RADIANT
Rare and Atypical Diabetes Network

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MANUAL OF PROCEDURES (MOP)
Version 03Apr23

Stages 1 and 2

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Sections denoted with # are particularly important for local site study coordinators to reference

1 SUMMARY AND OBJECTIVES

This Manual of Procedures (MOP) is a detailed blueprint of the RADIANT study designed to serve as the day-to-day instruction manual. It has been created to provide details concerning the design, conduct, performance, monitoring, recording, analysis, and reporting of RADIANT to assure that the data and reporting results are accurate and that the rights, integrity, and confidentiality of the participants are protected. The MOP provides the level of detail needed to conduct RADIANT in a standard and uniform fashion across sites and over time. The MOP is a 'living' document that will be updated as improved or new methods are agreed upon and added for RADIANT. The MOP supplements other study materials including the RADIANT Protocol and RADIANT Policies and Procedures document. Please refer to the RADIANT Policies and Procedures document for policies regarding topics such as the network structure (i.e. committees, study units), deeper phenotyping, duality of interest, ancillary studies, publications and presentations, and release of RADIANT data.

1.1 SUMMARY

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

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).

There are 14 Clinical Centers for participant enrollment and one Data Coordinating Center. The study will have a duration of approximately 4-5 years from the time of initial study participant enrollment to the completion of the data analyses. Study participant duration is expected to vary depending upon how far the participant proceeds in the study workflow and the nature of additional testing.

RADIANT will be funded as a cooperative agreement between the NIH through the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Coordinating Center and the RADIANT Co-Principal Investigators (the Study Chairman and PIs of the Administrative Cores). The Administrative Cores will be the primary awardee of the grant, and in turn, will execute sub-agreements with the clinical sites, the Chairman's Office, Central Laboratory, and subcontracts with other central units, as needed.

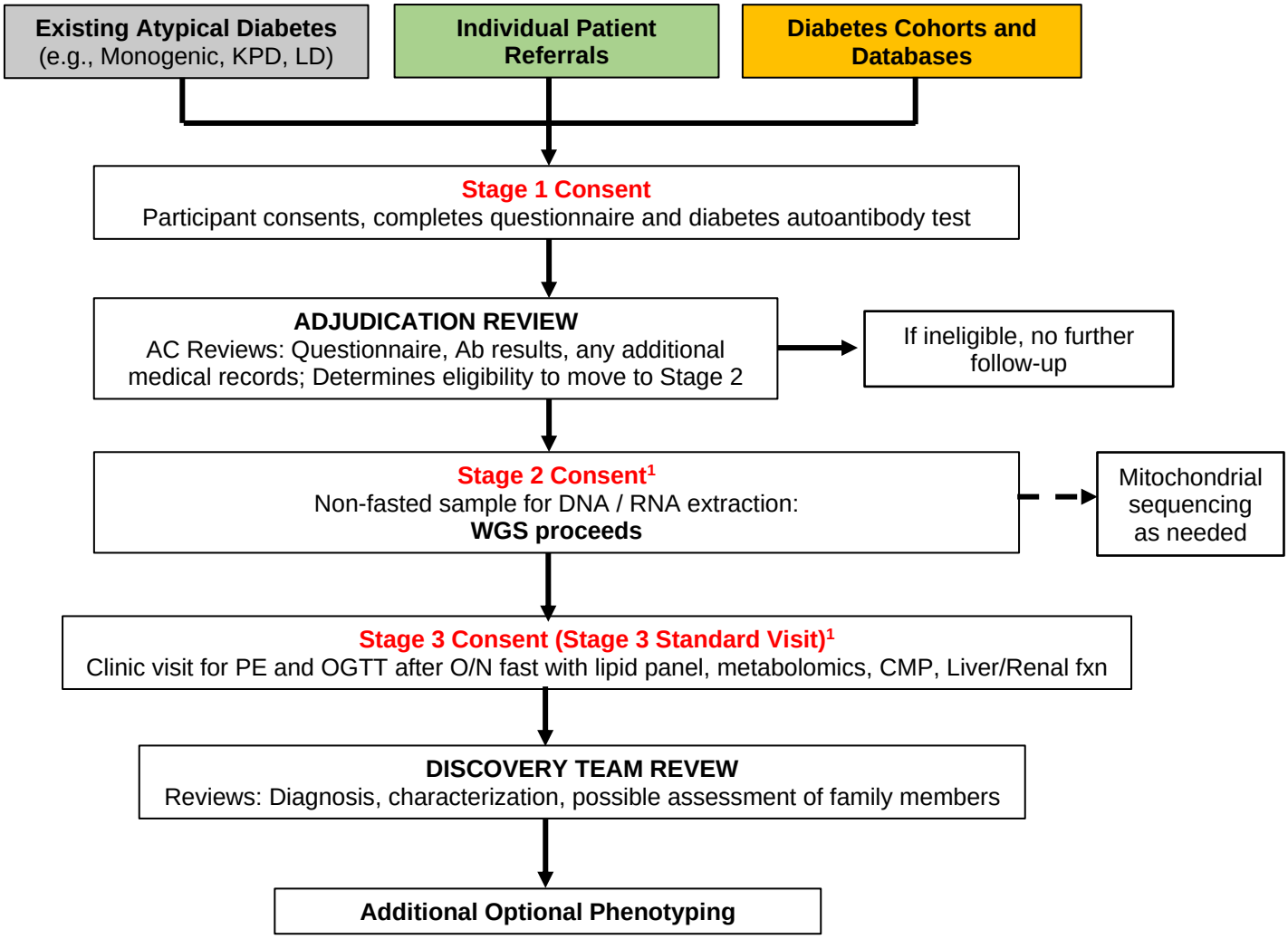
1.2 OBJECTIVES

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 with individuals/families 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

1.3 STUDY WORKFLOW[#]

Abbreviations in Study Workflow figure: AC – Adjudication Committee, Ab – antibody, WGS – whole genome sequencing, PE – physical exam, OGTT – oral glucose tolerance test, O/N – overnight, CMP – complete metabolic panel, fxn – function



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

2 STUDY ORGANIZATION

2.1 COMMITTEES

Committees include the RADIANT Steering Committee and a collection of sub-committees. The sub-committees include members of the RADIANT Research Group. The function of the sub-committees is to develop detailed policies and procedures, carry out those procedures as appropriate, and make recommendations to the Steering Committee. The RADIANT sub-committees include: Adjudication Committee, Discovery Team (Phenotypers and Clinicians Group, Genetics Group), Recruitment and Retention Committee, Protocol Oversight Committee (formerly Protocol Implementation Committee), Laboratory Implementation Committee, Publications and Presentations Committee, Ancillary Studies/Data & Sample Access Committee. Please refer to the RADIANT Policies and Procedures document for more information about the functions of these committees.

2.2 OBSERVATIONAL STUDY MONITORING BOARD AND SAFETY MONITORING

The RADIANT Observational Study Monitoring Board (OSMB) Members will be completely independent of RADIANT. They shall not be actively involved with RADIANT and must have no financial interest in the outcomes of RADIANT. The OSMB and chairperson(s) for RADIANT are to be appointed by the NIDDK and will reflect the scientific disciplines and medical expertise necessary to regularly monitor data from the 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.

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.

2.3 STUDY UNITS

2.3.1 ADMINISTRATIVE CORES

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. They will also assist with study coordinator training and serve as a resource for clinical sites throughout the project.

The Administrative Cores will maintain and manage compliance activities for the trial to include investigators' duality of interest, institutional review board approvals for the protocol, and documents related to study certification. The Administrative Cores also helps monitor protocol performance.

The Administrative Cores are the prime grant recipient; all other study sites will be funded through sub-agreements or subcontracts from the Administrative Cores.

