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The Rare and Atypical Diabetes Network (RADIANT) Study: Design and Early Results

The RADIANT Study Group

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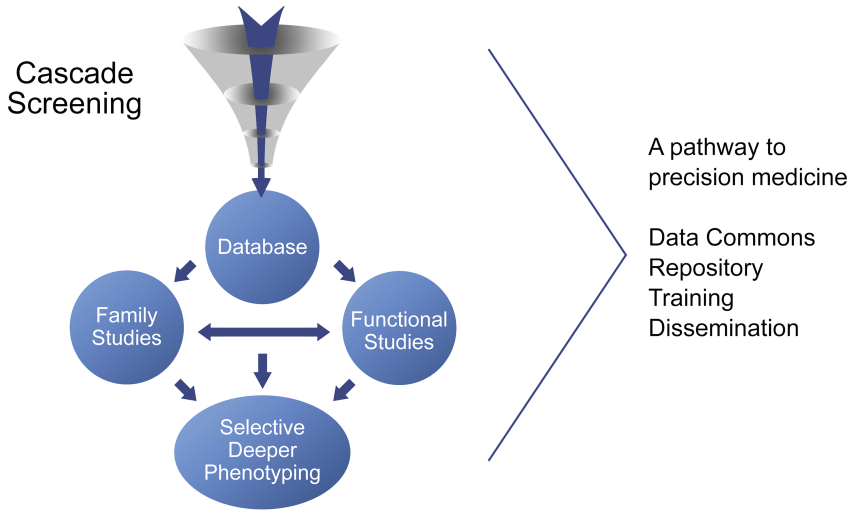

ARTICLE HIGHLIGHTS

- A study of rare and atypical diabetes (atypicaldiabetesnetwork.org) has been launched to identify and study non-typical forms of diabetes.
- Among 122 individuals with whole-genome sequencing results, there have been new monogenic variants identified in the *SMAD5*, *PTPMT1*, *INS*, *NFKB1*, *IGF1R*, and *PAX6* genes, and the most frequent phenotypic clusters are lean type 2 diabetes, autoantibody-negative and insulin-deficient diabetes, lipodystrophic diabetes, and new forms of possible monogenic or oligogenic diabetes.
- This study has far-reaching implications in that the genotypic and phenotypic analyses will lead to improved means to identification and possibly treatment of cases of atypical diabetes.

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OBJECTIVE

The Rare and Atypical Diabetes Network (RADIANT) will perform a study of individuals and, if deemed informative, a study of their family members with uncharacterized forms of diabetes.

RESEARCH DESIGN AND METHODS

The protocol includes genomic (whole-genome [WGS], RNA, and mitochondrial sequencing), phenotypic (vital signs, biometric measurements, questionnaires, and photography), metabolomics, and metabolic assessments.

RESULTS

Among 122 with WGS results of 878 enrolled individuals, a likely pathogenic variant in a known diabetes monogenic gene was found in 3 (2.5%), and six new monogenic variants have been identified in the *SMAD5*, *PTPMT1*, *INS*, *NFKB1*, *IGF1R*, and *PAX6* genes. Frequent phenotypic clusters are lean type 2 diabetes, autoantibody-negative and insulin-deficient diabetes, lipodystrophic diabetes, and new forms of possible monogenic or oligogenic diabetes.

CONCLUSIONS

The analyses will lead to improved means of atypical diabetes identification. Genetic sequencing can identify new variants, and metabolomics and transcriptomics analysis can identify novel mechanisms and biomarkers for atypical disease.

Atypical diabetes comprises both uncommon genetic syndromes as well as clusters of phenotypically distinct forms of diabetes that fall within a spectrum between the two poorly defined poles of "type 1" and "type 2" diabetes (1–20). However, many more unrecognized or uncharacterized forms of diabetes exist. The Rare and Atypical Diabetes Network (RADIANT) is designed to characterize new diabetes subtypes and reveal novel mechanistic or causal pathways that can be leveraged for prevention or treatment.

RESEARCH DESIGN AND METHODS

RADIANT, funded by the National Institutes of Health, consists of 14 clinical centers: Baylor College of Medicine (BCM), University of Chicago, University of Washington, Seattle Children's Hospital, University of Colorado, SUNY Downstate Health Sciences University, Indiana University, Columbia University, Massachusetts General Hospital, University of Maryland, University of Michigan, University of North Carolina, Vanderbilt University, and Washington University in St. Louis. The Data Coordinating

Corresponding author: Jeffrey P. Krischer, jpkrischer@epi.usf.edu

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**A complete list of members of the RADIANT Study Group can be found in supplementary material online.*

Center, University of South Florida, is responsible for the coordination and support of the study protocol and data collection and analysis.

