Rare and Atypical Diabetes Network (RADIANT)

RADIANT

Funded by: NIDDK
Version Number: v8.0
August 24, 2022

Protocol Chair/Study Principal Investigators: ASHOK BALASUBRAMANYAM, MD LOUIS H. PHILIPSON, MD, PHD JOSE C. FLOREZ, MD, PHD JEFFREY KRISCHER, PHD	**OSMB Chair:** JERRY VOCKLEY, MD, PHD
NIH Project Scientist: BEENA AKOLKAR, PHD	
Data Coordinating Center: University of South Florida 3650 Spectrum Boulevard Tampa, FL, 33612 Phone: 813-396-9512 Email: Jeffrey.Krischer@epi.usf.edu	**Central Laboratory and Biorepository:** University of Florida Health Pathology Laboratories Endocrine Laboratory/RADIANT 4800 SW 35th Drive Gainesville, FL 32608

| **Administrative Cores:**
(1) Baylor College of Medicine
One Baylor Plaza
Houston, TX 77030
Phone: 713-798-5757
Email: radiantstudy@bcm.edu
(2) University of Chicago
900 E. 57th St.
Rm 8142
Chicago, IL 60637
Phone: 773-702-1081
Project Manager: Lisa Letourneau-Freiberg
Email:
lletourneaufreiberg@medicine.bsd.uchicago.edu | **Genetics/Genomics Cores:**
(1) Baylor College of Medicine
One Baylor Plaza
Houston, TX 77030
Phone: 713-798-8253
Email: Jennifer.Posey@bcm.edu
(2) Broad Institute / Massachusetts General Hospital
75 Ames Street – 10th floor
Cambridge, MA 02142
Phone: 617-643-3308
Email: JCFlorez@mgh.harvard.edu |

Table of Contents

STATEMENT OF COMPLIANCE

Statement of Compliance: Study Investigators understand and will work according to the principles of Good Clinical Practice (GCP) as described in the United States Code of Federal Regulations (CFR) – 45 CFR part 46 and 21 CFR parts 50, 56, and 312, and in the International Conference on Harmonization (ICH) document Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance dated April 1996. Further, Study Investigators will conduct the study in keeping with local legal and regulatory requirements. Specifically, study investigators will perform study procedures according to the RADIANT Manual of Procedures.

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection Training (e.g. through the CITI Program; https://about.citiprogram.org/en/homepage/).

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the central Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.
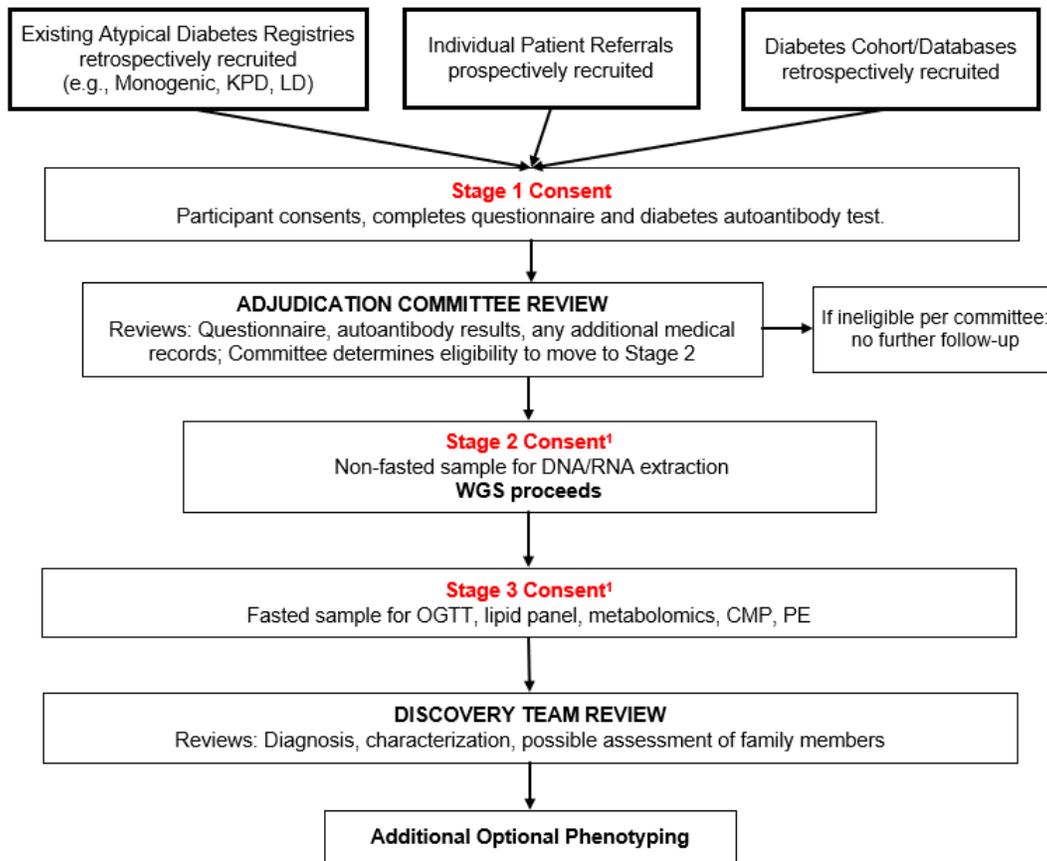
1   PROTOCOL SUMMARY

1.1   Synopsis

Title:	Rare and Atypical Diabetes Network (RADIANT)
Study Description:	This study defines a process for identifying and studying individuals/family members with rare and uncharacterized forms of diabetes. In that there is heterogeneity in the way diabetes presents clinically, this study will investigate referred cases to rule out type 1, type 2 and other known forms of diabetes. The remaining cases will be evaluated, and those deemed most informative will be studied further to gain greater insight into unknown, atypical and uncharacterized forms of diabetes. Detailed phenotyping/genotyping of these individuals and affected family members will help to characterize a range of subtypes present in the spectrum of diabetes in the general population, better understand the heterogeneity of type 2 diabetes, and reveal novel mechanistic pathways involved in the prevention and/or treatment of these forms of diabetes. Studying the underlying genetic background of these individuals may also lead to the identification of function for the variants in or near genes associated with type 2 diabetes and explain the contribution of specific loci to aspects of polygenic type 2 diabetes. These genetic and phenotypic studies may help in identifying new biomarkers for screening and diagnosis. Furthermore, genetic studies may help to identify drug targets and catalyze the development of therapies for use, not only in individuals with rare/atypical forms of diabetes, but also in newly identifiable subtypes of type 2 diabetes in the general population. The study will also create and manage a database and biospecimen repository of rare and atypical forms of diabetes for use by the broader research community and for future analyses. A detailed schematic illustrating the study intake process and a schedule of activities can be found in Sections 1.2 and 1.3.
Objectives:	The objective of this protocol is to define new forms of diabetes and the unique mechanisms underlying these forms of atypical diabetes. The specific aims are to: 1) Identify and enroll individuals and families with hitherto undiagnosed rare and atypical forms of diabetes. We will recruit from three broad sources: a. disease registries enriched in forms of atypical diabetes, b. population registries of persons with "type 1 diabetes" and "type 2 diabetes" across a wide geographic, ethnic and age spectrum that can be mined for suspected atypical diabetes cases (to include populations identified through systematic analysis of electronic health records), and c. self referral or provider referrals of participants with unknown forms of diabetes. 2) Determine the etiologic basis of the metabolic disorder among individuals and families with novel forms of rare and atypical diabetes.

	3) Understand the pathophysiology of individuals and families with novel forms of rare and atypical forms of diabetes. 4) Construct a database of genotypic and phenotypic data and a biorepository of samples from the participants with novel forms of rare and atypical diabetes for use in future studies. 5) Make data and specimens available for research by the outside research community.
Endpoints:	<u>Primary Endpoint:</u> The primary endpoint is the phenotypic and genotypic characterization of previously unknown forms of diabetes.
Study Population:	Approximately 400 participants (probands and family members) will be screened for evaluation of suspected atypical diabetes of unknown origin per year (the Screened Population). Among the pool of evaluated individuals, those found to have a known form of diabetes will be excluded from further study but will serve as a control/comparison population. The remaining participants (estimated 200 probands and family members per year) will be prioritized for genetic/genomic analysis and further testing (the Enrolled Population).
Description of Sites/Facilities Enrolling Participants:	There are 14 Study Clinics for participant enrollment and one Data Coordinating Center: Study Clinic Sites: Baylor College of Medicine, University of Chicago, University of Washington, Seattle Children's Hospital, University of Colorado, SUNY-Downstate, Indiana University, Columbia University, Massachusetts General Hospital, University of Maryland, University of Michigan, University of North Carolina, Vanderbilt University, Washington University in St. Louis Data Coordinating Center: The University of South Florida
Description of Study Procedures	Study procedures consist of collection of biospecimens and phenotypic data to better characterize the unknown forms of diabetes. This may involve sample collection, collection of personal/family data and genotyping or sequencing results.
Study Duration:	The study will have a duration of 4-5 years from the time of initial study participant enrollment to the completion of the data analyses.
Participant Duration:	Study participant duration is expected to vary depending upon how far the participant proceeds in the study workflow and the nature of additional testing. Those who continue to Stage 2 will have one in-person or remote study visit. Those who continue to Stage 3 may have 2 or more in-person study visits over the course of the project.

1.2 Study Schema

FIGURE 1. STUDY FLOW DIAGRAM

```
┌─────────────────────────────┐  ┌─────────────────────────┐  ┌─────────────────────────┐
│ Existing Atypical Diabetes  │  │ Individual Patient      │  │ Diabetes Cohort/        │
│ Registries                  │  │ Referrals               │  │ Databases               │
│ retrospectively recruited   │  │ prospectively recruited │  │ retrospectively         │
│ (e.g., Monogenic, KPD, LD)  │  │                         │  │ recruited               │
└─────────────────────────────┘  └─────────────────────────┘  └─────────────────────────┘
```

Stage 1 Consent
Participant consents, completes questionnaire and diabetes autoantibody test.

ADJUDICATION COMMITTEE REVIEW
Reviews: Questionnaire, autoantibody results, any additional medical records; Committee determines eligibility to move to Stage 2

If ineligible per committee: no further follow-up

Stage 2 Consent[1]
Non-fasted sample for DNA/RNA extraction
WGS proceeds

Stage 3 Consent[1]
Fasted sample for OGTT, lipid panel, metabolomics, CMP, PE

DISCOVERY TEAM REVIEW
Reviews: Diagnosis, characterization, possible assessment of family members

Additional Optional Phenotyping

[1]Stage 2 and Stage 3 participation may occur consecutively or concurrently.

1.3 Schedule of Activities (SoA)

1.3.1 Overview

Potential participants identified as possibly have a rare/atypical form of diabetes will, from these referring sources, 1) provide informed consent, 2) complete a detailed questionnaire on medical history, family history and clinical presentation, and 3) if atypical diabetes is suspected based on questionnaire responses, undergo a blood test for islet autoimmunity using a central laboratory (Stage 1, the Screened Population). These data will be collected and sent to an Adjudication Committee for thorough review. The Adjudication Committee will make a decision to either: 1. Exclude the participant because they do not present as having atypical diabetes; or 2. Include the participant (the Enrolled Population) and prioritize for whole genome sequencing (WGS). Stage 2 consists of a standard set of collections including samples for WGS, peripheral blood RNA analysis (e.g., RNA-Seq). Analysis of WGS data will include identification of known monogenic diagnoses Stage 3 will consist of a detailed physical examination, questionnaires, urine and blood collection for storage, and standard fasted laboratory analyses including lipid panel, metabolic panel, HbA1c, metabolomics, and glucose, insulin, and C-peptide measured during the course of an oral glucose tolerance test. A comprehensive review of all accumulated participant data will be performed by the Discovery Team. The Discovery Team may also

recommend additional deeper phenotyping workup for the participant and consider inclusion of informative family members. Family members may be offered enrollment as discussed in section 1.3.2, Enrollment Steps.

