion and phlebotomy will be done by trained PCTRC nurses. There is a risk of bruising and discomfort at the venipuncture site. Blood draw may result in temporary discomfort from needle stick, bruising, fainting, weakness, and rarely an infection at the site. To minimize discomfort, a topical numbing cream or spray will be offered. Slight swelling of the skin in response to the numbing medicine may occur in approximately half of all individuals. This goes away within about 4 hours in most cases.

Overnight Fast: Fasting may cause hunger pangs, upset stomach, headache, or light-headedness. However, the requested fasting period is no longer than usual for most individuals, and none of the participants will be taking medications that would place them at risk for hypoglycemia.

Anthropometric measurements and pubertal status: Exam poses minimal risks. The anthropometric assessment involves measurements of height, weight, and circumferences. Some individuals are uncomfortable with physical examinations. For this reason, during the encounter each step will be explained to the participant explicitly. Drapes and other barriers will be used if they are required to disrobe during the exam. The exam will be performed by staff experienced in obtaining measurements in children at all levels of cognitive ability. The measurements are obtained in a private room. The parent is permitted to stay with the child if it increases their comfort with the exam.

The puberty assessment will be performed by a pediatric endocrinologist in a private setting. The procedure will be explained to the child in advance, and the parent is permitted to be present if preferred by the child. The exam is performed by highly experienced personnel who are familiar with minimizing distress associated with the exam.

Blood pressure measurement by auscultation: Procedure may cause temporary numbness/tingling in the arm. Blood pressure will be obtained by trained PCTRC nurses.

Oral glucose tolerance test (OGTT) and at-home glucose challenge: The risks associated with the OGTT are the same as those for having blood drawn as described above. The OGTT is safe and is used clinically in children and adults of all ages. Glucose is a normal nutrient found in many different foods. About one out in ten people have mild nausea or an upset stomach with the glucose (sugar) drink that is given during the OGTT. This can be minimized by drinking the sugar drink slowly over 5 minutes. Rarely, some people experience a mild low blood sugar reaction (symptoms like nervousness or sweating) at the end of the test. Participants will be offered a snack to guard against this from occurring.

At-home mixed meal challenge: Participants are at no greater risk than usual when they consume foods of choice at home. Examples of foods that would satisfy the requirement of 50g carbohydrate with fat and protein include: 1) 1 banana (27g carbs) and 2 slices of bread

with butter or peanut butter (30g carbs); 2) 1.5 cup Honey Bunches of Oats cereal (35g carbs) with 1 cup soy milk (15g carbs); 3) 8 oz strawberry yogurt (31g carbs) with 1 cup of fresh blueberries (21g carbs) or 1 medium apple (25g carbs).

Wearing Dexcom G6 Pro device for 10 days: The primary risks with Dexcom G6 Pro wear include skin irritation due to adhesive; bleeding, pain or infection at insertion site; and remote chance of sensor wire breakage. Skin irritation is common among children with type 1 diabetes (approximately 40-50%), but is significantly more common among individuals who have been using CGM (including removing and replacing) for more than 1 year (OR 0.3, versus less than 1 year) and is most frequently described as "eczema" (35%) or "dry wound" (8-14%).(Berg, Olsen et al. 2018) To minimize risk of irritation or poor adhesion, participants will be asked to refrain from using insect repellent, sunscreen, perfume, or lotion on their abdominal skin. To minimize risk of insertion complications, only trained study staff will place CGM on participants. Staff will clean and dry hands, then put on gloves before insertion. The insertion site will be cleaned with alcohol wipes, and device inserted after the skin is dry. The device will be placed away from waistbands, scarring, tattoos, irritation, or bones (such as hip bone). To minimize risk of sensor wire breakage upon removal, participants will be instructed on safe removal technique via a Dexcom-created video as well as explanation by study staff. Sterile broken or detached sensor wires pose minimal medical risk. Participants will be encouraged to call the study team with any concerns as soon as possible and informed that they may remove the device at any time if needed. If there is concern that the sensor wire has broken off under the skin, participants will be advised to not remove it, but to contact the study team. They may also contact Dexcom's 24/7 Technical Support at 1-844-607-8398. Participants may require professional medical help if sensor wire is retained in skin, particularly if they have symptoms of infection or inflammation at the insertion site.

Participants will be asked to not undergo magnetic resonance imaging (MRI), computed tomography (CT), or diathermy while wearing CGM due to reading inaccuracies that may result from magnetic fields or heat.

Wearing an ActiGraph GT9X physical activity and sleeper tracker on wrist: Participants may experience discomfort or rash related to wearing the device. Participants will be allowed to remove the device at any time if needed due to discomfort or rash.

Interview and disordered eating questionnaire: Potential risks include momentary embarrassment or discomfort as well as breach of privacy and confidentiality. Participants may decline to answer any question during the interview for any reason. Every precaution will be taken to secure participants' personal information to ensure confidentiality.