The RADIANT Central Laboratory at the University of Florida is responsible for all biochemical analyses, autoantibody testing, and DNA and RNA extraction. Whole-genome sequencing (WGS) is done at the Broad Institute and RNA sequencing at BCM. Plasma metabolomics is performed at Duke University, and monocytes are preserved for pluripotent stem cell derivation at BCM. The study is overseen by the University of Utah Institutional Review Board.

The RADIANT study includes three stages of participation (Fig. 1).

Stage 1: Recruitment

The following criteria or phenotypes are considered for suspecting "atypical" participants:

- Type 2 diabetes diagnosed at a time when the individual was prepubertal or nonobese
- Mendelian pattern, especially with early onset (<18 years old)
- Syndromic (multiple systems involved)
- Lipodystrophic
- Extremes of BMI
- "Mitochondrial" characteristics (e.g., myopathy, hearing deficits)
- Nonprogressive
- Rapidly progressive ("fulminant")
- Low insulin requirements (<0.5 units/kg/day)
- Cyclical hyperglycemia with periods of remission
- Lean individuals with polycystic ovarian syndrome
- History of gestational diabetes mellitus when lean
- Lean insulin resistant
- If islet autoantibodies and β-cell function parameters have been measured (where A is islet cell autoantibodies and B is β-cell function): A^-B^- (i.e., lacking islet autoimmunity makers and lacking β-cell function) or A^-B^+ with unprovoked diabetic ketoacidosis at initial presentation (i.e., lacking islet autoimmune markers, with preserved β-cell function, but presenting with unprovoked diabetic ketoacidosis)

Exclusions from the study include the following:

- Those with high likelihood of typical type 1, typical type 2, known monogenic, or other known secondary forms of diabetes
- Refusal of consent for genetic testing
- 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)
- Women who are currently pregnant