1.3.2 Enrollment Steps

Individuals referred to RADIANT will provide informed consent and complete a standard questionnaire to determine the potential for having atypical forms of diabetes.

Stage 1
Participants identified as potentially atypical based on the above screening processes may be contacted by a member of the research team for a final eligibility check prior to receiving a sample collection kit and completing a more detailed questionnaire.

Participants will be able to take the sample collection kit to a lab, such as Quest, or a phlebotomy service provider for a blood draw. At this stage only islet autoantibodies will be tested, and a small amount of blood will be stored for future use in the RADIANT biobank. The samples will be analyzed by the RADIANT central lab and all results will be sent to the Data Coordinating Center (DCC) for adjudication committee review.

Selection by Adjudication Committee
This committee will assess the data collected in Stage 1 and select and prioritize candidates to proceed to Stage 2 for WGS and other testing. To assist with their review, the Adjudication Committee may also communicate with the participant's referring atypical registry, diabetes cohort/database or Study Clinic for additional information if the participant gives permission to do so. The participant may be asked for permission to contact their primary care provider or endocrinologist if additional information is required for adjudication – a medical record release form will be given to the participant to permit this contact.

Stage 2 Consent, Whole Genome Sequencing and Additional Testing
Based on the Adjudication Committee's recommendation, the participant will proceed to Stage 2. It is preferred that the participant have an in-person study visit at this point, but allowance will be made for those participants that are unable to travel to a clinic.

In-Person Visit: At or prior to the Study Clinic visit, the participant will provide informed consent and assent (if applicable) for Stage 2 Testing (including consent for genetic testing), and will have blood collected for DNA and RNA extraction, storage, and analysis. Blood will be collected for these tests by a standardized protocol and shipped per protocol to the RADIANT central lab. DNA and RNA will be extracted at the RADIANT central lab. The participant may also be asked about biological family medical history.

If the participant is unable to travel to a Study Clinic for the Stage 2 visit, the procedure will be as follows:
- Consent will be obtained remotely. The consenting study clinic will mail a blank consent form and assent form (if applicable) to the participant and schedule a time to discuss the consent and assent by telephone or web-based video or audio call (such as Skype, Webex, FaceTime, etc). The participant will be asked to sign the consent and assent (if applicable) and mail it back to the consenting study clinic.

- Once the signed consent and assent (if applicable) has been received by the study clinic, a specimen collection kit containing the required collection tubes will be mailed to the participant and additional information regarding the participant's family medical history will be collected.
- The blood samples will be obtained at a laboratory close to the participant's home, and shipped to the RADIANT Central Lab.

WGS will be performed at the Broad Institute. Genetic variant interpretation and the phenotypic implications of identifed variants will be performed by Discovery Teams at both the Broad Institute and Baylor College of Medicine, whose members will include clinical and molecular geneticists, bioinformatics experts, and experts in clinical diabetes and metabolic phenotyping. Variant calling of the WGS may include scrutiny of mitochondrial genome variants – in participants with a suspected mitochondrial disease phenotype or unclear finding from WGS, mitochondrial genome sequencing will be performed at Baylor College of Medicine.

For participants whose WGS results do not indicate a pathogenic/likely pathogenic variant in a known monogenic diabetes gene that is thought to explain the participant's diabetes, RNA-Seq testing will be performed at Baylor College of Medicine in order to better inform the Discovery Team's review.

The work of the Discovery Teams is expected to be an iterative process involving the expertise of their members in analyzing all data collected up to this point in the study to understand the significance of novel variants. In some instances, given sufficient pedigree information, it will be possible to identify alleles of genes that are highly likely to be causal with regard to the proband's diabetes-related phenotype(s). If such identification is not possible with the above data, or several genes are plausibly implicated, data on other individuals in the consortium's WGS data set, and data available from other exome or genome sequencing projects and genome wide association studies (GWAS) will be used to further analyze the genes and alleles identified. Additionally, the Discovery Team may determine that enrollment of the Proband's family members is necessary- see detail below under 'Enrollment of Family Members'. Details of Genome Sequencing and Interpretation procedures are provided in section 6.4.

Enrollment of Family Members
Upon review of a proband's data and test results in Stage 2, the Discovery Team may recommend that the proband's family members participate in RADIANT. This recommendation may be made for one of the following reasons, each involving different levels of participation:

(1) Family members with a suspected atypical diabetes phenotype may be of interest to the RADIANT study as participants in their own right who progress (potentially) through all stages of the study to provide complete genomic, molecular (other -omic), and deep phenotyping data. These individuals may also be genetically informative for study of the index case in a given family. Such family members with suspected atypical diabetes may be identified by the Adjudication Committee during family history review of the index case Family members with an atypical diabetes phenotype may be offered full enrollment in RADIANT, to follow all consent procedures, workflow, and sample collection (including blood sampling for DNA extraction) outlined above for index cases.

(2) Family members (affected or unaffected) may be identified by the Discovery Team as genetically informative solely for Sanger segregation of an identified HIGH SUSPICION atypical diabetes gene variant candidate. This identification would occur in Stage 2 or Stage 3, following an analysis of WGS data for the index case. Consent would be limited

to supporting blood sampling for DNA extraction for Sanger sequencing, a baseline questionnaire, and if the family members reports an unaffected DM status: fasting blood glucose (FBG) and hemoglobin A1c measurement (to confirm the individual's reported "unaffected" status). If FBG and HbA1c are normal but the family member is positive for the high suspicion variant and further phenotyping of these individuals is warranted, participants will be consented to Stage 3 procedures as determined by the Discovery Team. Results of the fasting blood glucose and HbA1c will be communicated to the enrolled family member, if they agree to receive these results. Family members who are negative for the high suspicion variant but screen positive for diabetes will typically not undergo further study, but RADIANT will maintain some flexibility to consider further phenotyping of relatives who have diabetes that is phenotypically distinct from that of the proband.

In this scenario, should the relative be unable to provide a blood sample (e.g., not able to visit a study clinic), collection of saliva for DNA extraction will be acceptable. In this scenario, after completion of fasting blood glucose and Sanger study of the HIGH SUSPICION atypical diabetes gene variant candidate, further phenotyping of this individual may be determined by the Discovery Team to be potentially informative for elucidation of the atypical diabetes phenotype in this family. In such a case, this relative may be contacted for participation in additional stages of the RADIANT study.

(Recognizing that parental samples may be informative in a substantial proportion of cases, and considering the opportunity cost of not enrolling parents simultaneously when they accompany pediatric-age participants for Stage 2 procedures, RADIANT will consider implementing parental consenting and sample collection in Stage 2.)

(3) The Discovery Team may in highly selected cases recommend trio-WGS (proband + both parents) as an additional analytic step to narrow down the variants of interest. This recommendation will be made for approximately 5 subjects per year depending on throughput and budget.

No direct contact of relatives will be performed by RADIANT team members without prior consent. Information about participation in RADIANT will be provided to the proband to share with their family members recommended by the Discovery Team. Family members who are interested will be instructed to contact RADIANT staff to provide consent and participate.

Stage 3
Probands who are invited to participate in Stage 3 will visit a study clinic to consent for Stage 3 and complete Stage 3 Standard procedures. Family members recommended for Stage 3 will complete procedures as recommended by the Discovery Team. Please refer to table 3 for further details. Blood will also be drawn in the fasted state to collect and store the following: a) blood monocytes for future inducible pluripotent stem cell (iPSC) derivation and analysis; and b) storage in the RADIANT biobank for future testing as approved by RADIANT. Urine will also be collected and stored in the RADIANT biobank for possible future tests.

Full iterative analysis of WGS, RNA, metabolomic, and deep phenotyping data will be performed to guide studies in additional family member, and the phenotyping experts on the Discovery Teams may recommend optional, individualized phenotyping tests to be performed on these participants and possibly on their family members, for the purpose of establishing genotype-phenotype correlations and understanding pathophysiologic mechanisms. The Discovery Team will determine if any additional family members of the participant should also be consented for Stage 1 data collection, Stage 2 data collection (i.e. WGS), or Stage 3 data collection (deeper

phenotyping procedures). This may occur if there are no clear candidate gene variants in the index case. In this scenario, and only after full analysis of all data has been completed, the Discovery Team may in highly selected cases recommend trio-WGS (proband + both parents) as an additional analytic step to narrow down the variants of interest. This recommendation will be made for approximately 5 subjects per year depending on throughput and budget. Parents would sign the applicable consent form and blood samples would be collected for DNA extraction.

The additional deeper phenotypic analyses may involve *in vivo* physiologic studies of affected individuals or relatives harboring the genetic variant who have not as yet developed the atypical phenotype, or *in vitro* studies of differentiated participant-specific iPSCs or other tissues or cells of these individuals. Details of Deeper Phenotyping procedures are provided in section 6.4.8.

2   INTRODUCTION

2.1   Study Rationale

Atypical diabetes comprises both uncommon genetic syndromes as well as clusters of phenotypically distinct forms of diabetes within a spectrum between two poorly defined poles of "type 1" and "type 2" diabetes. Distinct forms of atypical diabetes have traditionally been subsumed under the broad category of "type 1 diabetes" by virtue of certain characteristics (early onset, insulin requirement, or proneness to ketosis) or under the broad category of "type 2 diabetes" by virtue of other characteristics (later onset, response to oral agents, or coincident obesity, hypertension or dyslipidemia). A process to dissect the atypical forms away from the indistinct polar categories is essential to uncover their natural histories, novel mechanisms, and targeted therapies. Capturing rare patients, family members and subgroups with as yet undefined atypical diabetes syndromes will lay a foundation to uncover novel pathways leading to the final common endpoint of hyperglycemia and its complications. A comprehensive approach to identify and define new monogenic and oligogenic forms of diabetes, as well as phenotypic clusters of atypical diabetes across the diabetes spectrum is also predicted to reveal mechanisms and therapeutic targets that inform our understanding of the heterogeneity of "type 2 diabetes".

2.2   Background

Over 30 million adults in the U.S. have diabetes mellitus. There is considerable heterogeneity in the development and clinical presentation of diabetes in this broad patient population. Responses to pharmacologic therapy and development of complications from diabetes can also vary among patients. Our lack of understanding of this heterogeneity limits the goal of precision medicine in diabetes care, i.e., delivering therapy tailored to features of the affected individual. Diabetes has been traditionally classified as either type 1 (T1DM) or type 2 diabetes (T2DM); however, other subtypes of diabetes like latent autoimmune diabetes in adults (LADA), congenital generalized lipodystrophy, Wolfram syndrome, neonatal/congenital diabetes, maturity-onset diabetes of the young (MODY) and Ketosis-Prone Diabetes have been characterized and are now recognized. An even greater range of unrecognized forms of diabetes evidently exists, as many individuals in the clinical diabetes population fail to fit any these known types. The identification and study of new cases of rare or atypical forms of diabetes may yield greater insight into the heterogeneity of more common forms of T2DM.

Detailed genetic analysis and phenotyping of atypical individuals and their families may help to characterize subtypes within the spectrum of T2DM in the general population and reveal novel mechanistic or causal pathways that can be leveraged for prevention or treatment of T2DM. Studying the underlying genetic background of these individuals may also lead to the identification of function for polymorphisms in or near known T2DM genes and explain the contribution of specific loci to aspects of polygenic T2DM. These genetic and phenotypic studies may also help in identifying new biomarkers for screening and diagnosis. Furthermore, genetic studies may help identify drug targets and catalyze the development of therapies for use, not just by these individuals with rare/atypical forms of diabetes but also by patients with newly identifiable subtypes of T2DM in the general population.

Thus, dedicated efforts to discover and study rare/atypical forms of diabetes will aid affected individuals directly by informing their pathogenesis and treatment and also address the heterogeneity of T2DM seen in the broader populations by providing new insights on mechanisms, diagnoses, and treatments for T2DM.