Baylor College of Medicine
One Baylor Plaza
Houston, TX 77030
Phone: 713-798-3625
Principal Investigator: Ashok Balasubramanyam
Project Manager: Iliana Gonzalez
Email: Iliana.Gonzalez@bcm.edu

Baylor College of Medicine serves as the Administrative Core for the following sites:

- Indiana University
- Seattle Children's
- SUNY Downstate
- University of Colorado
- University of South Florida

University of Chicago
900 E. 57th St.
Rm 8142
Chicago, IL 60637
Phone: 773-702-0829
Principal Investigator: Louis H. Philipson
Project Manager: Lisa Letourneau-Freiberg
Email: lletourneau@uchicago.edu

University of Chicago serves as the Administrative Core for the following sites:

- Broad Institute
- Columbia University Medical Center
- Massachusetts General Hospital
- RADIANT Central Lab at the University of Florida
- University of Maryland
- University of Michigan
- University of North Carolina
- University of Rochester
- University of Washington
- Vanderbilt University
- Washington University St. Louis

2.3.2 DATA COORDINATING CENTER (DCC)

The University of South Florida Health Informatics Institute will serve as the Data Coordinating Center (DCC). Please refer to the RADIANT Policies and Procedures document for more information about the role of the DCC.

Contact Information:
RADIANT Data Coordinating Center
University of South Florida Health Informatics Institute
3650 Spectrum Boulevard
Tampa, FL, 33612

Jeffrey Krischer, PhD
Phone: 813-396-9512
Email: Jeffrey.Krischer@epi.usf.edu
DCC Project Manager Team: Contact@atypicaldiabetesnetwork.org

2.3.3 GENETICS/GENOMICS CORES

The Genetics/Genomics Cores refer to the Baylor College of Medicine Human Genome Sequencing Center and the Broad Institute, where whole genome sequencing, RNA sequencing, and mitochondrial sequencing will be performed.

Contact Information:
Baylor College of Medicine – RNA sequencing, mitochondrial sequencing, research-based Sanger sequencing
One Baylor Plaza
Houston, TX 77030
Phone: 713-798-8253
Email: Jennifer.Posey@bcm.edu

Broad Institute / Massachusetts General Hospital / Partners Laboratory for Molecular Medicine (LMM) – Whole Genome Sequencing
75 Ames Street – 10th floor
Cambridge, MA 02142
Phone: 617-643-3308

Email: JCFlorez@mgh.harvard.edu

2.3.4 CENTRAL LABORATORY

The RADIANT Central Laboratory (CL) is the University of Florida under the direction of Dr. William Winter and Dr. Clive Wasserfall.

Contact Information:
University of Florida Health Pathology Laboratories
Endocrine Laboratory/RADIANT
4800 SW 35th Drive
Gainesville, FL 32608
Email: winter@pathology.ufl.edu, wasserfa@pathology.ufl.edu

Lab Manager – David L. Pittman
Office phone: 352-265-9900 x 72054
pittman@pathology.ufl.edu

2.3.5 CLINICAL CENTERS

Each of the participating clinical centers will implement the RADIANT Protocol and follow the manual of procedures in accordance with all applicable study and institutional policies and regulations. Responsibilities of the clinical centers include: recruit eligible participants; follow participants according to the protocol and the manual of procedures; record participant data related to all of the above using the study designed data forms; maintain the security and confidentiality of participant data; review and enter information from the data forms using the web-based data management system; share clinically relevant data with the participant's healthcare provider, when warranted; and respond to queries from the DCC. Detailed staffing patterns at the clinical centers will be left flexible to best address clinic-specific needs. The PI will be responsible for the overall conduct of the study and implementation of the protocol at his/her site. The Study Coordinator will be responsible for the day-to-day conduct of the study. Clinical center staff will be expected to participate in the central study activities such as preparation of presentations and publications, and governance and management of the study through participation in committees, subcommittees and working groups. The clinical centers will be funded as sub-agreements to the Administrative Cores. Please refer to the RADIANT Policies and Procedures for more information about the role of RADIANT clinical centers.

Clinical Center	Site PI	Site Study Coordinator
Baylor College of Medicine	Adult: Ashok Balasubramanyam Peds: Maria Redondo	Iliana Gonzalez Ansley Davis
Columbia University Medical Center	Robin Goland	James Pring Anabel Evans Kaisha Mofford
Indiana University	Carmella Evans-Molina	Gabriela Monaco (Lead) Maria Spall
Massachusetts General Hospital	Miriam Udler	Evelyn Greaux Mariella Facibene
Seattle Children's	Cate Pihoker	Kathleen Santarelli (Lead)
SUNY Downstate	Mary Ann Banerji	Necole Brown

University of Chicago	Lou Philipson	Shanna Davis (Lead) Erin Papciak
University of Colorado	Neda Rasouli	Courtney King (Lead) Avinash Pyreddy
University of Maryland	Toni Pollin	Devon Nwaba
University of Michigan	Elif Oral	Adam Neidert
University of North Carolina	John Buse	Rachael Fraser (Lead) Alex Kass
University of Washington	Irl Hirsch	Lori Sameshima (Lead) Dori Khakpour Jesica Baran
Vanderbilt University	Kevin Niswender	Norma Edwards
Washington University	Fumi Urano	Stacy Hurst

2.4 NIDDK

The NIDDK Project Scientist and Program Official will play important roles in the implementation of RADIANT as described below.

The Project Scientist provides substantial scientific involvement in the conduct of the RADIANT study including:

- Serves on the Executive Committee
- Serves as voting member of the RADIANT Steering Committee
- Cooperates, coordinates, and works with RADIANT and its clinical sites by overseeing conduct of the research protocol, monitoring recruitment/retention, and ensuring that objectives of the study are achieved
- Participates in study publications
- Attends OSMB meetings

The Program Official provides substantial programmatic involvement in the conduct of the study including:

- Provides budgetary oversight
- Reviews study progress prior to annual study renewal
- Works with the study OSMB in study oversight by serving as liaison to the study Steering Committee

3 RECRUITMENT

3.1 RECRUITMENT OVERVIEW

3.1.1 STUDY POPULATION

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

3.1.2 RECRUITMENT GOALS#

- Recruitment goal: Approximately 400 participants will be evaluated for suspected atypical diabetes of unknown origin per year.
    - Among the pool of evaluated patients, those found to have a known form of diabetes that is either not atypical in presentation or atypical in presentation but with a known molecular cause will be excluded from further study but will serve as a control/comparison population.
    - The remaining patients that are deemed to be atypical, and where appropriate their families, will be enrolled for further testing.

- Study timeline: The study has an estimated duration of 4-5 years from the time of initial study participant enrollment to the completion of the data analyses.
    - Study participant duration is expected to vary depending upon the nature of the additional testing necessary. Those who only undergo testing needed to identify known forms of diabetes participate in at most two study visits, while those accepted for additional data and sample collection will participate in two or more visits over the course of the project.

- Study Recruitment Materials:
    - Study flyers
        - A collection of flyers has been central IRB approved and are available for recruitment. Sites may choose to use whichever flyers they think will be most helpful for their patient population.
        - Any flyers that contain local study contact information (with tabs) need to be approved by the site's local IRB and central IRB prior to use.
        - Flyers can be found on the Members Website
    - Participant recruitment letters (Pediatric and Adult versions)
        - Two participant recruitment letters have been central IRB approved and are available for recruitment. There is a pediatric and an adult version.
        - These letters contain local contact information, so they must be approved by the site's local IRB and central IRB prior to use.
        - Recruitment letters can be found on the Members Website
    - Provider slide deck (For use by investigators and study physicians)
        - A slide deck has been created to help investigators and study physicians share information about RADIANT with their colleagues, during lectures or presentations, etc. You may use all of the slides or choose which slides are most useful for your presentation.
        - IRB approval is not required for the slide deck because it is not participant-facing
        - The slide deck can be found on the Members Website

We will recruit from several sources, including:

1) Disease registries enriched in forms of atypical diabetes – ex: University of Chicago Monogenic Diabetes Registry, University of Michigan Lipodystrophy Registry, Baylor College of Medicine Ketosis Prone Diabetes Registry, University of Maryland Personalized Diabetes Medicine Program, etc.
2) 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)
3) Provider referrals of patients with unknown forms of diabetes
4) Self-referrals through atypical diabetes participant website; and