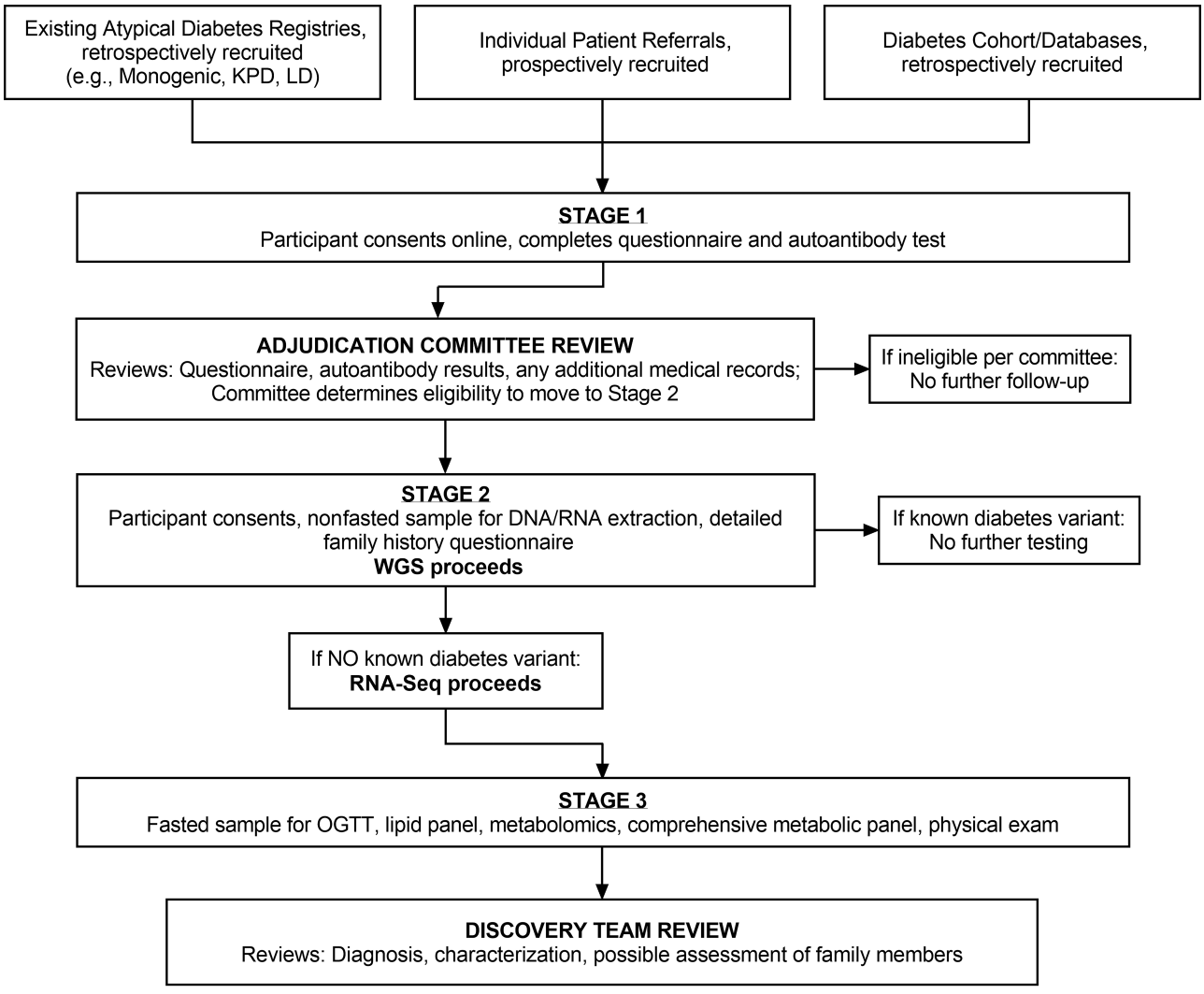

Figure 1—RADIANT protocol flow. OGTT, oral glucose tolerance test; RNA-Seq, RNA sequencing; KPD, ketosis-prone diabetes; LD, lipodystrophy.

All adults or parents/legal guardians of children are directed to an online stage 1 screening consent form. Participants then complete questionnaires (Supplementary Table 1) for exclusion of autoimmune type 1 diabetes, typical type 2 diabetes, and secondary diabetes, as well as to reveal atypical features of diabetes. All questionnaires, available in Spanish and English, can be downloaded for manual completion. Participants are asked to sign a medical record release form for the RADIANT team. Where continuation in RADIANT is deemed appropriate, participants are sent a sample collection kit to draw a sample for diabetes autoantibody testing.

Samples are analyzed for GAD autoantibodies (GADA). If negative for GADA, the samples will be analyzed for insulinoma antigen 2 (IA-2) and zinc transporter 8 (ZnT8) autoantibodies. The RADIANT Adjudication Committee reviews the data collected in stage 1 and then selects candidates with potential atypical diabetes to proceed to stage 2 (Fig. 2).

Stage 2 Procedures

Participants deemed eligible for participation in stage 2 are contacted to provide informed consent/assent, including consent for genetic screening for known forms of monogenic diabetes, medically actionable variants as defined by the American College of Medical Genetics and Genomics (ACMG), and for blood collection for DNA and RNA extraction, storage, and sequencing (WGS and RNA sequencing). Participants are also asked to complete an online questionnaire about their family history to construct a pedigree (Fig. 3).

WGS is performed in a College of American Pathologists (CAP)/Clinical Laboratory Improvement Amendments (CLIA) laboratory. Identified variants are mapped to the human reference genome assembly. Analysis of identified nuclear and mitochondrial-encoded variants proceeds in two phases.

1. Clinical reporting phase: participants can elect to receive identification of known pathogenic variants in (a) known monogenic diabetes genes and (b) genes identified by the ACMG as medically actionable.
2. Discovery phase: identification of candidate causative variants for the atypical diabetes phenotype. This information is not shared with participants at this stage of the study.