2.3 Data/Sample Collection

Under this protocol, participants identified as having a previously unrecognized atypical form of diabetes will contribute data and biospecimens for further analysis. Data will include personal identifying data, personal and family histories, photography, questionnaires, and information about their clinical diabetes presentation and management. Peripheral blood samples may be collected for: immunological and genetic testing, metabolic testing (ex. fasting C-peptide, fasting glucose, lipids, metabolic panel, HbA1c), metabolomics, and RNA-Seq. Participants may be asked to provide additional samples to replace samples that have been depleted or insufficient volume, did not pass a quality control check, or that were never received by the central lab. Blood volume restrictions will be adhered to as described in section 2.3.1.

Samples of whole blood, serum, plasma and extracted DNA/RNA may be collected, submitted to the NIDDK repository and RADIANT biobank and stored for use in future testing. (Appendix 1, Appendix 2)

Samples collected outside of RADIANT may also be analyzed as part of the RADIANT study if available and in accordance with applicable regulatory requirements.

2.3.1 Collection of Peripheral Blood

Blood collection is a routine procedure for patients with diabetes under standard-of-care practice. Blood collection, especially the planned volume, confers no additional risk greater than that inherent in standard-of-care blood collection.

RADIANT will follow the below guidelines for minimal risk blood draws:
- For healthy adults: The amount of blood drawn may not exceed the lesser of 10.5 mL/kg or 550 ml in an 8-week period.
- For children: The amount of blood drawn may not exceed 5 mL/kg in a single day and no more than 9.5 mL/kg may be drawn in an 8-week period.

The potential benefits include unique and novel knowledge about immunological state (diabetes-related autoantibodies), metabolic state, genetic markers, disease-related integrative

in vitro physiology (utilizing target tissues derived from iPSCs) and disease-related whole body *in vivo* physiology (utilizing a range of techniques).

2.3.2 Collection of Saliva

Saliva collection is an alternative to blood collection for DNA extraction. Although blood samples primarily will be used for DNA extraction, saliva samples will be acceptable from relatives of a proband who are: 1) identified as genetically informative for further study of an identified candidate variant of HIGH SUSPICION in the proband; 2) do not reside in geographical proximity to a RADIANT study phlebotomy site. In these cases, a standard saliva collection kit will be utilized. [Note: All proband DNA will be collected from blood samples, as described above.]

2.3.3 Genetic Testing

To fully examine the genetic basis of atypical forms of diabetes, this study seeks a comprehensive determination of genomic variation, through WGS, for all participants selected and prioritized by the Adjudication Committee to be further evaluated for atypical diabetes in Stage 2. Nuclear WGS of germline DNA will be performed on such participants (as well as potentially his/her mother and father to support a trio-based genomic variant analysis if recommended by the Discovery Team, as described above in section 1.3.2).

Identified variants will be mapped to the human reference genome assembly; variant calling will be performed using well-established pipelines. Analysis of identified nuclear and mitochondrial-encoded variants will proceed in 2 phases:
1) Identification of pathogenic or likely pathogenic variants in (a) known monogenic diabetes genes and (b) genes identified by the American College of Medical Genetics and Genomics (ACMG) as medically actionable. Genes identified by the ACMG as medically actionable that are ALSO known monogenic diabetes genes will be retained in the primary analysis for all subjects, even in cases for which a subject has opted-out of medically actionable secondary findings.
2) Identification of candidate causative variants for the atypical diabetes phenotype

In addition to WGS, mitochondrial DNA sequencing will be done on selected participants and RNA sequencing will be done on all participants whose WGS results do not indicate a pathogenic/likely pathogenic variant in a known monogenic diabetes gene that is thought to explain the participant's diabetes.

WGS data that are to be made available with specific data-sharing restrictions will be submitted with the appropriate consent/data sharing information to the database of Genotypes and Phenotypes (dbGaP), through the dbGaP Registration Portal/System, or other databases/repositories as applicable. All identified variants ultimately considered etiologic for atypical diabetes will also be submitted to ClinVar.

3   OBJECTIVES AND ENDPOINTS

This protocol defines the process by which RADIANT will seek to identify cases for further study. The purpose and objectives of RADIANT are:
- To become a national leader in comprehensive efforts to discover and study individuals

and families with rare/atypical forms of diabetes
- To identify rare/atypical forms of diabetes and promote collaborations to characterize molecular mechanisms underlying these rare disorders
- To develop a strategy and process for identifying individuals/families with rare/atypical forms of diabetes
- To create a strategy for accomplishing research on individuals/family members with rare/atypical forms of diabetes
- To build and manage a database and biospecimen repository to store data and samples from individuals with atypical diabetes
- To facilitate use of data and samples by the broader research community

Cases that cannot be classified as a known form of diabetes through the screening process will be enrolled into this study for further evaluation.

4   STUDY DESIGN

4.1   Overall Design

This is an observational study of individuals and family members with rare and atypical forms of diabetes.

4.1.1   Identification and Study of Rare/Atypical Forms of Diabetes

Participants with potential atypical forms of diabetes will be consented, screened and evaluated with questionnaires and antibody testing. A committee of selected expert RADIANT consortium members, the Adjudication Committee, will review this data on up to 400 participants per year (probands and affected family members) and determine which participants are eligible for further evaluation with WGS. Participants who may have a new form of rare/atypical diabetes will be further studied with laboratory testing, physical exams, and additional phenotyping tests to better characterize and understand the pathophysiology underlying their atypical diabetes.

4.1.2   Primary Endpoint Summary

The primary endpoint for RADIANT is to become a national leader in identifying rare and atypical forms of diabetes among individuals and families, investigating and defining their molecular and metabolic bases, and developing processes as well as a database and biorepository to enhance further understanding of atypical diabetes by the broader research community.

5   STUDY POPULATION

5.1   Summary Description of Study Population

The study aims to enroll individuals and family members with hitherto undiagnosed rare and atypical forms of diabetes. Individuals with suspected atypical diabetes may be referred by existing atypical diabetes registries, RADIANT study clinics, diabetes cohorts and prospective clinic registries, other existing databases and EHRs, clinical providers, or may be self-referred.

5.2 Inclusion Criteria

The study will enroll participants with atypical diabetes and their affected family members.

The following criteria or phenotypes will be considered for suspecting "atypical" participants:
- Type 2 diabetes diagnosed at a time when the individual was prepubertal or non-obese
- Mendelian pattern, especially with early onset (<18 years old)
- Syndromic (multiple systems involved)
- Lipodystrophic
- Extremes of BMI
- "Mitochondrial" characteristics (e.g., myopathy, hearing deficits)
- Non-progressive
- Rapidly progressive ("fulminant")
- Low insulin requirements (<0.5 u/kg/day)
- Cyclical hyperglycemia with periods of remission
- Lean persons with polycystic ovarian syndrome (PCOS)
- History of gestational diabetes (GDM) when lean
- Lean insulin-resistant persons
- <u>If islet autoantibodies and beta-cell function parameters have been measured</u> (where "A" = islet cell autoantibodies, "B" = beta-cell function):
  - A-B- (i.e., lacking islet autoimmunity makers and lacking beta cell function)
  - A-B+ with unprovoked DKA at initial presentation (i.e., lacking islet autoimmune markers, with preserved beta-cell function, but presenting with unprovoked DKA)
  - A-B+ of very young onset (pre-pubertal) (i.e., lacking islet autoimmune markers, with preserved beta-cell function, but very early onset T2D-like phenotype)

Family members without atypical diabetes may also participate in research studies as recommended by the Discovery Team to inform the understanding of atypical diabetes. Their participation will be informative for the genomic analysis, variant interpretation, and deeper phenotyping components of this study. Such family members may be offered to participate in Stages 1, 2, and/or 3 of this study (as requested by the Discovery Team); however, unaffected child family members will not be asked to participate in Stage 3 (deeper phenotyping).

A full list of possible study procedures by stage, tier (for Stage 3), and participant population is in Appendix 1.

5.3 Exclusion Criteria

1. Those with high likelihood of typical type 1, typical type 2, known monogenic, or other known secondary forms of diabetes
2. Refusal of consent for genetic testing
3. Islet autoantibody positive (participants who are islet autoantibody positive but present with additional atypical features i.e. syndromic, strong linear family history of diabetes may not be excluded)
4. Women who are currently pregnant

5.4   Strategies for Recruitment and Retention

5.4.1 EHR Screening

This strategy will leverage RADIANT study sites with the capability to recruit through EHR. Initial EHR recruitment will be based on EHR searches through data query systems developed based on inclusion and exclusion criteria. Individuals identified through EHR will be contacted according to the policy of the institutions - in most instances, letters or notifications (e.g., secure email messages or phone calls with scripts) through their primary care provider or specialist with the option to opt out of the study or further contact. If an individual (or family, in the case of a pediatric age patient) is interested in the study, they will be directed to the online application form or a RADIANT site for screening for the study, or a letter will be sent with information for recruitment and screening for the study.

5.4.2 Diabetes Cohort/Databases

The study will use diabetes cohorts and databases that are known to have valuable datasets that include potential "atypical" individuals.

We have identified cohorts with key features that make them ideal for this approach: large databases, longitudinal follow-up, stored samples of fasting serum, stored DNA (or PBMC's from which to extract DNA), large geographic spread, and a wide range of age and ethnic groups. There are also unique strengths in some of these cohorts. For example, the SEARCH cohort is exceptionally large (n=4900 in the longitudinal arm) and diverse (54% non-Hispanic White (NHW), 21% African-American, with other US ethnic and racial groups well represented), and includes every form of pediatric and adolescent diabetes from across the United States. In addition, most of these cohorts have the ability to re-contact participants for follow-up studies or additional testing. Most cohorts code participants as having type 1 or type 2 diabetes. There is generally no coding for forms of atypical diabetes, except for monogenic diabetes in some cohorts. We have devised a filtering process to identify participants with atypical diabetes tailored to the individual cohort or database. We also will reserve a very large cohort (diabetes patients in the Department of Veterans' Affairs' Million Veterans Project) to serve as a validation cohort.

The process of case selection for possible enrollment will follow the same model as specified above for searches of the EHR. RADIANT will utilize study data and linked genetic data (if available) to identify suspected cases, regardless of the diagnosis currently associated with the case. Once suspected cases are identified, the cohort/database sponsor will contact them on behalf of RADIANT and solicit interest in participation. Individuals interested in participating will be asked to consent, sign a medical record release form if applicable, and follow the general steps toward enrollment specified in 1.3.2.

5.4.3 Atypical Diabetes Registries

Existing atypical diabetes registries will be approached for participant recruitment. In addition to the monogenic, lipodystrophic and ketosis-prone diabetes registries already mentioned, RADIANT has access to extensive genetic disease registries, which enable identification of atypical diabetes participants and families with likely monogenic, oligogenic and mitochondrial genetic etiologies. Thus, existing genomic/genetic data generated from participants and families

with atypical diabetes in these registries will jumpstart the discovery aspects of RADIANT if available.

The process of case selection for possible inclusion will follow the same model as specified above for searches of the EHR. Once suspected cases are identified, the registry sponsor will contact the participants for possible participation in the study. Those expressing an interest will be asked to consent, sign a medical record release form if applicable, and follow the general steps toward enrollment specified in 1.3.2.