Sharing of private health information (PHI): There is the potential risk for a breach of confidentiality. Private health information will be collected, accessed and stored according to HIPAA guidelines, including the use of multilevel password protection and enforcement of system user privileges on the database. To limit the risk of disclosure to the minimum necessary to conduct the study, all direct identifiers will be removed as soon as possible and codes will be substituted for personal identifiers. Records of individuals are stored with ID

numbers and a code with no discernible personal identifiers. Code lists and data files will be stored in separate, secure locations. Data will be stored on institutional secure servers hosted and accessed on password-protected computers. To maintain confidentiality, codes will be used in the database, presentations and publications.

9.3.3 Potential Benefits of Trial Participation

Participants may indirectly benefit from identification of abnormalities such as diabetes from the hemoglobin A1c or OGTT. If clinically relevant abnormalities are found, the family will be notified. With the consent from the family, clinically relevant tests results will be shared with the subject's primary care physician. Participants found to have an impaired fasting glucose or impaired glucose tolerance who are not already under care for the condition will be referred appropriately for further management and treatment.

9.3.4 Risk-Benefit Assessment

As the risk is no more than minimal and there is significant potential direct and indirect benefits, the risk-benefit balance is favorable.

9.4 Recruitment Strategy

Potential subjects will be identified through weekly review of Pediatric Endocrinology and Diabetes clinic schedules. In addition, a list of potentially eligible patients will be generated via review of a list of patients with diagnosis of prediabetes or obesity and insulin resistance from current and previous research conducted by the PI or the PI's mentor and co-investigator, Dr. Silva Arlsanian. The Wellness and Obesity Registry, monitored by Dr. Silva Arslanian, will be used to screen for potential subjects as well.The CAYAH RESEARCH INTEREST FORM will also be used for recruitment purposes. This is a REDCap form with a survey link that will contain questions for adolescents to answer self-screen questions which are non-sensitive. Center for Adolescent and Young Adult Health (CAYAH) clinical staff will manage and distribute this survey. CAYAH clinical research staff will advertise the study to the teen. If the teen (age 13 or older) indicates interest in the study by viewing the study advertisement within the CAYAH RESEARCH INTEREST FORM, they will provide their contact information to the CAYAH clinical research staff who will then share it with the study team. Medical records of potential subjects will be screened by the study team using the protocol inclusion and exclusion criteria. Those who appear to meet the criteria will be approached by a member of the study team by phone, email, or in-person and asked if they would like to hear about the study. Subjects and/or their parent/guardian will provide demographic, social, and medical information about themselves, their child, or family (as applicable) to confirm eligibility.

9.5 Informed Consent/Assent and HIPAA Authorization

9.5.1 Screening

Information obtained via chart review will be preparatory to enrollment and will be limited to the minimum necessary information to determine eligibility for the main study.

9.5.2 Informed consent

Consent/assent (as applicable) will be signed electronically via REDCap. A combined consent/assent-authorization document will be used, and subjects will be provided with a copy of the consent form. Subjects will be allowed to read the consent form and ask questions. Written consent/assent will be obtained from the family after all the questions and discussions have been completed and we are reassured that subjects comprehend the nature of the study, the study procedures and the risks-benefits of participation. To maximize subject privacy, the discussion will take place in a private location in or near PCTRC or the Endocrinology clinic, or via phone. A copy of the fully signed and completed consent form will then be provided via email.

To avoid coercion, we will explain that study participation is voluntary and the subject does not have to partake in the study in order to receive care at CHP. Decision not to participate or decision to withdraw after consent for study participation will not cause penalties or loss of any benefits otherwise entitled to the subject as a patient. In addition, the subject's current and future medical care at CHP will not be affected by final decision for or against study participation.

9.5.3 Re-Consent Plan for Subjects Who Reach Age of Majority

Individuals who turn 18 while enrolled in the study will be contacted by phone and will be asked to provide consent/HIPAA authorization for their continued participation via REDCap.

9.6 Payment to Subjects/Families

All study procedures and expenses will not be billed to the participant but rather to the study's funding source.

9.6.1 Reimbursement for travel, parking and meals

Reimbursement will be provided for travel/parking for study visit: $20, given via Vincent.

Incentives and compensation will be provided via Vincent as described below.

9.6.2 Payment Schema

Study Visit: Compensation: $100; Reimbursement for travel/parking: $20; paid upon receipt of CGM transmitter and ActiGraph

ActiGraph wear during Observation Period: Incentive of $20 if worn on at least 8 days out of 10

Individual interview by phone/videoconference: Compensation of $15

Total: Max compensation $135; max reimbursement for travel: $20

10 PUBLICATION

After completion of the study, the investigator and study team will review and analyze the data for reporting and publication. All published data will be de-identified. No individually identifiable PHI will be published.

11 REFERENCES

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