DNA samples from participants with a suspected mitochondrial disease phenotype undergo mitochondrial genome sequencing, performed at BCM. Participants who have a causal genetic variant that is already known and consistent with the phenotype will not proceed to the next stage of the RADIANT study. If a participant elects

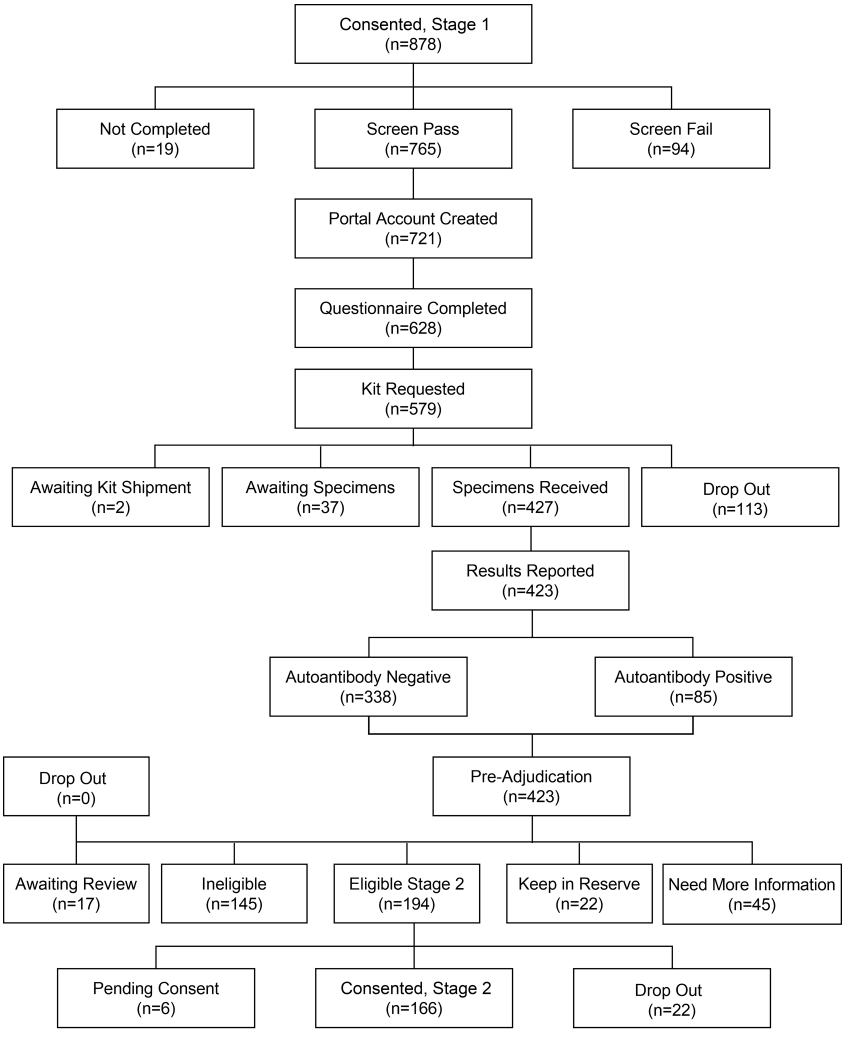

Figure 2—Consolidated Standards of Reporting Trials (CONSORT) diagram: stage 1.