5.4.3.1 Other Recruitment Strategies

RADIANT will use a range of strategies, including:

1: Printed Advertisement inside Clinics and Primary Care Practitioner Offices

2: Social Media/Internet

3: Patient Advocacy Groups

4: Healthcare provider letters and information sessions

5.4.3.2 Specific Strategies To Recruit Historically Under-Represented Populations

Increased enrollment of underrepresented minorities in clinical research studies permits better generalizability of results and provides a richer dataset for medical discovery. In particular, clinical trial registries could be a mechanism to engage individuals and research volunteers in the medical discovery process. Underrepresented racial and ethnic minority stakeholders and patients have provided feedback on the development of disease registry platforms. Their voices offer valuable insight on recruitment and retention challenges for research volunteers, feasibility of enrollment expectations, ease of the informed consent process and return of value propositions. Early engagement of diverse stakeholders is necessary for identifying a broad swath of facilitators to research engagement and participation among cross sections of the population such as older adults, sexual minorities, low literacy and low-income individuals. Ongoing efforts relevant to this area include adopting a comprehensive and multilevel approach to engage a large, diverse group of stakeholders in the development of disease registries. Based on the goals of this project, the Recruitment Innovation Center (RIC) and the Faster Together supplement (supported by NIH, U24TR001579-01S1) will provide guidance on multimodal registry recruitment strategies to engage and recruit underrepresented minority populations. Our participating Study Clinics were chosen in part because their locations are in population centers that will assist in recruiting underrepresented populations.

5.4.4 Retention Strategies

Once participants or family members are enrolled at Stage 1, it is important to keep them engaged and retained in the study through the subsequent stages. This retention will be facilitated by frequent communication (phone, email, text) between the participant and the study team. Some of these communications will be driven by the need to report back results (biochemical, genetic); in addition, if there are long gaps in moving from one stage to the next

for a given participant, the study team will contact the participants to ask if they are doing well and if any questions or concerns have arisen.

6 STUDY ASSESSMENTS AND PROCEDURES

6.1 Study Approach

6.1.1 Screening for Study Eligibility

Screening criteria will be applied to the three sources of participant recruitment: existing atypical diabetes registries, individual referrals (from Study Clinics, non-study clinicians and self-referral) and diabetes cohorts/databases (Figure 1). The atypical diabetes registries and diabetes cohort/databases have established specific data queries to mine their participant data to identify potential candidates with atypical diabetes of unknown etiology. Once they are identified, participants who are contactable will be contacted according to individual registry rules and asked to enroll in the study.

All participants regardless of recruitment method will provide informed consent for Stage 1 and complete initial screening questions to exclude autoimmune type 1 diabetes, typical type 2 diabetes and secondary diabetes, as well as queries to reveal key features of atypical diabetes.

Initial screening data from participants will be reviewed by RADIANT staff. Participants who pass the initial screening questions (i.e., they potentially have atypical diabetes) will be instructed to complete additional questionnaire sections about themselves, including their medical history, clinical presentation, and family history. Participants may also be asked to provide medical records or other previous test results if available, to verify their questionnaire responses and to help further determine eligibility by the adjudication committee. The questionnaire will be available on paper and via an online portal where the participant will have a secure log in to access and complete the questionnaire sections at their convenience. At this point, RADIANT staff may request medical records and optional information from the participant's physician describing why they think the patient is atypical. RADIANT staff will review the questionnaire data. Participants who are deemed appropriate to continue will be sent a sample collection kit to perform autoantibody testing. RADIANT staff will be available to answer any concerns of the participant and will establish a line of communication for future study team contact with the participant as the evaluations proceed.

6.2 Visit Schedule, Events, and Activities

In-person study visits will occur: 1. At Stage 2 (unless the participant performs procedures remotely); and 2. At Stage 3 (for deeper phenotyping). An in-person study visit may also occur for Stage 1 as an alternative to remote/online participation, if preferred by the participant and study clinic. Follow-up procedures may involve additional visits.

Note on nomenclature:
- "Study Clinic coordinator" refers to a designated person at each participating Study Clinic who will interact with participants who visit or plan to visit that Study Clinic as part of the RADIANT protocol.

- "RADIANT Administrative Cores" refer to the University of Chicago and Baylor College of Medicine – Project Managers at these centers will oversee the workflow related to movement of participants through the protocol, from screening to deeper phenotyping.
- "RADIANT Central Lab" refers to laboratory where all baseline blood tests will be processed, DNA will be extracted, and samples will be stored.
- "Data Coordinating Center" or "DCC" refers to the University of South Florida where data will be received, stored and transferred as needed, all electronic forms will be developed and implemented, and the RADIANT website will be developed and monitored.
- "Sequencing Centers" refer to the Baylor College of Medicine Human Genome Sequencing Center (for mitochondrial genome sequencing and RNA-seq) and the Broad Institute (where nuclear WGS will be performed).

Participants identified by screening as potentially "atypical" will have all questionnaire, antibody testing and any other additional medical data reviewed by the Adjudication Committee. If the Adjudication Committee determines that the participant appears to have a new rare/atypical form of diabetes, the participant will be invited to participate in Stage 2 laboratory procedures at the most conveniently located Study Clinic or by a remote kit collected as done for Stage 1.

Prior to Stage 2 procedures, the participant will provide informed consent and assent (if applicable) to undergo the Stage 2 tests. Blood samples will be collected per protocol and shipped to the RADIANT central laboratory for sample storage and DNA/RNA extraction. Laboratory results will be shared with the participant if they so designate at the time of consent. Additional family medical history will also be collected at this stage. This information will be used to create a pedigree of the proband's family.

After WGS of participants in Stage 2, WGS data review, variant analysis and bioinformatics analysis will be conducted by the core Genetics group of the Discovery Team and the two sequencing centers (Baylor and Broad/MGH). If the WGS results do not indicate a pathogenic/likely pathogenic variant in a known monogenic diabetes gene that is thought to explain the participant's diabetes, RNA-Seq will be performed and mitochondrial genome sequencing and analysis may be performed at Baylor College of Medicine.

In Stage 3, all participants will be required to have an in-person visit at a study clinic to obtain the Stage 3 standard visit consent and assent (if applicable), as well as a standard set of tests and procedures, including a comprehensive physical exam with photography, specimen collections, and additional questionnaires. Participants may be invited to participate in Stage 2 and Stage 3 at the same time. This may involve both the Stage 2 and Stage 3 procedures occurring during the same visit. Or, participants may complete the Stage 2 procedures (i.e. consent, questionnaire, blood collection) prior to the Stage 3 visit. If WGS is completed before the Stage 3 visit and a known pathogenic/likely pathogenic variant in a monogenic diabetes gene thought to explain the participant's diabetes is found, the participant may be asked to not proceed to Stage 3.

The Stage 3 standard tests are: fasted blood draw for lipid profile, comprehensive metabolic panel, HbA1c, and metabolomics. Blood will also be drawn in the fasted state to collect and store blood monocytes for future inducible pluripotent stem cell (iPSC) derivation and analysis, as well as store additional blood and urine samples for future testing in the RADIANT and NIDDK repository. Following this, a standardized oral glucose tolerance test (OGTT) will be performed. Glucose and C-peptide will be measured at all time points of the OGTT, and these measurements will be used to calculate quantitative estimates of insulin secretion and insulin

sensitivity. Insulin will be collected and stored and will only be measured later for selected set of partcipants that the Discovery Team deam necessary for further analysis. Additional standard testing, such as physical functioning assessment and questionnaires, are described in Section 6.4.8.

All the data acquired in Stages 1, 2, and 3 will be reviewed and analyzed in an iterative manner by the Discovery Team – comprising both core Genetics group members and phenotyping experts and diabetes clinicians from the RADIANT consortium. After final analysis or working diagnosis of a novel form of diabetes at this stage, the Discovery Team phenotyping experts may develop and prioritize an additional, optional, individualized "deeper phenotyping" plan for each participant/additional family members.

Additional, optional Stage 3 deeper phenotyping tests are categorized in 2 "tiers" based on burden, risk and cost. During the consent process, the participant will be consented for each test recommended by the Discovery Team. The specific additional phenotyping options plus travel arrangements to specialized phenotyping core sites will be discussed with the participant and the process will be facilitated through a RADIANT Administrative Core to ensure that the participant has access to all the research resources for testing that the study offers to its atypical diabetes participants to understand their disease. The additional, individualized deeper phenotyping recommendations of the Discovery Team will be reviewed by the RADIANT Steering Committee for final approval or modification based on considerations of budget, safety and participant burden.

6.3 Study Procedures

6.3.1 Informed consent

RADIANT includes three Stages, and therefore at least three points for consent, for participants and potentially family members. They will complete Stage 1 consent and then complete Stage 2 consent and Stage 3 consent if they continue to those stages. Other family members may also be referred to consent for Stage 1, Stage 2, or Stage 3 study procedures per the Discovery Team's recommendation; however, unaffected pediatric family members will not be referred for consent/assent to Stage 3 study procedures. Study participants will be asked to provide assent for Stages 2 and 3 if applicable.

Three methods of informed consent are possible for RADIANT:

1) In-person informed consent / assent at a Study Clinic (Stage 1, 2 and 3 – and family member consent / assent for Sanger Sequencing or WGS-Trio)
2) Informed consent / assent over phone or video (Stage 1, 2 and some Stage 3 tests – and family member consent / assent for Sanger Sequencing or WGS-Trio)
3) Online informed consent (Stage 1 only)

The informed consent process for each method above is described in section 8.1.1.

6.3.1.1 Stage 1 Questionnaire

The Stage 1 questionnaire will be completed by the study participant (with caregiver assistance, if necessary) at home or anywhere the study participant has internet access (if completing

electronically). If the participant has questions, they may contact the RADIANT study team for assistance.

The Stage 1 questionnaire contains 5 sections as described here:

Section number	Section content
1	Screening
2	Demographics, physicians, recruitment information
3	Diabetes status, diabetes history, current height/weight
4	Birth history, medical history
5	Family history

6.3.1.2 Medical Record Collection

Participants may be asked to sign a medical record release form for the RADIANT team to obtain their medical records from their physician and/or referring registry. These records may be used to further assess whether the participant qualifies for the RADIANT study and advance discovery aspects of the study. Medical records may be collected for RADIANT participants, with a signed medical record release form, at any time for as long as they are in this study.

6.3.1.3 Proband Pedigree

During Stage 2, additional information regarding the proband's biological family medical history may be collected. This information will be used to create the proband's pedigree and to help determine whether family member enrollment would be beneficial. Participants may be asked about diabetes and non-diabetes related family medical history. For pediatric participants, this information will be collected from the participant's parents or legal guardian.

6.3.1.4 Physical Exam

A detailed, standardized physical examination will be performed at the Stage 3 in-person visit and will include vital signs, biometric measurements, anthropometrics, physical function tests, questionnaires and photography.

If the participant consents to photography as part of the standardized physical exam, we will take a series of photographs to capture overall fat and muscle distribution as well as the proportions of body weight in different parts of the body (face, trunk, extremities). We plan to take closeup photographs of the face/neck region, trunk (from neck to hips including arms) lower extremities, and full body front, back and sideways photographs. These photographs will be obtained and securely transmitted to the DCC. The photographs are helpful to understand variability in the presentation of fat and muscle distribution that is an important part of the study of atypical diabetes. "Morphomics" can be as powerful a tool as genomics or transcriptomics, or can enhance the power of the other "omics" platforms. Body and facial morphometrics represent an integration of gene expression and epigenetic influences. Machine learning algorithms using simple digital photography have been used successfully to identify important genetic conditions. In the study of rare and unusual forms of diabetes, there may be physical features specific or sensitive enough to diagnose a new form of the disease.

6.3.1.5 Other Procedures

Laboratory procedures and Stage 3 deeper phenotyping procedures are described in section 6.4. A table of all procedures with the participant population noted is included in Appendix 1.

6.4 Laboratory Evaluation and Phenotypic Characterization

6.4.1 Stage 1 Sample Collection

All participants will undergo autoantibody testing during Stage 1. A sample collection kit will be mailed to the participant which includes all of the required materials needed for a capillary collection or a venous blood draw.

Blood will be collected and shipped to the RADIANT Central Lab. The RADIANT Central Lab will analyze samples for diabetes autoantibodies. A list of samples and data expected to be available for outside investigators/NIDDK Central Repository can be found in Appendix 2.

6.4.2 Processing and Shipping

Blood samples will be collected by staff according to established procedures and will be shipped per established protocol to the RADIANT Central Lab.