5) Community Organization Outreach

3.1.3 ELECTRONIC HEALTH RECORDS (EHR) RECRUITMENT#

EHR recruitment will be based on EHR searches through data query systems developed based on inclusion and exclusion criteria. In this effort, IU, Geisinger Medical, BCM and USF have worked individually to define computable phenotypes of atypical DM. For example, using criteria such as “T2D without metabolic syndrome and low BMI. Below are two possible approaches to define computable phenotypes using EHR data searches:

a. The first approach is to manually identify participants who did not fit the conventional definition of type 2 diabetes (T2D) or type 1 diabetes (T1D) based on the inclusion and exclusion criteria of various clinical phenotypic data. For example, “History of diabetic ketoacidosis (DKA) and GAD65Ab-negative”, an atypical diabetic phenotype, was considered as an inclusion criterion and “Current insulin usage and GAD65Ab-positive”, a typical T1D phenotype, was used as an exclusion criterion.

b. The second approach is to utilize a machine learning procedure instantiated by a 2-step filtering process followed by a robust spatial clustering algorithm to identify a similar subset to the one found in the first approach. Clustering methods previously used include partitioning around medoids (PAM, a form of k-medoids clustering), Clustering Large Applications (CLARA), and hierarchical clustering methods.

Data analysts from these institutions can provide assistance if further questions arise about using EHR data query systems. Please contact the study Project Managers or DCC.

Patients identified through EHR will be contacted according to the policy of the institutions - in most instances, participant recruitment letters and/or notifications through their primary care provider with the option to opt out of the study or further contact. For those participants interested in the study, the information for recruitment and clinical site contact information for the study will be included in the recruitment letter. The local RADIANT clinical site will be the point of contact for the participant who will be directed to enroll in STAGE 1 via the public RADIANT participant enrollment website www.atypicaldiabetesnetwork.org.

Note: The participant recruitment letter templates (both pediatric and adult versions) are available on the Members Website (members.atypicaldiabetesnetwork.org) under recruitment materials. These letters must include the local site information and must be approved by your local IRB and Central Utah IRB.

3.1.4 RECRUITMENT FROM EXISTING ATYPICAL REGISTRIES#

Existing atypical diabetes registries that permit contacting the enrolled participants will be considered for potential case identification. We have identified the Monogenic, Lipodystrophic and Ketosis-prone diabetes registries; in addition, 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.

The process of case selection will consist of a tailored data query approach that each individual registry will use to sort through their registry (i.e., applying inclusion/exclusion criteria in a similar fashion as EHR query). Once suspected cases are identified, the registry sponsor will contact the patients for possible participation in the study with the option to opt out of the study or further contact. The registry sponsor will utilize RADIANT participant recruitment letters that provide information about the study and the clinical site contact information associated with the registry. Those expressing an interest will be directed to the RADIANT participant enrollment site to complete Stage 1 of RADIANT at www.atypicaldiabetesnetwork.org.

3.1.5 RECRUITMENT FROM STUDY CLINICAL CENTERS#

Potentially “atypical” participants may be identified by RADIANT investigators or their colleagues at RADIANT

Clinical Centers.

Participants who are identified at RADIANT Clinical Centers as potentially “atypical” should be directed to the RADIANT public website www.atypicaldiabetesnetwork.org to sign up for the study. Consenting for Stage 1 of RADIANT is done through an online consent form that is accessible from the public website. Or, participants may be consented by local RADIANT sites using the IRB-approved RADIANT Stage 1 paper consent form.

If a potential participant has any difficulty in accessing the public website to sign up, local RADIANT study staff can support them by:

- Inviting the participant to come in-person to the Clinical Center – the local RADIANT site staff can use the RADIANT iPad or another device (clinic laptop, etc.) to help walk the participant through the online consent process or use the Stage 1 paper consent form.
- Call the participant over the phone to guide them through the online consent process. The participant must be the one to actually complete the consent online (the site cannot complete the consent on behalf of the participant).
- Consider use of paper questionnaires. See Section 4.2.5.

3.1.6 SELF-REFERRALS OR OUTSIDE REFERRALS

Participants may learn about the study from a social media post, a study flyer or word of mouth. Those who enter the pipeline as individual referrals from non-study physicians and clinics or by self-referral will be directed to the RADIANT public website www.atypicaldiabetesnetwork.org to sign up for the study.

Participants who complete STAGE 1 have the option to select the nearest RADIANT Clinical Site to come for study visits for STAGE 2 and 3 if eligible.

3.1.7 OTHER RECRUITMENT SOURCES/STRATEGIES

Print media, websites and social media, atypical diabetes advocacy groups, television, and radio may also be effective avenues of communication to potential RADIANT participants. The effectiveness of these methods as well as the specific print and electronic media selected may depend on the site-specific media market. An NIH press release will be available to all sites to distribute to their institutions for local PR use (i.e., sharing press release with local news outlets, hospital PR communication across clinical departments).

All recruitment materials used for RADIANT must be approved by the central IRB prior to use.

3.1.7.1 Social Media/Internet

Websites and social media may also provide excellent venues for publicizing the study and reaching out to potential participants. Links to the RADIANT website (www.atypicaldiabetesnetwork.org) may be posted on websites of willing organizations with a special interest in diabetes (e.g., local American Diabetes Association website, University Diabetes Centers, local health departments and other health related organizations).

3.1.7.2 Patient Advocacy Groups (PAGs)

Formal Patient advocacy groups like the National Organization of Rare Disorders, Monogenic Diabetes Research and Advocacy Consortium (mdrac.org) or informal advocacy groups and other small organizations can be a source for word of mouth for RADIANT recruitment. If you know of such organization in your local market, you can approach them, provide more information about RADIANT, and refer them to the RADIANT website.

3.1.7.3 Healthcare provider letters and information sessions

Make physicians, nurses, and other health care providers inside and outside your practice aware of RADIANT.

Present RADIANT to your colleagues by placing approved study flyers in their mailboxes, posters, and brochures in common waiting rooms, clinic rooms, and nursing stations, as well as providing educational programs, grand rounds, and in-service meetings.

Meet with appropriate medical staff (e.g. primary care physicians) to review lists of identified potential participants and flag those who fulfill eligibility criteria. RADIANT Principal Investigators and Study physicians have access to a slide deck that contains study information to present at meetings and engage with providers. The slide deck and study flyers can be accessed on the members' website (members.atypicaldiabetesnetwork.org) under recruitment materials.

All RADIANT Clinical Centers must obtain the appropriate permission/approvals to contact providers and/or potential participants, as per guidelines of the central IRB and local institutional regulations, before initiating recruitment efforts.

3.1.7.4 Contact with Referring Clinicians

Inform referring clinicians that, if the participant agrees to share results with the healthcare provider, they will be kept informed of the participant's testing results throughout the participant's duration of RADIANT. This will promote further referrals and cooperation during the study in notifying or obtaining information regarding events.

The Principal/ Co-investigators at each site must be involved for successful recruitment. Although each clinical site will develop its own strategies, for many sites the most successful techniques involve personal contact with referring clinicians. Possible strategies include:

- Formal presentations (Grand Rounds, in-services, research conferences)
- Informal presentations (house staff rounds, informal clinic in-services)
- Letters from the primary care physician to their patients, brochures describing the center, phone calls and /or conversations with physicians soliciting referrals.

3.1.7.5 Community Organization Outreach

Community outreach activities include communication about RADIANT to groups, organizations, and residents of communities served by institutions close to RADIANT clinical sites. Community engagement is a process of working collaboratively with study communities to build relationships and secure long-term support and endorsement of the study from potential participants and the clinics or programs that serve them. For example, reaching out to community clinical centers, local diabetes or rare disease organizations, and partner medical institutions. In this particular effort, outreach to minority and underrepresented populations will be a priority for RADIANT as part of their commitment to inclusion and diversity in the study.