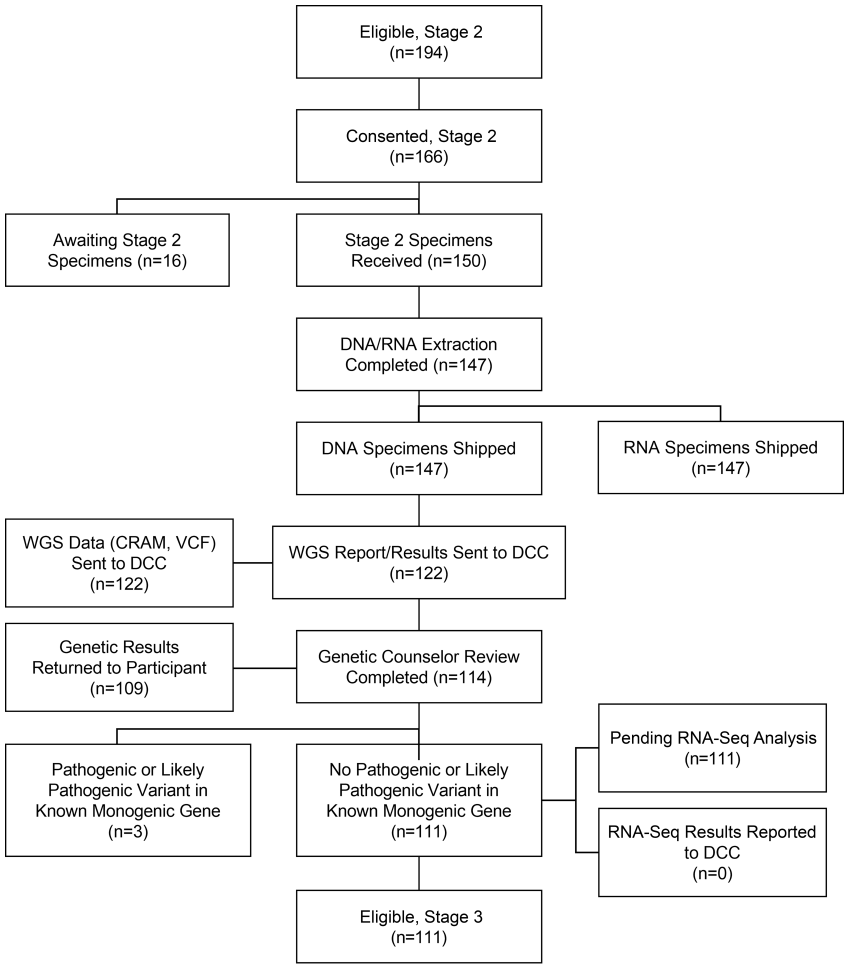

Figure 3—Consolidated Standards of Reporting Trials (CONSORT) diagram: stage 2. DCC, Data Coordination Center, University of South Florida; RNA-Seq, RNA sequencing.

to have the results of these analyses returned to them, results will be explained by a RADIANT genetic counselor. RNA sequencing of peripheral blood leukocytes is performed by the Human Genome Sequencing Center at BCM (Supplementary Fig. 1).

Whole blood, serum, plasma, and extracted DNA/RNA samples will be archived at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Central Repository. Additionally, WGS data with specific data-sharing restrictions may be submitted with the appropriate consent/data sharing information into one or more scientific databases, such as the database of Genotypes and Phenotypes (dbGaP); Analysis, Visualization, and Informatics Labspace (AnVIL); and the clinical variant database ClinVar.

Stage 3 Procedures

All participants eligible for stage 3 visit a study clinic and consent to a fasted blood draw for lipid profile, metabolic panel, metabolomics studies, and hemoglobin A_{1c} measurement, followed by a standardized oral glucose tolerance test for glucose, insulin, and C-peptide measurements (Fig. 4). Quantitative estimates of insulin secretion and insulin sensitivity are derived (Supplementary Table 2). A comprehensive physical provides vital signs, biometric measurements, and optional photography.

These data are considered by the RADIANT Discovery Team comprising genetics experts as well as clinical phenotyping and diabetes experts. Initially, a genome reviewer, a phenotyper/clinician reviewer, and an RNA sequencing reviewer will present the case for discussion and recommendations for deeper phenotyping (tiers 2 and 3 tests as described in Fig. 4 and Supplementary Material).

Enrollment of the proband's family members may be recommended for additional genomic testing to determine if a candidate variant segregates with the identified phenotype in the family.

Data Analysis

Participants with known monogenic forms of diabetes are referred to experts who specialize in those forms of diabetes. Secondary findings (such as those recommended by ACMG) are reported back to the participant, if consent was given. For participants younger than 18 years of age, results returned include only information directly related to diseases and disorders with pediatric onset. When they reach 18 years of age, participants may request additional information. Genetic counseling is available for all RADIANT participants.

Bioinformatic and statistical analysis will include several clustering methods, including partitioning around medoids recursive partitioning analysis and Bayesian nonnegative matrix factorization (21–24).