6.4.3 Stage 1 Laboratory Results

Test results will be returned to the DCC. The DCC will alert the Study Team that results are available and make them available for viewing by the Study Team on a secure web platform. If the participant has agreed to receive their results, the results will become available to them on a secure web platform. The Study Team will also share the results with the participant's healthcare providers (if requested on their consent form).

6.4.4 Stage 2 Laboratory Tests and WGS

Participants will have their blood drawn for samples required for DNA and RNA sequencing in Stage 2. Full participant instructions for Stage 2 will be reviewed with a RADIANT staff member over the phone or in-person when they are consented for Stage 2.

We will follow the blood draw amount guidelines described in section 2.3.1 for ensuring minimal risk blood draws. The samples will be shipped to the Central Lab. A list of samples and data expected to be available for outside investigators/NIDDK Central Repository can be found in Appendix 2.

Coded DNA samples from participants who proceed to, and provide informed consent for, Stage 2 of the study, will be sent for genome sequencing analysis to the Genomics Platform at the Broad Institute. DNA will be subjected to high-throughput genomic sequencing in a CAP/CLIA environment using the most current, start-of-the-art technologies, and quality control checks used to ensure adequate depth of coverage and confirm sample identity and reported pedigree

relationships. Standard, well-described platforms for alignment to the human genome reference sequence, and for calling of single nucleotide, indel, and copy number variants will be employed. Variant annotation will be performed using available and public aggregated variant databases.

RNA sequencing will be performed at Baylor College of Medicine in this stage if the WGS results do not indicate a pathogenic/likely pathogenic variant in a known monogenic diabetes gene that is thought to explain the participant's diabetes. Standard protocols for cDNA library preparation and next-generation sequencing, and alignment will be used for quantification of transcript expression and identification of variant transcripts (such as alternative splicing events). Mitochondrial DNA sequencing may also be performed at Baylor College of Medicine if the Adjudication or core Genetics group deems the participant's presentation warrants it, and will be performed using a long-range PCR technique to eliminate confounding nuclear-encoded mitochondrial pseudogenes.

Certain samples will be stored in the RADIANT Biobank for use by RADIANT or outside investigators (with study approval). Prespecified banked samples in the RADIANT Biobank will be transferred to the NIDDK Biorepository per Biorepository guidelines. Samples in the NIDDK Biorespository may be accessed by future investigators. A list of samples and data expected to be available for outside investigators/NIDDK Central Repository can be found in Appendix 2.

6.4.5 Initial WGS Analyses For Known Conditions

Analysis of identified genome sequence variants will proceed in 2 phases. In the first phase, analysis will focus on identification of pathogenic or likely pathogenic variants in: (a) known monogenic diabetes genes and (b) genes identified by the American College of Medical Genetics and Genomics (ACMG) as medically actionable (see section 6.4.7 for information on return of genetic results).

We anticipate that this stage of analysis will identify a small proportion of individuals with pathogenic or likely pathogenic variants in one of the genes currently recognized by the ACMG as 'medically actionable'.

6.4.6 WGS Analysis For Discovery

Genome sequencing data will be analyzed jointly at Baylor and Broad using a variety of bioinformatic programs and tools. A rare variant, family-focused analysis approach will take advantage of pedigree structure and genome sequencing data from studied relatives (parents, available siblings) to identify potentially etiologic variants that segregate in a pattern consistent with the observed mode of inheritance (e.g. *de novo*, autosomal dominant, autosomal recessive, X-linked) for each family. The most likely etiologic variants will be rare (not present, or rarely present in population databases) and either likely gene disrupting or predicted to have a deleterious effect on protein function. Identified high confidence variants will be confirmed using a second, orthogonal method, such as dideoxy Sanger sequencing, as needed.

6.4.7 Return of results for genetic testing

Primary genetic results will be returned to the participant if consent was given for this (Stage 2 consent forms). The results may include information such as a diagnosis of a certain type of diabetes and/or a pathogenic or likely pathogenic variant in a gene associated with diabetes. Variants of uncertain clinical significance (VUS) will not be returned to participants. Participants found to have known monogenic forms of diabetes will be connected with experts who specialize in those forms of diabetes. All results will be explained to the participant by a trained RADIANT team member.

Secondary findings (such as those recommended by ACMG) will be reported back to the participant if consent was given for this (Stage 2 consent form). In rare cases, the Geneticists Team may identify variants in genes beyond the ACMG guidelines that are medically actionable. A careful review of such findings and their actionability would be performed with our ethical team in order to determine the appropriateness of reporting this type of secondary finding.

Genetic results shared with the participant will also be shared with the participant's healthcare provider if consent was given for this (Stage 2 consent form).

For participants less than 18 years of age, results returned will include only that information directly related to diseases and disorders that affect children (pediatric-onset). These participants, when they turn 18 years of age, may then choose to request additional information regarding the results of the RADIANT study for the duration of the RADIANT study.

Rarely, we may identify cases of misattributed paternity or other misassumed familial relationships. In general, we will not share this information. However, there may be rare circumstances where we would need to share this information, such as to give correct information about recurrence risks if the participant requested that information.

Genetic counseling will be available for any participant who requests it. This genetic counseling will be available and paid for by RADIANT for the duration of this study.

Participants will be given the option to designate another person to receive results in the event that the participant loses decision-making capacity prior to receiving all study results (Stage 2 consent forms).

6.4.8   Deeper Phenotypic Analysis (Stage 3)

Stage 3 of RADIANT includes a standard set of tests and procedures, and possibly additional, optional deeper phenotypic testing. In addition to the participant, additional informative family members could be invited to participate in study procedures from Stage 1, Stage 2 or Stage 3. Unaffected child family members will not be asked to participate in Stage 3. (Section 5.2; Appendix 1)

Blood sampling for the Standard Tests in Stage 3
Participants will be required to be fasting (no food or drink except water for 10 hours prior to visit) for the Stage 3 standard visit blood draws (HbA1c, CMP, Lipid profile, OGTT, metabolomics, and plasma/serum for storage). Glucose, and C-peptide measurements will be analyzed for all OGTT time points, aliquots for insulin testing will be collected and stored for future testing as determined by the Discovery Team. We may ask participants to hold their medications on the morning of their Stage 3 visit. Participants will be asked to bring their

medications to the visit and may resume their usual medication regimen after all blood samples have been collected. If a participant is not fasting or otherwise does not meet visit/OGTT eligibility criteria, all or part of the visit may be rescheduled for another day.

We will follow the blood draw amount guidelines described in section 2.3.1 for ensuring minimal risk blood draws.

Additional, optional deeper phenotyping tests in Stage 3
The participants/family members may also be considered for additional, individualized deeper phenotyping tests to characterize the novel syndrome and understand its pathogenesis. The nature and order of these additional deeper phenotyping tests will be recommended by the Discovery Team on a case-by-case basis, depending upon: a) the novelty of the phenotype; b) clues from the genetic variant analysis, laboratory tests and clinical features; c) burden to the participants; d) cost; e) relevance to the goals of RADIANT to diagnose and characterize new forms of diabetes.

Clinically-indicated testing
If the participant's condition warrants it, the Discovery Team may recommend clinically-indicated testing, for example, vision testing and hearing testing in persons with visual or hearing impairment. These are optional and would not be part of RADIANT; thus, they would need to be coordinated by the participant's health provider and would be billed to their insurance company. If the participant agrees and signs a medical record release form, we may request to see the results of this testing to better understand their condition.

Discovery Team
The Discovery Team includes phenotyping experts who will use the above parameters to prioritize which probands / family members to characterize phenotypically beyond the standard Stage 3 tests, and what would be the most informative and cost-effective additional deeper phenotyping test(s). The highest priority will be assigned to the most unique atypical participants or to those prototypical of a group of atypical participants with a similar syndrome. The additional deeper phenotyping recommendations of the Discovery Team will be reviewed by the Steering Committee for final approval. When possible, the Discovery Team will try to group deeper phenotyping procedures together to minimize travel burden to the participant, with the caveat that some procedures may be available only at specialized centers. RADIANT will either 1) reimburse participants for allowable travel expenses, or 2) pay upfront for allowable travel expenses. See section 6.5 for additional information.

There is considerable depth and breadth of phenotyping expertise and resources available among the RADIANT consortium members to characterize participants who proceed to the additional deeper phenotyping phase of Stage 3. All of the available tests (described below) can provide information that falls within the scope of RADIANT to characterize atypical forms of diabetes, but since they are not clinically indicated and involve additional burden or risk to the participant, they require additional consent. Hence, before proceeding to these additional deeper phenotyping tests, participants will provide further informed consent that includes specific permission for each of the tests recommended by the Discovery Team (see Section 8.1.1, Stage 3 consent).

Stage 3 Testing Tiers

To assist the Discovery Team and Steering Committee with prioritization of additional deeper phenotyping for individual participants, the Stage 3 tests are categorized in 3 "tiers" based on burden, risk and cost:

Tier 1 (Standard for all Stage 3 participants)
- Tier 1 tests are low risk, low burden, and low cost:
    - Fasting blood draw for standard collection as described above
    - 2-hour OGTT
    - Full Physical Exam:
        - Vitals
        - Anthropometrics
        - Acanthosis Staging
        - Hirsutism exam
        - Tanner Staging
        - Michigan Neuropathy Screening Instrument (MNSI) physical and self assessment
        - Physical functioning assessment
        - Mini-Mental State Examination
        - Photography
    - PBMC collection and storage (with potential derivation/analysis of a patient-specific pluripotent stem cell line from stored monocytes)
    - Blood collection for biobanking and future testing
    - Additional questionnaires to either be completed at the in-person visit or post visit:
        - ASA24 Food Recall
        - Physical Activity and Physical Fitness questionnaire
        - PROMIS questionnaires
        - Education Level Questionnaire
        - Environmental Questionnaire
    - Medication Inventory
- Tier 1 tests may be performed at any study clinic.

Tier 2 (Optional)
- Tier 2 tests are low risk, low to moderate burden, and high cost:
    - Specialized vision testing
    - Specialized auditory testing
    - Dual Energy X-ray Absorptiometry (DXA)
    - Abdominal Magnetic Resonance Imaging (MRI)
    - MMTT – Short Format
    - Continuous Glucose Monitoring (CGM)
    - Standardized meals with CGM
    - Wearable device (such as fitbit, actiwatch or other marketed fitness tracking device)
    - Additional PROMIS surveys
    - Wolfram Scale

- o Vineland Assessment
- o Patient Health Questionnaire depression scale (PHQ8)
- o General Anxiety Disorder (GAD-7)
- Tier 2 tests will be performed at specialized RADIANT phenotyping centers or remotely if possible.
- Tier 2 tests represent higher burden to the participants than Tier 1 tests, mainly because they may involve travel to and stay at the specialized centers.

Tier 3 (Optional)
- Tier 3 tests are low to moderate risk, high burden, and high cost:
  - o Frequent sampling intravenous glucose tolerance test (FSIVGTT) (Permitted for adults and children aged 0-17)
  - o 2-step hyperinsulinemic-euglycemic clamp (Permitted for adults and children aged 7-17)
  - o Hyperglycemic Clamp with Arginine Stimulation (Permitted for adults and children aged 7-17)
  - o MMT - long format (Permitted for adults and children aged 0-17)
  - o *Fat Biopsy
  - o *Muscle Biopsy
  - o *Liver Biopsy
  - o *Skin Biopsy

    Note: * Permitted for adults only.

- Tier 3 tests will be conducted in affected pediatric participants if recommended by the Discovery team and based on maximum blood volume and ONLY if no sedation is required to perform such tests.
- Tier 3 tests will be performed at specialized RADIANT phenotyping centers.
- Participants may need admission to inpatient Clinical Research Centers.

The above approach to additional deeper phenotyping is designed to identify and characterize participants and family members with novel, atypical forms of diabetes. However, highly informative analyses of participants / family members or their stored samples that enhance understanding of the novel atypical forms of diabetes and expand the scope of mechanistic discovery can also be performed through independently funded ancillary studies. RADIANT has developed a policy and procedures for an Ancillary Studies Committee to encourage, receive and review proposals to perform such analyses.