3.2 RECRUITMENT OF FAMILY MEMBERS/ TRIOS

Upon review of a proband's data and test results, the Discovery Team may recommend that the proband' s family members participate in RADIANT. 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 – see Section 6 for more information. Family members who are interested will be instructed to contact RADIANT staff to provide consent and participate.

This recommendation may be made for one of three 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. If NO known monogenic diabetes diagnosis is identified in the index case during Stage 2, 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 3, following an iterative analysis of ALL available RADIANT data for the index case. Consent would be limited to supporting blood sampling for DNA extraction and, for "unaffected" family members, a basic fasting blood glucose and HbA1c measurement (to confirm the individual's reported "unaffected" status). In this scenario, should the relative be unable to provide a blood sample (e.g., not able to visit a Clinical Center), collection of saliva for DNA extraction will be acceptable.

(3) Full, iterative analysis of WGS, RNA, metabolomic, and deep phenotyping data may yield no clear candidate gene variants in the index case. In this scenario, and only after full analysis of all available 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. Consent would also include blood sampling for a basic fasting blood glucose and HbA1c measurement for "unaffected" parents (to confirm the individual's reported "unaffected" status). This recommendation will be made for approximately 5 participants per year depending on throughput and budget. Parents would consent, and blood samples would be collected for DNA extraction.

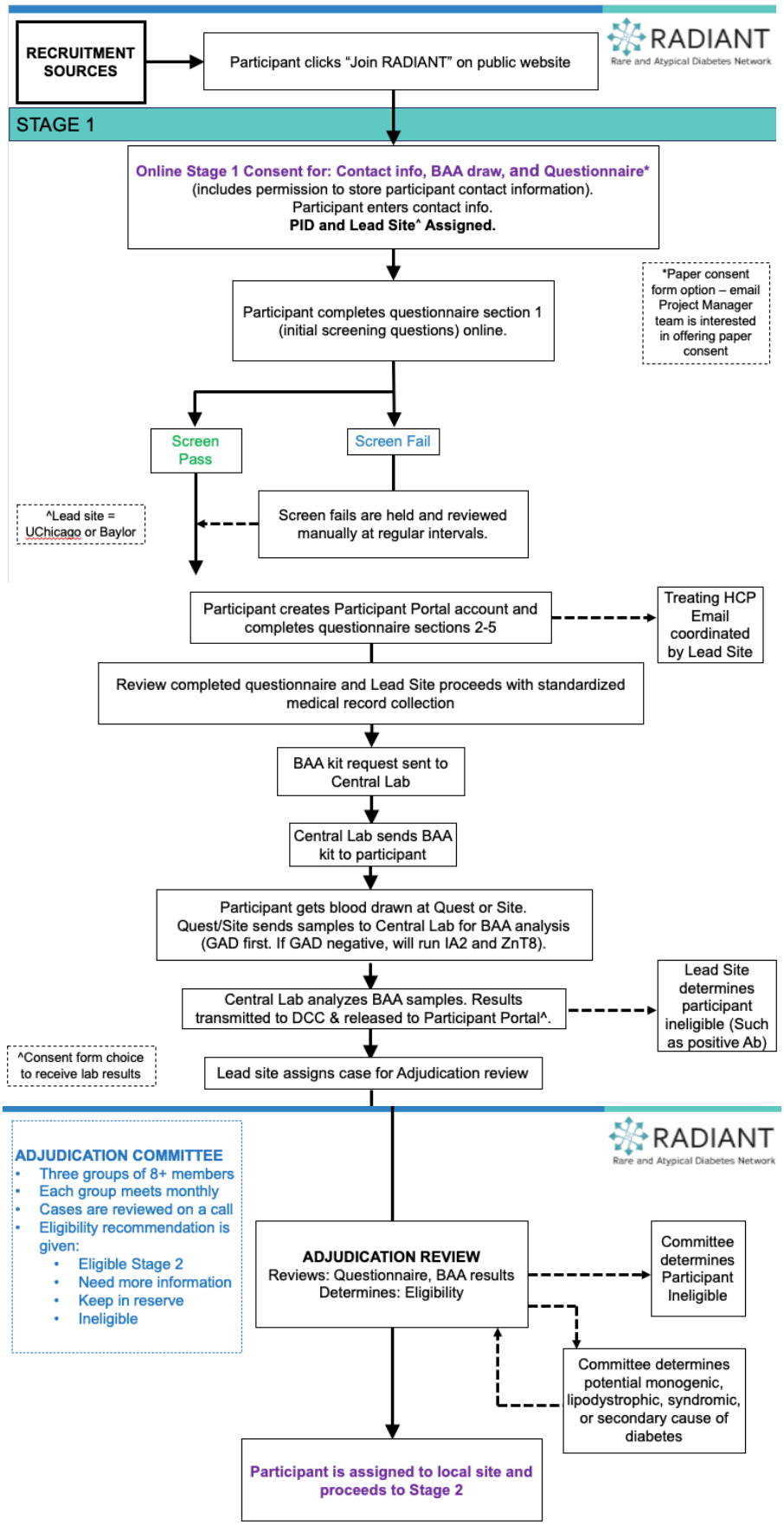
Recognizing that parental samples may be informative in a substantial proportion of cases, and considering the opportunity cost of not enrolling parents simultaneously when they accompany pediatric-age participants to a Clinical Center for Stage 2 procedures, RADIANT will consider implementing parental consenting and sample collection at the Stage 2 clinic visit IF both parents are present at that visit.

4 STAGE 1 (SCREENING) PROCEDURES

4.1 STAGE 1 OVERVIEW#

The purpose of RADIANT Stage 1 is to screen patients for atypical diabetes and determine if they should continue in the RADIANT study. Stage 1 of the RADIANT protocol includes: Informed consent, Stage 1 questionnaire including screening questions, sample collection for autoantibodies, treating healthcare provider email, medical record request, and adjudication.

Figure 1. RADIANT Stage 1 Workflow with Online Consent
Abbreviations in Stage 1 Workflow figure: BAA – biochemical autoantibodies (diabetes autoantibody testing); PID – participant identifier; HCP – healthcare provider; DCC – Data Coordinating Center



Stage 1 consent may occur online or on paper (with appropriate cIRB/local regulatory approvals). For more information about the paper consent process, please see section 4.2.2.1.

4.2 STAGE 1 PROCEDURES

4.2.1 STAFF RESPONSIBILITIES – STAGE 1#

The following table indicates which RADIANT staff are responsible for procedures in Stage 1:

Procedure	RADIANT staff responsible *(Note: Site must have Central IRB approval for these procedures and have completed the Stage 1 training.)*	Notes
Directing interested participants to the RADIANT public website to enroll	All staff	
Stage 1 consent (online)	None (Participants must complete online consent form)	RADIANT staff may provide participants with an iPad/internet access/space at site to complete the online consent. RADIANT staff may assist participants in understanding the Stage 1 consent form by talking them through it over the phone or in-person.
Stage 1 consent (paper)	RADIANT study staff at sites with IRB approved Stage 1 paper consent forms	
Stage 1 questionnaire	None (Participants must complete questionnaire)	RADIANT staff may assist participants in understanding the questionnaire by talking them through it over the phone or in-person. For participants who consent online: Section 1 (screening questions) will be entered by the participant online after the consent, so the screening algorithm can work correctly. For participants who consent on paper: Site staff will give the paper Section 1 form to the participant or complete Section 1 via phone call after consent. Then, site staff will follow the procedures in section 13.3.6.1 to register the participant and enter the consent and section 1 data. If participant needs to complete a paper version of the questionnaire for sections 2-5, please see Section 4.2.5 of this MOP.