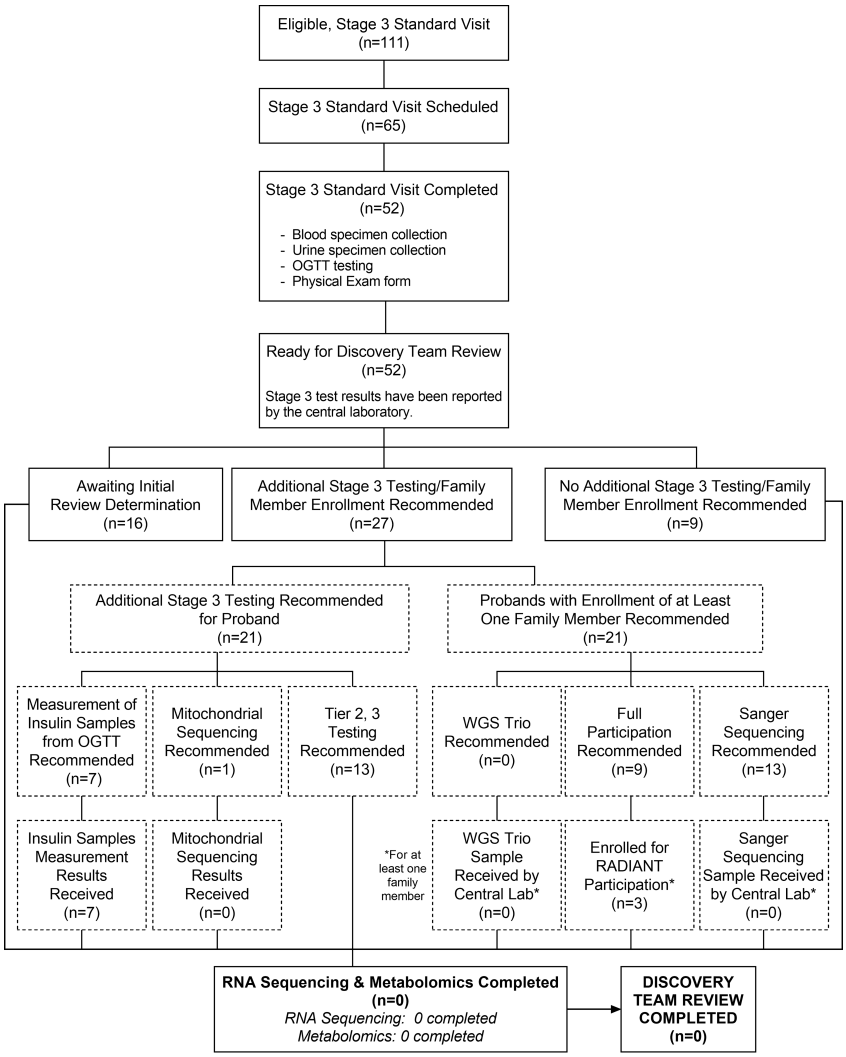

Figure 4—Consolidated Standards of Reporting Trials (CONSORT) diagram: stage 3. Boxes with dashed lines represent additional recommended testing that has not started as yet. OGTT, oral glucose tolerance test.

Data and Resource Availability

By signing the study consent forms, participants agree to have their samples and data stored for future research and that data may be deposited into controlled-access databases such as dbGaP. They may change their mind up until the end of the study, at which point information that identifies them to the sample will be destroyed. Any data collected prior to the date the participant withdraws will be maintained within the RADIANT database. When the study is completed, access to study data and/or biospecimen samples will be provided through the NIDDK Central Repository.

RESULTS

Stage 1 opened on 30 September 2020, 878 participants enrolled through 19 July 2022 (Fig. 2). A pathogenic or likely pathogenic variant in a known diabetes monogenic gene was found in 3 of 122 (2.5%) individuals for whom WGS results have been received. To date, six new monogenic variants have been identified: *SMAD5* [c.844C>T (p.Arg282Cys)], *PTPMT1* [NM_175732.2 c.349T>A p.Phe117Ile], *INS* [NM_000207.2 c.188-11C>A], *NFKB1* [NFKB1(NM_003998.4):c.1753-1G>C], *IGF1R* [c.1447G>A], and *PAX6* NC_000011.9:g.31822258_31822284delins [GGTCG;NC_012920.1:m.(10929_?);NC_012920.1:m.(?_10674)].

The most frequent phenotypic clusters are lean type 2 diabetes, autoantibody-negative and insulin-deficient diabetes, and new forms of possible monogenic, oligogenic, or lipodystrophic diabetes. Special interest groups have been formed to study each in more depth.

CONCLUSIONS

RADIANT has far-reaching implications. The genotypic and phenotypic analyses will lead to improved means of identifying cases with atypical diabetes. Genetic sequencing could help identify new variants and metabolomics and transcriptomics analysis novel pathogenic mechanisms and biomarkers for atypical forms of the disease. Ultimately these findings may permit a more precise, etiologically based clinical classification of diabetes.

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Author Contributions. All RADIANT investigators contributed to the design of the RADIANT study and reviewed and approved the manuscript. Jeffrey Krischer (Health Informatics Institute, Morsani College of Medicine, University of South Florida, Tampa, FL) also contributed to the design of the RADIANT study, wrote the initial draft, and reviewed and approved the final manuscript. Jeffrey Krischer is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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