We recognize that state-of-the-art disease discovery approaches that go beyond novel gene/variant correlation with the clinical phenotype can move in two directions in the case of atypical diabetes syndromes: a) in-depth exploration of phenotypic variation that reveals how a putative gene variant or mechanism affects the diabetes phenotype or its complications; b) defining unequivocally the cause of the new forms of diabetes. The deeper phenotyping tests described above largely facilitate discovery in the first direction, i.e., exploring and characterizing phenotypic aspects of the novel atypical syndromes of diabetes. To facilitate discovery in the second direction – defining the causative mechanisms of these syndromes – RADIANT intends to leverage, through its Ancillary Studies process, the many innovative

advances in model organisms, high-throughput molecular interaction studies and iPSC-based rapid knock-in technology available in institutions both within and outside the RADIANT consortium.

6.5   Participant Compensation

If participants are asked to travel to a Study Clinic for any Stage of RADIANT, we will cover the cost of their parking at the Study Clinic. If participants are asked to mail materials back to study sites at any Stage of RADIANT, we will provide them with a prepaid envelope/prepaid postage for mailing. If participants are asked to travel to a Study Clinic for deeper phenotyping (Stage 3), we will either pay upfront for allowable travel expenses or reimburse them for allowable travel expenses, and provide compensation for the study visit as approved by the Central IRB and Local IRB (if applicable). All travel arrangements will be discussed with the Study Clinic in advance to ensure they are allowable expenses. Participants may also receive meals or snacks during visits to the study clinics.

7   STATISTICAL CONSIDERATIONS

In addition to the process of screening, adjudication, genetic/genomic testing, discovery and deeper phenotyping described above, biostatistical and bioinformatics experts in the RADIANT consortium will develop algorithms for case identification as well as machine learning clustering processes for identification of atypical diabetes syndromes.

7.1   Atypical Case Discovery

RADIANT bioinformaticists will develop an algorithm utilizing all available data provided in Stage 1, including the questionnaire and laboratory tests data, to select possible cases of atypical diabetes. The review of those cases by the RADIANT Adjudication Committee will provide feedback to the algorithm by which to make modifications to improve its specificity. This will be a continuing, iterative process over the 4-5 years of RADIANT to provide continuous refinement and improve performance.

7.2   Planned Sources for Case Identification

    a. Existing "atypical diabetes" registries
RADIANT will take advantage of existing registries that are already enriched for participants with different phenotypic forms of atypical diabetes. This includes monogenic diabetes registries at the University of Chicago and the University of Maryland, a lipodystrophy registry at the University of Michigan, the Ketosis-Prone Diabetes registry at Baylor College of Medicine (BCM), and five different BCM Genetics labs and programs. Potential atypical diabetes participants from these populations will be initially identified and referred by the scientific investigators responsible for the registry based on pre-existing genotypic and phenotypic data. We will then use the same dynamic filtering algorithm described for the diabetes cohorts/registries below to both cross-validate the manually selected atypical diabetes subcohort as well as identify potential atypical diabetes individuals not included in the manual approach.

b. RADIANT Study Clinics
We have organized 14 Study Clinics, led by RADIANT co-investigators, serving diverse populations encompassing the demographics and geography of the entire U.S., for identifying atypical diabetes individuals in a prospective manner.

c. Diabetes cohorts and prospective clinic registries
RADIANT will reach out to established collaborations with large diabetes databases and cohorts which include participants from all parts of the the US with data and biosamples. From these diabetes cohorts, we will identify atypical diabetes individuals using a dynamic screening process that excludes "typical" type 1 and "typical" type 2 diabetes patients while including specific criteria characterizing known forms of atypical diabetes. To account for discrepancies in the availability of specific data variables across cohorts and registries, the screening algorithm will be flexible enough to use substitutable criteria for both the exclusion and inclusion filters.

d. Other existing databases including those containing EHRs.
RADIANT will use the same dynamic filtering algorithm described above to identify atypical diabetes individuals in other non-diabetes-specific patient databases including those containing EHRs. For databases containing EHRs information, we will leverage existing methods to parse data (e.g. R packages EHR, cleanEHR) for use in the filtering algorithm.

e. Self-referral and non-study provider referral of individual cases.
Individuals who self-refer or are referred by their non-study provider will be directed to the Stage 1 consent and questionnaire. The Adjudication Committee will apply the same filtering process described above to filter these cases for review.

7.3   Genotype-phenotype Analysis Approach

The aim of RADIANT is to differentiate the various forms of atypical diabetes among the patients identified from the sources described above. After an atypical diabetes patient has been identified, consented, and enrolled, we will collect both genetic (e.g. whole genome sequencing (WGS), mitochondrial genome sequencing, RNA Sequencing (RNA-Seq) etc.) and phenotypic data in addition to the questionnaire data and medical record data, subject to the the participant's authorization to do so. We will then use unsupervised machine learning methods, such as cluster analysis with both the genotypic and phenotypic data, to discover etiologically and phenotypically distinct endotypes within the atypical diabetes population.

7.4   Whole-Genome Sequencing Data Analysis

The whole-genome sequencing (WGS) data will be generated using the Illumina platform with paired-end reads. FastQC, MultiQC [1] and FastQ Screen [2] will be used to identify low-quality sequences and contaminants (such as adapters) in the raw sequence data. The raw sequences will be aligned to the Genome Reference Consortium Build 38 (GRCh38DH) or later builds if available, and post-alignment processing will be performed by utilizing the University of Michigan's (UM) Docker-alignment pipeline (*https://github.com/statgen/docker-alignment*) based on Burrows-Wheeler Aligner (BWA) [3]. UM's QPLOT [4] tool (*https://github.com/statgen/qplot*) will be used to obtain mapped sequence QC with various QC-metrics including base qualities,

insert sizes, mapping qualities, coverage, GC bias, etc. Moreover, Picard tools (*https://broadinstitute.github.io/picard/index.html*) will be used to obtain the summary of alignment metrics, whole genome sequencing-related metrics, mean quality by cycle, etc. Variant calling will be performed independently for each sample via the GATK HaplotypeCaller [5] to produce an intermediate "gVCF" representation per sample. The gVCFs of multiple samples will then be combined to produce a joint variant "call set." Call sets will then be filtered with the GATK method for variant score quality recalibration. Finally, samples of low genotyping quality will be flagged by computing a variety of metrics across samples (such as the number of called variants, mean genotype quality, global heterozygosity), stratifying or adjusting samples by ancestry or (if needed) sequencing date, and excluding samples that are outliers. Variant annotation will be performed using WGS annotator (WGSA) [6] which integrates 10 sets of functional prediction scores (CADD, FATHMM-MKL, Funseq, Funseq2, RegulomeDB, DANN, fitCons x 4, GenoCanyon, Eigen and Eigen-PC, GenoSkyline-Plus x 127), 4 conservation scores (GERP++, PhyloP, phastCons, SyPhy) and variants in 4 disease related databases (ClinVar, COSMIC, GWAS_catalog, GRASP2).

Fully annotated variant call files (VCFs) will be transferred securely to Baylor College of Medicine, such that a joint analysis of WGS data can be performed by the Discovery Teams at Baylor and Broad. WGS analysis will be a joint and interative process, requiring synergy between the WGS data generated at Broad with additional -OMICs data as they become available for each case. Such data may include RNAseq (generated at Baylor), mitochondrial genome sequencing (generated at Baylor), and metabolomics.

7.5   RNA Sequencing Data Analysis

The RNA sequencing (RNA-Seq) data will be generated on the Illumina platform with paired-end reads with a targeted 50 million reads per sample. FastQC, AfterQC [7], and MultiQC [1] will be used to identify low-quality sequences, potential biases and contaminants (such as adapters) in the raw sequence data. verifyBamID [8] will be used to compare the RNA-Seq data to the variants from the WGS data to identify mislabeled, swapped or contaminated samples. The raw sequences will be aligned to the genome against the Gencode Genome Reference Consortium Build 38 (GRCh38.p12), or later if available, and to the transcriptome against the Gencode Comprehensive Gene Annotation (GRCh38) using the STAR aligner [9] based on the Trans-Omics for Precision Medicine (TOPMed) GTEx RNA-Seq analysis pipeline (*https://github.com/broadinstitute/gtex-pipeline*). Post-alignment QC metrics will be generated using RNA-SeQC [10] including overall gene counts, rRNA percentage and percentage transcript-associated reads, etc. Gene expression will be calculated and normalized into Transcripts per Kilobase Million (TPM) using RNA-SeQC and isoform expression is calculated and normalized into TPM using RSEM [11]. Batch effects will be removed using ComBat/svaseq [12, 13]. The erccdashboard [14] will be used to measure dynamic range, diagnostic performance, limit of detection of ratio (LODR) estimates and expression ratio bias and technical variability.

7.6   Metabolomics Data Analysis

Metabolites will be analyzed by gas chromatography time-of- flight mass spectrometry (GC-TOF MS) or charged surface hybrid column with electrospray ionization (CSH-ESI) on ultra high pressure liquid chromatography quadrupole time-of-flight mass spectrometry (UHPLC-QTOF

MS). Mass spectrum peaks in the raw data will be detected by Mass Spectrometry–Data Independent Analysis (MS-DIAL) [15] and annotated in terms of m/z value and retention time. We will remove metabolites with more than 50% of missing values from further analysis. Principal component analysis will be performed to identify outliers and batch effects. Signal drift correction, batch effect removal and normalization will be performed using systematical error removal using random forest (SERRF) [16].

7.7 Bioinformatics and Statistical Analysis

Several clustering methods can be employed including partitioning around medoids (PAM, a form of k-medoids clustering), recursive partitioning analysis (RPA, a form of hierarchal clustering), and Bayesian non-negative matrix factorization (bNMF, a soft clustering approach) to analyze clinical phenotypic data. Different clustering algorithms may partition the data differently, and no single algorithm is optimal. Furthermore, partitions using the same clustering algorithm can differ significantly based on changes in the parameters like feature selection, distance matrix, and the number of clusters in a dataset. To deal with these nuances, we will use an ensemble clustering approach to exploit the complementary nature of different partitions. The main goal of ensemble clustering is to implement strategies for finding a single robust clustering based on the many robust clusterings that can be created by perturbing different algorithms with different parameters. We will identify a robust clustering by applying an ensemble approach that finds common shared clustering patterns by comparing different clusterings and algorithms within both the genotypic and the phenotypic data.

Simultaneous, parallel, co-clustering of genotypic and phenotypic data is an important technique in two-way data analysis. Hence, we will apply an "overlap clustering step" using regularized non-negative matrix tri-factorization (R-NMTF) [17] to co-cluster the phenotypic markers and the genomic markers and simultaneously detect associations between the phenotypic and genomic clusters.

We will perform the following analysis:
    (1) We will define different exclusion and inclusion criteria for atypical diabetes based on the Stage 1 questionnaire as well as preliminary clinical test results. A multivariate comparison across potentially different phenotypes, presented in both graphical and analytic formats, will be informative as to the extent to which they overlap or are distinct.
    (2) We will calculate weighted genetic risk scores (GRSs) for T1DM (based on the 67 variants known to be associated with T1DM) and for T2DM (based on the 100 variants known to be associated with T2DM) using WGS data. We will utilize the weighted GRSs as an exclusion criterion in combination with the available clinical phenotypic variables.
    (3) We will use R-NMTF to co-cluster the phenotypic markers and the genomic markers.
    (4) We will use a tree-based algorithm such as random forest to get a more accurate and stable prediction of atypical diabetes cases.
    (5) WGS data will be used to identify novel and *de-novo* variants associated with atypical diabetes.
    (6) The transcriptome and metabolome data will be integrated by the sparse partial least squares regression (sPLS) using MixOmics package [18]. PLS is a supervised method, which selects correlated variables (genes, metabolites) across the same samples by maximizing the covariance between the datasets. The sPLS will be used to select the most correlated variables using the least absolute shrinkage and selection operator (LASSO) penalization on the pair of loading vectors.