Reviewing questionnaire for completeness and sending Stage 1 sample collection kit request to Central Lab	Administrative Core staff (Baylor and University of Chicago) OR local sites that have requested a participant site transfer in Stage 1	Email Project Manager team to request a site transfer.
Collection, processing, and shipment of Stage 1 samples	Primarily Quest staff, local site staff or other lab as needed	Quest collection is preferred. Please see Section 4.2.7 for more details.
Stage 1 results sharing	None	Participants will see results in their RADIANT Participant Portal account, if they agreed to receive results in the Stage 1 consent. If participants consented to share Stage 1 results with a healthcare provider, Administrative Core staff (Baylor and University of Chicago) will share these results.
Standardized medical record requests	Administrative Core staff (Baylor and University of Chicago)	For all participants who completed a medical record release form.
Adjudication of cases in Stage 1	Adjudication Committee	If a participant had prior genetic testing with variant identified, variant interpretation may occur with specific staff. Please see Section 4.2.12.5 for more details.
Documenting any participant communications in the Contact Log section of the Participant Profile	All sites, as needed	Any interactions with the participant should be documented in the Contact Log.
Transferring participant to local site to continue on in RADIANT Stage 2	Administrative Core staff (Baylor and University of Chicago)	

Responsibilities of Sites in Stage 1

All sites that have Stage 1 IRB approval and are up to date on Stage 1 training (version 2022):	Sites that wish to be more involved in Stage 1*	Baylor/Chicago only
• Assisting with online and paper consent completion • Describing the study and answering questions about the study • Providing iPad/computer/internet access for the participant to complete consent • Assisting with questionnaire completion (online or on paper) • Collecting Stage 1 blood sample • Assisting with adjudication 'need more information' requests when asked by the PM team	• Completing data entry for paper Stage 1 questionnaires • Checking address and questionnaire for completeness • Requesting Stage 1 antibody kit • View participant's Stage 1 antibody results *Upon submission of the online consent form, all Stage 1 participants are assigned to either Baylor or Chicago in the RADIANT Members Website. Sites may become more involved by emailing the RADIANT PM team to transfer specific participants to their local site. This would change the participant's assigned site in the Members Website. If sites request this, they should perform all of the functions in this column and the column to the left.	• Requesting medical records • Requesting treating healthcare provider surveys • Reporting antibody results to healthcare providers (if consent given) • Deciding whether participants with positive antibodies are ineligible or may continue to adjudication • Assigning participants to the Adjudication Committee • Updating participant statuses after adjudication

PM team = RADIANT Project Manager team radiantteam@atypicaldiabetesnetwork.org

4.2.2 STAGE 1 ONLINE INFORMED CONSENT#

The participant will be presented with an online consent form explaining Stage 1 of RADIANT (i.e. questionnaire, autoantibody testing). If they click to agree, they will be prompted to enter their contact information and then proceed to the online Stage 1 questionnaire. Upon agreeing to the online Stage 1 consent, participants will be emailed a copy of the Stage 1 consent form.

RADIANT staff (with appropriate Central IRB approval and Stage 1 training completion) may assist participants in understanding the Stage 1 consent form by talking them through it over the phone or in-person at a Clinical Center. Using the RADIANT iPad may be helpful for participants who come to a local Clinical Center for assistance in completing the online consent form.

The Stage 1 online consent form is available in English and Spanish. The patient can select their preferred language on the online consent form.

4.2.2.1 Stage 1 Paper Informed Consent

For participants who are unable to complete the Stage 1 consent online, a paper consent form is available. Study staff should complete the informed consent process. Stage 1 paper consent may be obtained remotely or in-person.

The participant must provide informed consent and assent (if applicable – ages 7-17 years old) for the Stage 1 Procedures before any Stage 1 Procedures occur.

- Forms needed:
  - Current IRB-approved Paper Stage 1 Consent Form
- Instructions:
  1. Print out all necessary forms. If Stage 1 consent will be completed remotely, mail the consent forms and schedule a consent phone call for a time after the forms arrive.

2. Meet with participant (and/or caregivers or legally authorized representative if needed) in person in a quiet place, or call participant at scheduled time for remote Stage 1 consent.
3. Explain what you are asking them to do for this stage of RADIANT and what is contained in the consent form. Encourage them to ask you any questions they may have as you go through the form. When you finish explaining the form, ask them "what questions do you have for me?" After all questions have been answered, ask "do you want to proceed with participating in this study?"
    i. If no → Thank them for their time and do not proceed with entering Stage 1 consent information in the Members Website.
    ii. If yes → Proceed to step 4 below.
4. Direct the participant to areas where they need to initial and/or sign on the consent/assent forms. If Stage 1 consent is completed remotely, provide a prepaid FedEx label* for participant to mail the consent form back to you.
5. Sign and date as the consenter on the last page. If your local site requires PI signature, ensure PI has signed as well.
6. Make a copy of the signed consent/assent forms and return the copy to the participant (and/or caregivers or legally authorized representative if applicable)
7. Document consent process locally
8. Give participant the paper Stage 1 Section 1 screening questionnaire to complete and return to you (see Section 4.2.3.1). The Stage 1 screening questionnaire may be mailed to participant or completed verbally over the phone. If the screening questionnaire is completed verbally, record the responses on the paper Stage 1 screening questionnaire, and document interaction in a local Note To File.

9. In the RADIANT Members Website: Register participant, enter consent information, and enter Section 1 paper form responses (see Section 13.3.6.1). If Stage 1 consent is completed remotely, do not complete this step until the signed Stage 1 consent form is received by the site.

*RADIANT FedEx account should only be used for approved RADIANT participant shipments:
Username: radiantstudy
Password: 2*YGaj.Cjedf42

4.2.3 ONLINE QUESTIONNAIRE SECTION 1 (SCREENING QUESTIONS) AND SCREENING DECISION

Screening criteria will be applied to the sources of participant recruitment (existing atypical diabetes registries, individual referrals, and diabetes cohorts/databases). 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 (section 3.1.4).

After completion of the online Stage 1 consent form, participants will complete Section 1 of the Stage 1 questionnaire. The Stage 1 questionnaire is 5 sections total; section 1 is the screening questions. The Stage 1 questionnaire is available in English and Spanish.

Upon submission of Section 1 of the questionnaire online, the system will automatically assign the participant a status of "Screen Pass", "Screen Pause", or "Screen Fail" based on a screening algorithm coded in the system to determine whether it is likely the participant has atypical diabetes according to their Section 1 responses and whether they may continue in the study.

- *Please see Section 4.2.3.1 for how to complete a paper version of this Section 1 questionnaire.

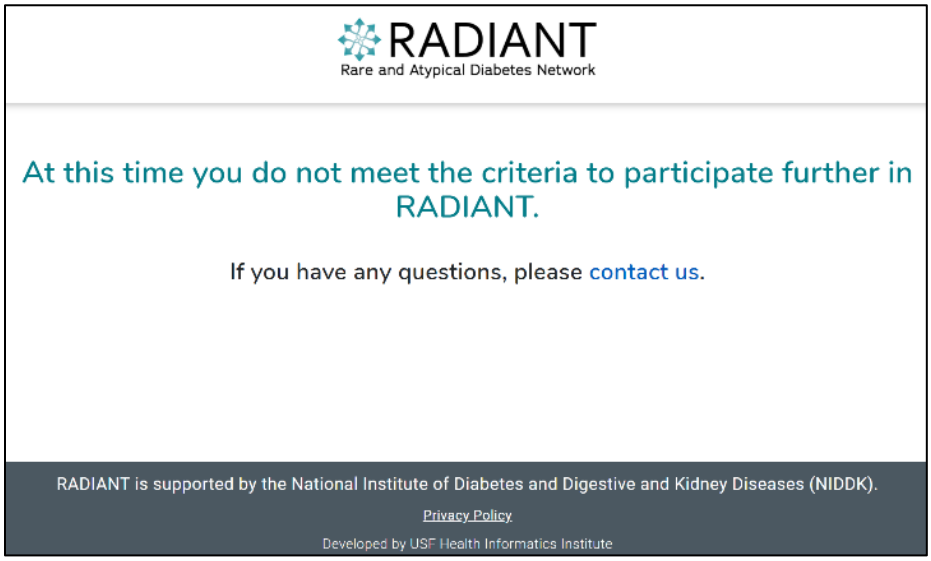
Screen fail criteria include:

- Answers ‘Yes’ to Question 1: Are you pregnant now? and would have been a Screen Fail based on other criteria listed below
    - If they answered Yes but would otherwise have been a Screen Pass, see Screen Pause section below
- Answers 'No or Don't Know' to Question 2: Have you been diagnosed with diabetes? AND 'No or Don't Know' to Question 3: Do you take diabetes medications?
- Answers 'Yes' to Question 4: Have you ever had diabetic ketoacidosis (DKA)? AND '0-9 years' to Question 5: What age were you diagnosed with diabetes (years)? AND 'Yes' to Question 7: Have you been continuously treated with insulin since diagnosis?
    - Note that if participant selects ‘Negative’ to Question 8a: What was the result of the antibody testing, that will override the screen fail criteria for questions 4/5/7
- Answers ‘Positive’ to Question 8a: What was the result of the antibody testing?
- Answers 'No' to Question 9a: Did the diabetes stay or come back at any time after you were pregnant?
- Answers 'No' to Question 10a: Did the high blood sugars continue or come back after steroid treatment was stopped?
- Answers 'Yes' to Question 11: Did you have a pancreatectomy before you were diagnosed with diabetes?
- Answers 'Yes' to Question 13: Were you undergoing chemotherapy before you were diagnosed with diabetes?
- Answers 'Yes' to Question 14: Did you have HIV or take medications for HIV before you were diagnosed with diabetes?
- Answers 'Yes' to Question 15: Do you have cystic fibrosis?
- Answers 'Yes' to Question 16: Do you have hemochromatosis?
- Answers 'Yes' to Question 17: Do you have Cushing's syndrome?
- Answers 'Yes' to Question 18: Do you have acromegaly?

- If a participant selects any RADIANT investigator in Question 21: Have you ever been told by a physician that your diabetes is atypical, rare or cannot be classified, they will be an automatic SCREEN PASS, regardless of the rest of their screening questionnaire responses.

<u>Screen Fail</u>

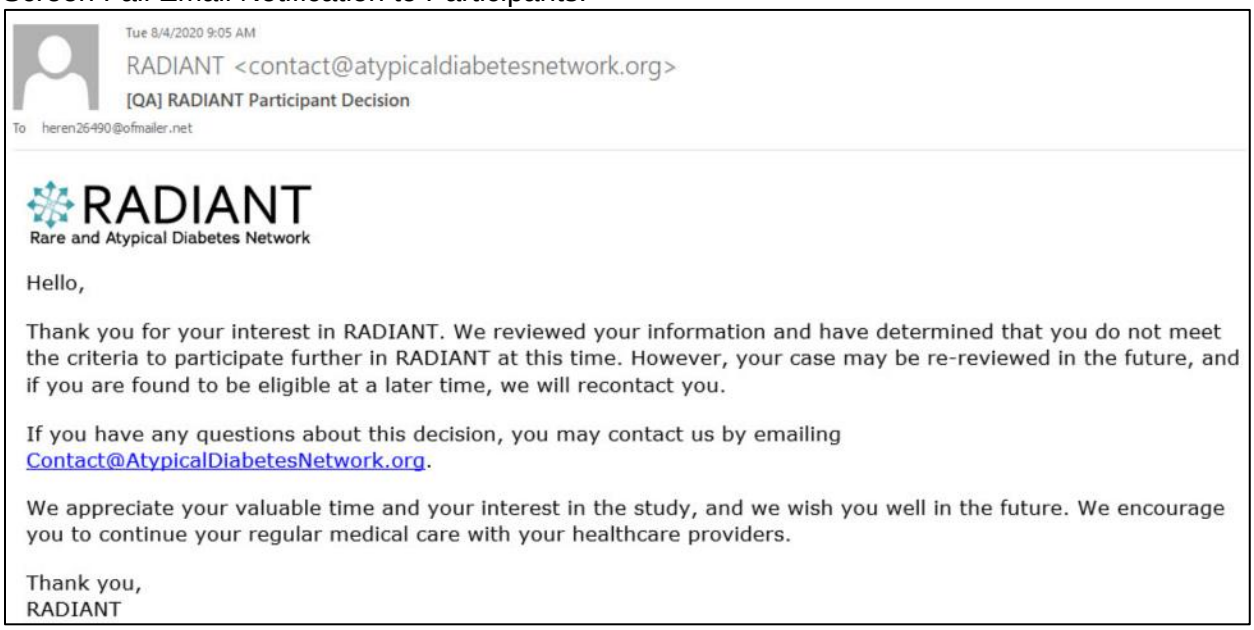
Participants who complete Section 1 online and are determined to have the status of “Screen Fail” will receive the following message:



An automated email will also be sent to Screen Fail participants to let them know they are not eligible at this time, but they may be recontacted in the future if they are deemed to be eligible (see screenshot below).

Manual review of all Screen Fail cases will occur by RADIANT Screen Fail Manual Review Committee at regular intervals (see Section 4.2.12.8).

Screen Fail Email Notification to Participants:



Tue 8/4/2020 9:05 AM

RADIANT <contact@atypicaldiabetesnetwork.org>

[QA] RADIANT Participant Decision

To heren26490@ofmailer.net

RADIANT
Rare and Atypical Diabetes Network

Hello,

Thank you for your interest in RADIANT. We reviewed your information and have determined that you do not meet the criteria to participate further in RADIANT at this time. However, your case may be re-reviewed in the future, and if you are found to be eligible at a later time, we will recontact you.

If you have any questions about this decision, you may contact us by emailing Contact@AtypicalDiabetesNetwork.org.

We appreciate your valuable time and your interest in the study, and we wish you well in the future. We encourage you to continue your regular medical care with your healthcare providers.

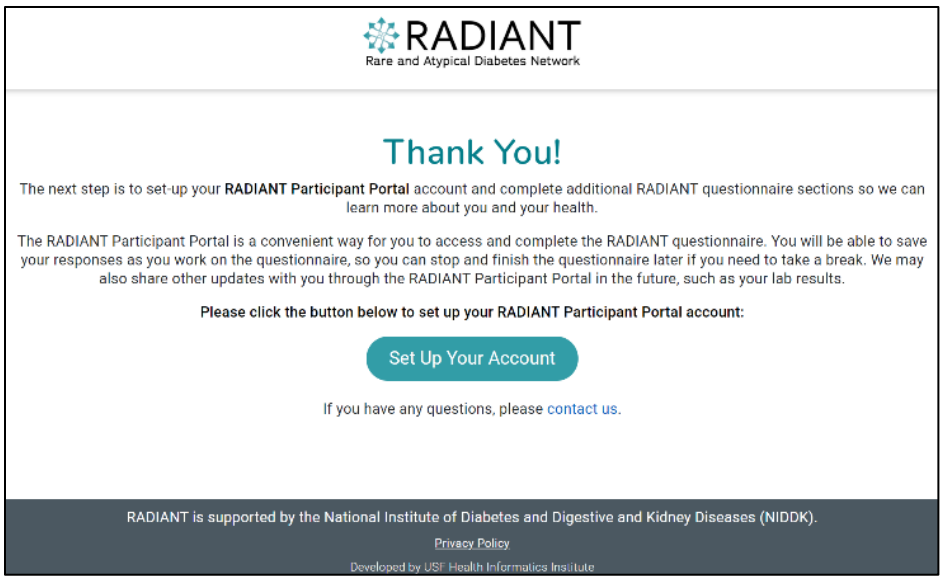
Thank you,
RADIANT

Screen Pause

- Pregnancy: If a participant answers 'Yes' to Question 1: "Are you pregnant now?" but would otherwise have been a Screen Pass, they will be marked as Screen Pause. The participant will receive a message that a member of the study team will review their case and get back to them on next steps. The site assigned to the participant should reach out to confirm the participant is currently pregnant, and to let them know they can come back to the study when they are no longer pregnant. Their status should be updated by the site to 'Withdrawn' with the reason for withdrawing as 'Pregnancy'. Once they are no longer pregnant, if the participant wishes to continue in the study, the site can request that the DCC update their status to Screen Pass by emailing radiantteam@atypicaldiabetesnetwork.org.
- Legally authorized representative: Screen pause status may also be used for participants with an unconfirmed legally authorized representative. Please see Section 8 for more information.