(7) Expression quantitative trait loci (eQTLs) and metabolite quantitative trait loci (mQTLs) analyses will be performed to assess the extent of the genetic contribution to the observed changes in the gene expression and metabolite.

(8) We will perform sensitivity and specificity analysis for various available clinical phenotypic variables based on the known atypical diabetes cases.

(9) We will apply different clustering methods to identify endotypes of atypical diabetes.

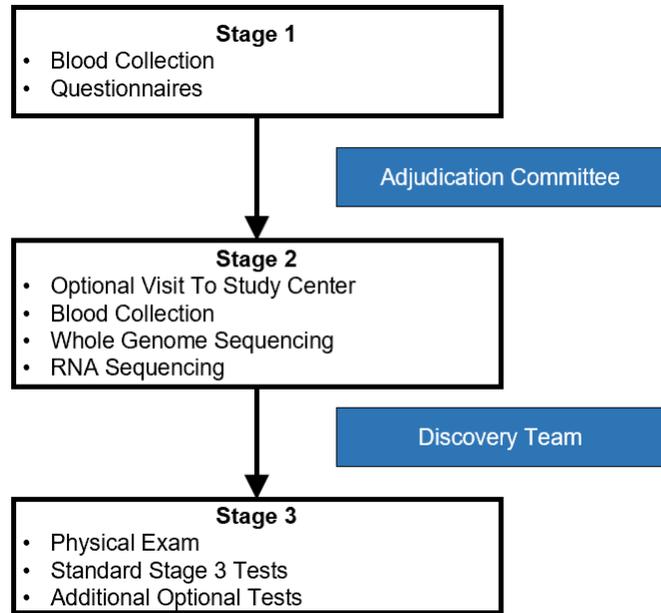# 8 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

8.1 Regulatory, Ethical, and Study Oversight Considerations

8.1.1 Informed Consent Process

The informed consent process is initiated prior to an individual agreeing to participate in the study and continues throughout the individual's study participation for each of the three stages. When in person informed consent is obtained, designated research staff at each Study Clinic will administer the informed consent forms and assent forms (if applicable) that have been approved by the IRB. A verbal explanation suited to the participant's comprehension of the purposes, procedures, and potential risks of the study will be provided. Each study participant will have sufficient time to fully read the consent/assent forms and have any questions answered. They will be told that they can take paper copies of the consent/assent forms home and request consultation with other individuals. For patients that may need to travel a long distance to the Study Clinic, a copy of the informed consent form and assent form (if applicable) will be sent to the patient prior to their travel to allow for sufficient time to consider participation before travel is booked. The participant (or their guardian, in the case of minors) will sign the informed consent document prior to any procedures being done for the study. Minors will also sign an assent form when applicable. Copies of signed consent forms and assent forms will be stored. A copy of the signed informed consent forms and assent forms will be given to participants for their records.

Three methods of informed consent are possible for RADIANT:

1) Online informed consent (Stage 1 only): The participant will be presented with an online consent form explaining Stage 1 of the study (i.e. questionnaire, autoantibody testing, and consent to save contact information). If they agree, they will then be instructed to complete the initial screening questions and proceed to the other Stage 1 steps as described in Section 6.1.1.

Stage 1
- Blood Collection
- Questionnaires

Adjudication Committee

Stage 2
- Optional Visit To Study Center
- Blood Collection
- Whole Genome Sequencing
- RNA Sequencing

Discovery Team

Stage 3
- Physical Exam
- Standard Stage 3 Tests
- Additional Optional Tests

2) Informed consent and assent over phone/video (Stages 1, 2, and 3): A phone or video call will be scheduled. The consent form and assent form (if applicable) will be emailed or mailed to the participant prior to the call. During the call, study procedures will be explained, along with risks and benefits, and an opportunity to ask questions will be given. If the participant chooses to proceed, signature will be obtained on hard-copy of the consent form and assent form (if applicable), which will then be mailed back to the Study Clinic.

The informed consent and assent process (if applicable) may occur remotely (i.e. over phone/video) as described above for:
- Stage 1 informed consent, as an alternative to the online Stage 1 consent form
- Participants who are not able to come to a Study Clinic in Stage 2 or prefer to participate in Stage 2 remotely
- Participants in Stage 3 who are consenting for additional deeper phenotyping, if the tests recommended by the Discovery Team can be completed remotely
- Family members who are consenting for Sanger Sequencing or WGS Trio

3) In-person informed consent and assent (Stages 1, 2 and 3) will be used for the following scenarios:
- Stage 1 informed consent, as an alternate to the online Stage 1 consent
- Participants in Stage 2 who are able to meet with the study team in-person
- All participants in Stage 3 Tier 1
- Participants in Stage 3 who are consenting for additional deeper phenotyping, if the tests recommended by the Discovery Team require an in-person visit

RADIANT will consent relatives of proband participants at one of three levels, dependant on the stated goal of relative enrollment:

1) When the goal of relative enrollment is study of a relative with a suspected atypical diabetes phenotype who may be of interest to the RADIANT study as a participant in his/her own right, individuals will progress (potentially) through all stages of enrollment, beginning with Stage 1, as detailed above for proband enrollment.
2) When the goal of relative enrollment is to perform Sanger segregation of an identified

HIGH SUSPICION atypical diabetes gene variant candidate, consent would be limited to supporting blood samples for DNA extraction for Sanger sequencing, a baseline questionnaire, and if the family member reports an unaffected DM status: fasting blood glucose and an HbA1c measurement (to confirm the individual's reported "unaffected" status). If FBG and HbA1c are normal but the family member is positive for the high suspicion variant and further phenotyping of these individuals is warranted, participants will be consented to Stage 3 procedures as determined by the Discovery Team. However, unaffected pediatric family members will not be asked to participate in Stage 3 procedures.

3) When the goal of relative enrollment is to perform a trio-WGS (proband + both parents) as an additional analytic step to narrow down the variants of interest, relatives (parents) would complete a consent form for the trio-WGS, a baseline questionnaire, and if the family member reports an unaffected DM status: fasting blood glucose and an HbA1c measurement (to confirm the individual's reported "unaffected" status). If further phenotyping of these individuals is warranted, participants will be consented to Stage 3 procedures as determined by the Discovery Team. However, unaffected pediatric family members will not be asked to provide consent/assent for Stage 3 procedures.

The initial informed consent form and assent form (if applicable) and any subsequent revised written informed consent form / assent form and any written information provided to the participant must receive IRB approval in advance of use, per the requirements of the IRB. The participant will be informed in a timely manner if new information becomes available that may be relevant to their willingness to continue participating in the study. Communication of this information will be provided and documented via a revised consent/assent form or addendum to the original consent/assent form that captures the participant's dated signature.

Pediatric participants who turn 18 years old during the course of RADIANT will be reconsented. They will need to provide consent to continue to participate in the study.

8.1.1.1 Consent and collection of specimens for genetic and other biomedical research

In the informed consent, it will be made clear that the tests could include transcriptomic analyses and the production and study of cells differentiated from blood monocyte-derived inducible pluripotent stem cells. The study participant will also be made aware that specific archived blood samples will be stored for any future research in the RADIANT biobank and in an NIDDK controlled access biorepository, and that data may be deposited into controlled access databases such as dbGaP. By signing the study consent forms, participants are agreeing to have their samples and data stored. If a participant withdraws from the study, any data collected prior to the date the participant withdraws will be maintained within the RADIANT database.

8.1.1.2 Privacy and confidentiality

Every participant's privacy and confidentiality will be respected throughout the study. All data and records generated during the study will be kept confidential in accordance with Institutional policies and HIPAA recommendations for participant privacy. Each participant will be assigned a study identification code to protect participant confidentiality.

Study Participant Confidentiality

The study participant's data will be securely stored in the DCC server. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations. The study data entry and study management systems used by research staff will be secured and password protected.

As this is an NIH-funded sudy, a Certificate of Confidentiality will be in place to protect the research participants.

Identifying Source Data

The investigators are required to keep accurate records to ensure that the conduct of the study is fully documented. The results of all clinical and clinical laboratory evaluations will be maintained in case report forms (CRFs). Safety data will be recorded on CRFs specifically designed for this purpose. All the SAEs will be reported on an SAE report form. The OSMB and/or the IRB have the authority to withdraw any participants and/or terminate the study because of safety findings.

Permitting Access to Source Data

The investigational sites participating in RADIANT will maintain the highest degree of confidentiality permitted for the clinical and research information obtained from the participants in this study. Medical and research records will be stored and maintained in the DCC in the strictest confidence. However, as a part of the quality assurance and legal responsibilities of an investigation, RADIANT will permit authorized representatives of the sponsor(s) and health authorities to examine (and when required by applicable law, to copy) clinical records for the purpose of quality assurance reviews, audits, and evaluations of the study safety and progress. Unless required by the laws that permit copying of records, only the coded identity associated with documents or with other participant data may be copied (and all personally identifying information must be obscured). Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that is linked to identify individuals. The investigational site will normally be notified before auditing visits occur.

Quality Control and Quality Assurance

Investigators at the RADIANT Study Clinics are required to keep accurate records to ensure that the conduct of the study is fully documented. RADIANT Study PIs are responsible for regularly reviewing the conduct of the study, for verifying adherence to the protocol, and for confirming the completeness, consistency, and accuracy of all documented data. RADIANT will establish a Laboratory Implementation and Data Quality Assurance Committee that will have oversight over quality control and quality assurance, train Study Clinic staff in quality procedures and may also perform virtual site visits to assess site performance.

Data Handling

Investigators at the RADIANT Study Clinics are required to keep accurate records to ensure that the conduct of the study is fully documented. The investigators are required to ensure that all CRFs are completed for every participant entered in the study. RADIANT Study PIs and teams at the RADIANT DCC will regularly review the conduct of the study, verifying adherence to the

protocol, and confirming the completeness, consistency, and accuracy of all documented data. RADIANT will establish a Protocol Committee that will have oversight over all matters related to protocol adherence and performance. Study staff at the Study Clinics will collect source information on CRFs and enter information into the electronic database. Data quality will be ensured through research team and database processes for detection and correction of errors. The database will be maintained on a secure, restricted access computer system.

8.1.1.3 Data and Safety Monitoring Plan

The RADIANT DCC is responsible for managing the collection and analysis of genomic, phenotypic, and clinical data. The DCC will establish the data acquisition, transfer, and management system; develop procedures for ensuring participant confidentiality and safety; develop procedures for quality control, training, and certification; develop and produce a manual of operations and other study materials; and supervise the orderly collection and transmission of data.

The Observational Study Monitoring Board (OSMB) and chairperson(s) for RADIANT are appointed by the NIDDK and reflect the scientific disciplines and medical expertise necessary to regularly monitor data from this observational study, review and assess the performance of the consortium's operations, and make recommendations to NIDDK with respect to: (1) performance of study centers, (2) issues related to participant safety, confidentiality and informed consent, (3) adequacy of study progress, including recruitment, quality control, data analysis and publications, (4) issues pertinent to participant burden, and (5) overall scientific directions of the study. Ad hoc members may be appointed for specific protocols, as circumstances require. Such appointments will be made by the NIDDK.

The OSMB will act as the observational study monitoring board for RADIANT. Members will be completely independent of the studies being reviewed. They shall not be actively involved with RADIANT. They will have no financial interest in the outcomes of any studies reviewed by the OSMB.

OSMB members will:

- Review all protocols and procedures for studies in atypical diabetes to be performed and to advise the sponsors of RADIANT (NIDDK) of any concerns.

- Examine recruitment and data, including safety data and adverse events, and make recommendations to the NIDDK of any concerns and/or recommendations regarding continuation, termination or other modification of studies.

- Review the general progress of the studies and assist in resolving any problems which arise.

- Provide scientific advice on developments and opportunities that may facilitate or accelerate research in the identification and study of atypical diabetes.

- Provide feedback to NIDDK regarding the future plans of RADIANT.

The physical risks of participation in this protocol will be described in the consent forms in a stepwise fashion from the simple risks of venipuncture in Stage 1 to the specific risks of individual procedures that could be performed for the deep phenotyping in Stage 3.

Screening for genetic markers associated with a severe and currently incurable disease, such as diabetes, raises important ethical issues. RADIANT places special emphasis on: 1) voluntary participation ensured by the informed consent process; 2) disclosure of the results to participants if desired, combined with education and genetic counseling; and, 3) confidentiality of genetic information that cannot be disclosed to health providers or other parties without participant consent. The informed consent involves genetic counseling. Since the significance of genetic variants found in RADIANT may be uncertain, psychological support of the participants will be made available as needed, so that undue anxiety is not induced. Participants who are found to have known monogenic forms of diabetes will be referred for counseling concerning the best follow-up and treatment.

Adverse Event Reporting and Safety Monitoring

For this study an adverse event (AE) will be defined as any occurrence or worsening of an undesirable or unintended sign, symptom or disease that **is associated with study procedures**. Throughout the study, the study team must record AEs related to study procedures on source documents regardless of severity. Only AEs that meet the following National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) grading criteria <u>AND</u> are related to study procedures must be reported in the electronic RADIANT Adverse Event Management System:

- Hyperglycemia Grade 4 or greater
- Hypoglycemia Grade 4 or greater
- Other AEs Grade 2 or greater

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that is associated with study procedures AND:

- results in death,
- Is life-threatening,
- Required inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

Other important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

All events reported will be graded using the NCI CTCAE to classify AE severity. This will allow for a standardized grading across the network.

The RADIANT Steering Committee will review adverse event reports on a regular basis and will determine if further action is required. Otherwise, the OSMB will conduct regular safety reviews approximately every six months. Summaries of reportable adverse events will also be provided to the IRB annually.

RADIANT is cognizant of its responsibility to protect the safety of study participants and confidentiality of study records. RADIANT will maintain a secure website that includes the ability to report, review and disseminate information regarding any observed adverse event. It is a complete reporting and review system enabling adverse events to be forwarded to an external reviewer, automatically relay the reviewer's comments to the site, collect additional information from site if requested, keep track of and report to the OSMB in tabular form. Study relatedness is adjudicated and rapid communication to study investigators is automatic. As RADIANT is an *observational* study, it is possible to distinguish between possible protocol related events and those that are totally unrelated. Adverse events will be tabulated for communication to and review by local site IRBs and communicated to the central IRB. The guidelines for reporting and review of AEs are contained in any protocols to be established and their Manual of Operations. The coding conventions confirm to FDA standards and employ the Common Toxicity Criteria Adverse Event reporting developed by the NCI. They are both GCP and ICH compliant.

Except in the instances where individual study participant information is needed (and allowed for by the consent form), care will be taken that data are presented in the aggregate so as to preclude identification of any study participant.

8.1.1.4 Conflict of Interest/Duality of Interest

If any members of the RADIANT study team, including but not limited to the principal investigators, Study Clinic investigators and staff, has a real or potential conflict of interest/duality of interest relating directly to the study conduct, study procedures, data interpretation and/or publication, it will be disclosed on the consent and assent forms in a clear manner as required.

The independence of RADIANT from any actual or perceived influence by the pharmaceutical industry is critical and, therefore, the pharmaceutical industry will play no role in the study. The study leadership and their institutions in conjunction with the NIH have established policies and procedures for all study group members to disclose all conflicts of interest; should any be disclosed, mechanisms for their management will be instituted in line with NIH policies.

8.1.2 Future Use of Stored Specimens and Data

During the conduct of the study, an individual participant can choose to withdraw consent to continue participation at which point data and samples will no longer be collected. Data and samples collected up until the time of withdrawal will be retained and stored in the biobank and repository. All samples and data will be deidentified after the study is completed.

Access to study data and/or samples will be provided through the the NIDDK data and biospecimen repositories, once sample inventory and study data has been transferred to the appropriate repositories.

8.1.3 Central IRB

The University of Utah IRB will be the central IRB (cIRB) for this study, having been selected through the NCATS Trial Innovation Center (TIC). Dr. Krischer will be designated lead investigator for cIRB purposes, and he will appoint a member of the DCC at USF as RADIANT IRB liaison to be the point of contact for all RADIANT sites with participant contact and access

to protected health information (PHI). Dr. Philipson will be designated sub-lead investigator per Utah cIRB guidelines. Each site will submit the same basic protocol through USF to the Utah cIRB following the site control model. Prior to beginning any research at each site involved in the RADIANT protocol, that site will need to confirm that they have met all requirements of their local human research protections program (HRPP).

The RADIANT investigators are responsible for all aspects of the IRB application and review process for all participating sites. The TIC team will work closely with RADIANT investigators to move the cIRB process forward.

The cIRB will designate a cIRB project manager for RADIANT.
1. The cIRB project manager will maintain contacts with the designated lead investigator (Dr. Krischer). They will be the main contact for the SIRB application/review and be the main cIRB contact for all participating sites.
2. The RADIANT IRB liaison will work with the cIRB project manager to obtain access to the University of Utah's SIRB online system (ERICA) to prepare and submit this study for SIRB review.
3. The cIRB project manager will work with the local IRB/HRP to confirm agreement to SMART and registration with IREx (online systems associated with the SIRB process) for all clinical sites.

9   COMMUNITY RESOURCE FOR ATYPICAL DIABETES RESEARCH

A central goal of RADIANT is to develop a community resource to advance research in atypical diabetes through a database to facilitate the collection and dissemination of phenotypic and genetic data with biorepository samples and a living biobank for access by the diabetes research community.

The DCC will create and manage a study database for rare/atypical forms of diabetes, and the RADIANT Central Lab will create a living biobank and biospecimen repository. The DCC will also create a public portal for use by the diabetes research community in future studies. An Ancillary Studies Committee will encourage and facilitate future investigation of all forms of atypical diabetes by internal and external investigators, and greater understanding of novel mechanisms of diabetes pathogenesis by providing researchers access to a rich compendium of genomic, metabolomic, transcriptomic, clinical and functional data, as well as biobanked materials and the living biobank.

The consortium will also send samples and data to the NIDDK repository to make these resources available for researchers.

10 APPENDICES

Appendix 1. Study procedures by Stage

Table 1. Stage 1 Procedures

Procedure	Participant Population				Risk Type
	Affected Adult (18+)	**Affected Child* (0-17)**	**Unaffected Adult (18+)**	**Unaffected Child* (0-17)**	
Islet Autoantibody Testing	X	X	X	x	Minimal Risk
Questionnaires	X	X	X	x	Minimal Risk
Medical record collection	X	X	X	x	Minimal Risk

Table 2. Stage 2 Procedures

Procedure	Participant Population				Risk Type
	Affected Adult (18+)	**Affected Child* (0-17)**	**Unaffected Adult (18+)**	**Unaffected Child* (0-17)**	
Blood collection	X	X	X	X	Minimal Risk
Genetic testing (WGS, RNA-Seq, Mitochondrial DNA Seq)	X	X	X	X	Minimal Risk
Medical record collection	X	X	X	X	Minimal Risk
Pedigree Collection	X	X	X	X	Minimal Risk

*For the purposes of this study, a child is considered 'affected' when they have a diagnosis of diabetes or prediabetes. An unaffected child is a child who does not have a diagnosis of diabetes/prediabetes

Table 3. Stage 3 Procedures

Procedures	Affected Adult (18+)	Affected Young Child* (0-6)	Affected Older Child (7-17)	Unaffected Adult (18+)	Risk Type**	Estimated Duration of Procedure
Standard Tier 1						
Urine Collection	x	x	x	x	Minimal Risk	10 minutes
Physical exam with biometric measurements and photography	x	x	x	x	Minimal Risk	2 hours
Laboratory testing (HbA1c, Lipids, CMP, metabolomics)	x	x	x	x	Minimal Risk	10 minutes
OGTT (glucose and C-peptide will be measured, at all timepoints. Insulin will be collected but only measured in selected participants.)	x	x	x	x	Minimal Risk	2.5 hours
PBMC Collection with potential future derivation of a stem cell line from stored monocytes	x	x	x	x	Minimal Risk	10 minutes
Blood collection for biobank storage and future testing	x	x	x	x	Minimal Risk	5-10 minutes
Questionnaires	x	x	x	x	Minimal Risk	60 minutes
Urine pregnancy[a]	x		x	x	Minimal Risk	10 minutes
Medical record collection	x	x	x	x	Minimal Risk	10 minutes
Medication Inventory	x	x	x	x	Minimal Risk	10 minutes
Additional Optional Tier 2						
Mixed Meal Tolerance Test (MMTT) - Short	x	x	x	x	Minimal Risk	2.5 hours
Standardized Meal with CGM	x	x	x	x	Minimal Risk	130 minutes
CGM	x	x	x	x	Minimal Risk	5-10 minutes to put sensor on; up to 14 days wearing CGM

					Minimal Risk	1 hour
Additional PROMIS questionnaires	x	x	x	x	Minimal Risk	1 hour
Vineland Assessment	x	x	x	x	Minimal Risk	1 hour
Specialized vision testing	x	x	x	x	Minimal Risk	20-30 minutes
Specialized auditory testing	x	x	x	x	Minimal Risk	30-90 minutes
Wolfram Scale	x	x	x	x	Minimal Risk	60 minutes
DXA	x	x	x	x	Minimal Risk	30 minutes
Abdominal MRI	x	x	x	x	Minimal Risk	40 minutes – 1 hour
Actigraphy	x	x	x	x	Minimal Risk	Up to 14 days
Questionnaires (GAD-7, PHQ8)	x	x	x	x	Minimal Risk	10 minutes
Additional Optional Tier 3						
FSIVGTT	x	x	x	x	Minor increase over minimal risk	4 hours
Hyperglycemic Clamp with Arginine Stimulation	x		x	x	Minor increase over minimal risk	5 hours
2-step Hyperinsulinemic-Euglycemic Clamp	x		x	x	Minor increase over minimal risk	7.5 hours
MMT – Long format	x	x	x	x	Minor increase over minimal risk	4 hours
Fat Biopsy	x			x	Minor increase over minimal risk	30 minutes
Muscle Biopsy	x			x	Minor Increase over minimal Risk	30 minutes
Liver Biopsy	x			x	More than minor increase over minimal risk	60 minutes
Skin Biopsy	x			x	More than minor increase over minimal risk	30 minutes

*For the purposes of this study, a child is considered 'affected' when they have a diagnosis of diabetes or prediabetes.
**Risk Types are listed for individual procedures. In pediatric participants, due to the burden of completing multiple procedures at any single visit, ALL STAGE 3 PROCEDURES IN CHILDREN will be classified as minor increase over minimal risk.
a If applicable

Appendix 2. Samples and data stored for NIDDK Central Repository

Samples	- Serum aliquot(s) - Plasma aliquot(s) - DNA aliquot(s) - RNA aliquot(s) - Urine aliquot(s) - Peripheral blood monocytes
Clinical Data	- Information from questionnaire sections including demographics, lifestyle history, birth history, reproductive history, other medical history, diabetes status and history, family history, physical activity, medications inventory, ASA24, PROMIS, environmental exposures - Biometric data (height, weight, blood pressure, anthropometrics, details of standardized physical exam) - Additional anthropometric data and/or questionnaire data may be available if completed in deeper phenotyping
Genetic and Omics Data	- WGS results - Mitochondrial sequencing results - Transcriptomic data - Metabolomic data
Laboratory Data	- Islet autoantibody information - Fasting Glucose and C-peptide - Lipid Panel, Comprehensive Metabolic Panel, HbA1c - OGTT - Other laboratory data may be available if completed in deeper phenotyping (e.g., results of clamp studies, data from studies on iPSCs derived from peripheral blood monocytes, etc)