Screen Pass

Participants who complete Section 1 online and are determined to have the status of "Screen Pass" will receive a Thank You message that invites them to set-up a Participant Portal account and continue to sections 2-5 of the questionnaire:



For participants who complete Section 1 on paper and are determined to have the status of “Screen Pass”: Once the coordinator enters the Section 1 responses in the RADIANT Members Website, the participant status will automatically update to “Screen Pass” and an automated email will be sent to the participant with next steps to set-up their Participant Portal account and continue to Sections 2-5 of the questionnaire.

If the Administrative Core Project Managers determine a participant who was previously deemed a “Screen Pass” should not continue in the study, they will update the participant status to “Screen Fail” on the Participant Profile (section 13.3.6, How to Edit Participant Status), which will send the “Screen Fail” automated email notification to the participant.

4.2.3.1 Paper Version of Section 1 Screening Questionnaire

A paper version of the Stage 1 Section 1 Screening Questionnaire is available.

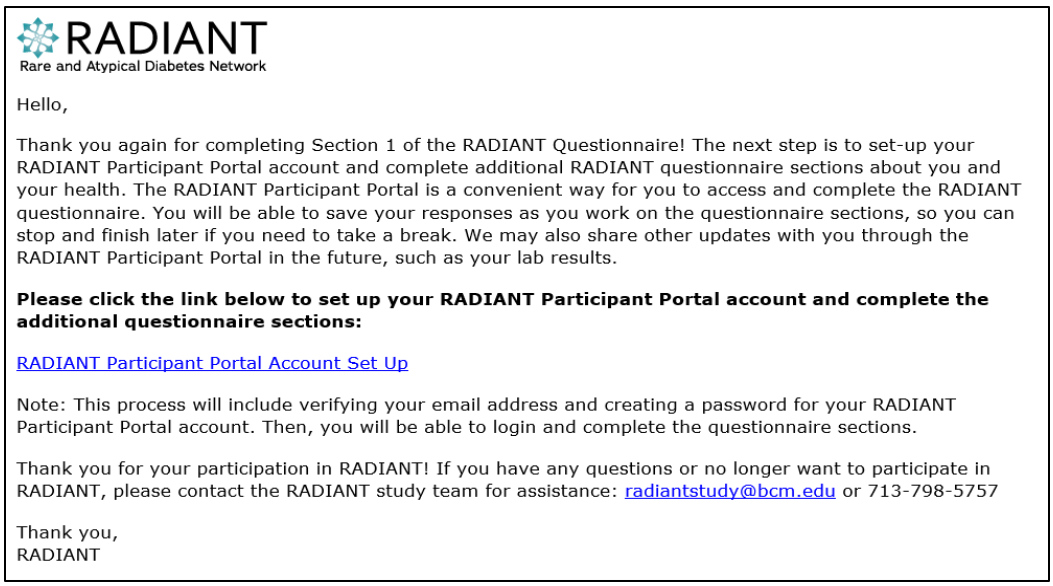
For all participants who consented for Stage 1 on paper, study staff at the assigned site will give the paper version of the Stage 1 Section 1 Screening Questionnaire to the participant for completion (via mail or in-person) or schedule a phone call with the participant to complete it verbally. If it is completed by the participant verbally, the study staff will record the participant responses on the paper Stage 1 Section 1 Questionnaire. After completion, the study staff will enter the participant Section 1 responses into the electronic form via the Participant Profile in the RADIANT Members Website. This will allow the automated screening algorithm to determine if they are a screen pass, screen pause, or screen fail.

Participants who consent for Stage 1 online will be prompted to complete the Stage 1 Section 1 Screening Questionnaire online as well. If the participant is unable to complete the Stage 1 Section 1 Screening Questionnaire online, they may be offered the paper version of Section 1 as an alternative. Site staff would then enter the paper form responses into the electronic form via the Participant Profile in the RADIANT Members Website.

4.2.4 PARTICIPANT PORTAL ACCOUNT SET-UP

Participants who pass the screening questions in Section 1 of the Stage 1 questionnaire will receive a message on the website (if completed online) and/or an automated email asking them to create a RADIANT Participant Portal account (see section 13.2 for screenshot and details). Participants will follow the procedure detailed in section 13.2.1 to set-up their Participant Portal account.

Participants will also receive automated email reminders with a link to set-up their Participant Portal account if they have not yet completed set-up. The email will include contact information for the assigned site. Example:



RADIANT
Rare and Atypical Diabetes Network

Hello,

Thank you again for completing Section 1 of the RADIANT Questionnaire! The next step is to set-up your RADIANT Participant Portal account and complete additional RADIANT questionnaire sections about you and your health. The RADIANT Participant Portal is a convenient way for you to access and complete the RADIANT questionnaire. You will be able to save your responses as you work on the questionnaire sections, so you can stop and finish later if you need to take a break. We may also share other updates with you through the RADIANT Participant Portal in the future, such as your lab results.

Please click the link below to set up your RADIANT Participant Portal account and complete the additional questionnaire sections:

RADIANT Participant Portal Account Set Up

Note: This process will include verifying your email address and creating a password for your RADIANT Participant Portal account. Then, you will be able to login and complete the questionnaire sections.

Thank you for your participation in RADIANT! If you have any questions or no longer want to participate in RADIANT, please contact the RADIANT study team for assistance: radiantstudy@bcm.edu or 713-798-5757

Thank you,
RADIANT

After Participant Portal account set-up, the participant can login to the Participant Portal to complete study tasks (ex. Sections 2-5 of the Stage 1 Questionnaire, view test results, upload medical records, etc.). See section 13.2 for more information on Participant Portal functionality.

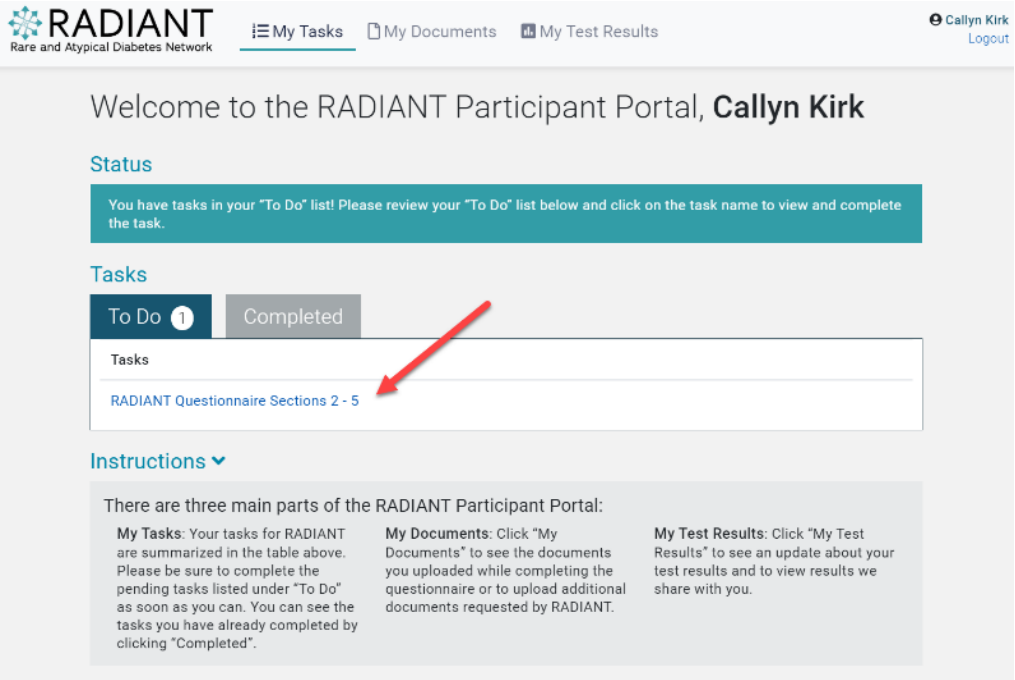
4.2.5 QUESTIONNAIRE SECTIONS 2-5

Sections 2-5 of the Stage 1 questionnaire assess the following information:

- Section 2: Demographics, contact information, healthcare provider information, referral method
- Section 3: Diabetes status, diabetes diagnosis information, DKA history, HbA1c and antibody history, treatment history, blood sugar testing
- Section 4: Birth history, medical history, past testing for monogenic diabetes/lipodystrophy/syndromic diabetes
- Section 5: Family history

All screen pass participants will be asked to complete Sections 2-5 of the Stage 1 Questionnaire. Online completion through the RADIANT Participant Portal is preferred, but a paper version is available, if needed (see paragraph on paper questionnaires at the end of this section).

Completing Questionnaire Sections 2-5 in the Participant Portal:
After setting up their Participant Portal account and logging in (see section 13.2.1), participants will see a homepage as shown in the screenshot below. “RADIANT Questionnaire Sections 2-5” will be listed in the To Do section of the portal homepage. The participant will click on “RADIANT Questionnaire Sections 2-5” to begin those sections. The participant can save and return later as needed.



An automated reminder email to complete Questionnaire Sections 2-5 will be sent to participants 3, 10, and 17 days after they set-up their Participant Portal account, if they have not yet completed the questionnaire sections. The email will include contact information for the assigned site. Example:

RADIANT
Rare and Atypical Diabetes Network

Hello,

Thank you again for participating in RADIANT and creating a RADIANT Participant Portal account! We noticed you have not yet completed all of the RADIANT questionnaire sections. Please remember to login to the RADIANT Participant Portal and complete the remaining RADIANT questionnaire sections:

RADIANT Participant Portal

You will be able to save your responses as you work on the questionnaire sections, so you can stop and finish later if you need to take a break.

We also have a paper version of the RADIANT questionnaire available. If you would prefer to complete the questionnaire on paper instead of online through the RADIANT Participant Portal, we can mail a printed version of the questionnaire to you.

If you have any questions, would like to complete the questionnaire on paper instead, or no longer want to participate in RADIANT, please contact the RADIANT study team for assistance: radiant@uchicago.edu or 773-702-0829

We greatly appreciate your participation in RADIANT!

Thank you,
RADIANT

Upon completion, RADIANT Questionnaire Sections 2-5 will be removed from the To Do section in the Participant Portal and displayed in the Completed section instead. The completed questionnaire will also be available for the RADIANT Administrative Core Project Managers or local site staff* to view via the Participant Profile in the RADIANT Members Website (Section 13.3.6).

*Upon submission of the online consent form, all Stage 1 participants are assigned to either Baylor or Chicago in the RADIANT Members Website. Sites may become more involved by emailing the RADIANT Project Manager team to transfer specific participants to their local site (if site has appropriate Central IRB approval and completed Stage 1 training). This would change the participant's

assigned site in the Members Website. If a local site requests this, they would be responsible for checking the participant's questionnaire for completeness and requesting the Stage 1 antibody kit. If a participant consents for Stage 1 on paper, the participant will be assigned to the site that consented the participant and entered the consent information in the RADIANT Members Website.

Incomplete questionnaires and applying new screening criteria:
If a participant has incomplete questionnaire sections 2-5, study staff at assigned site may review the questionnaire and, if applicable, apply the current screening questionnaire criteria to the participant's record. If a screen fail is appropriate, they may request that the DCC update the participant record to screen fail and manually send a screen fail email notification to the participant.

- For example: A participant may have completed the screening questionnaire prior to the addition of the historical antibody question, and thus screen passed. However, upon further review, a Project Manager may note that the participant wrote in a free text box that they previously had positive antibodies. The Project Manager may then request this participant be marked as screen fail even though their questionnaire sections 2-5 were not yet complete. This will limit the number of participants who are continuing to advance in RADIANT yet don't meet current screening criteria.

Completing Questionnaire Sections 2-5 on Paper:

It is preferred that participants complete the electronic questionnaire. However, if a participant needs to complete a paper version of the questionnaire, this can be done by following the steps below:

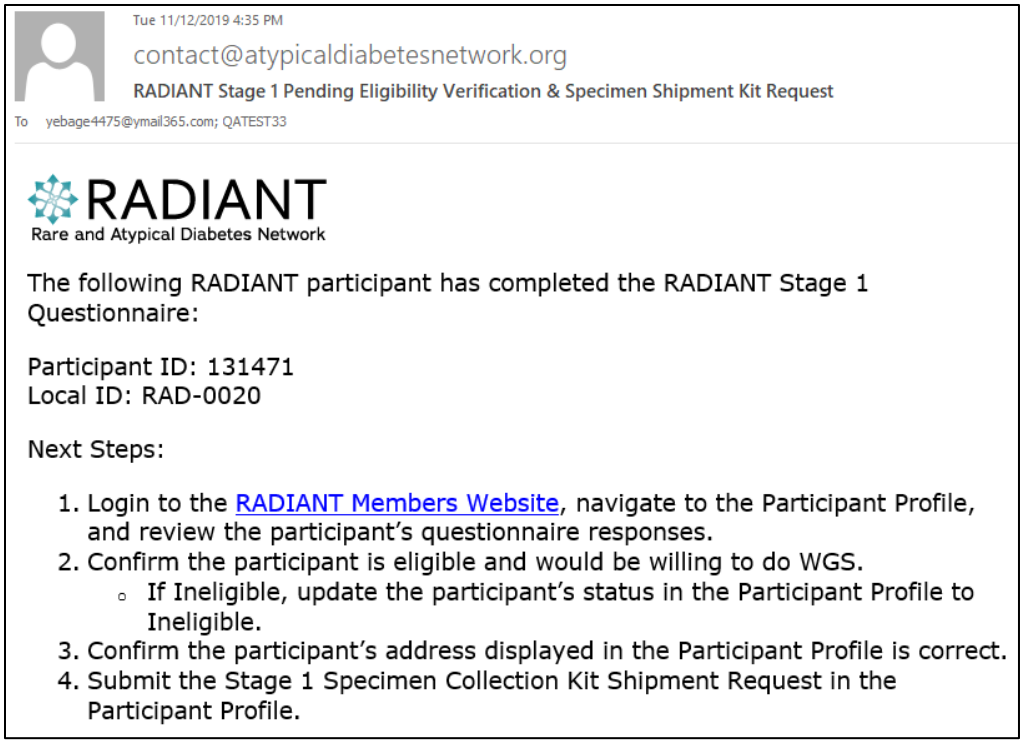
1. The participant will contact the RADIANT Administrative Cores or local site to ask for a paper questionnaire.
2. The RADIANT Administrative Core or local site will mail the paper questionnaire to the participant with a pre-paid return envelope.
3. The participant will complete the paper questionnaire and return it to Baylor/UChicago or the local site (if the participant is assigned to the local site)*.
4. Baylor/UChicago or the local site* will enter the participant's responses into the questionnaire via the Participant Profile (Section 13.3.6).

*Local sites may assist with questionnaire completion online or on paper if they have appropriate Central IRB approval to do so and have completed the required Stage 1 training. Local sites that have requested additional involvement in Stage 1 (requested participant transfer to their site) and/or have consented the participant for Stage 1 on paper may complete data entry for the Stage 1 paper questionnaires – see Section 4.2.1.

4.2.6 REVIEW OF COMPLETED STAGE 1 QUESTIONNAIRES

After the participant completes the Stage 1 Questionnaire, study staff at the participant's assigned site will review the questionnaire responses as follows:

The DCC will send an automated email notification to the study staff at the participant's assigned site after the Stage 1 questionnaire is submitted by a participant:



Tue 11/12/2019 4:35 PM

contact@atypicaldiabetesnetwork.org

RADIANT Stage 1 Pending Eligibility Verification & Specimen Shipment Kit Request

To yebage4475@ymail365.com; QATEST33

RADIANT
Rare and Atypical Diabetes Network

The following RADIANT participant has completed the RADIANT Stage 1 Questionnaire:

Participant ID: 131471
Local ID: RAD-0020

Next Steps:

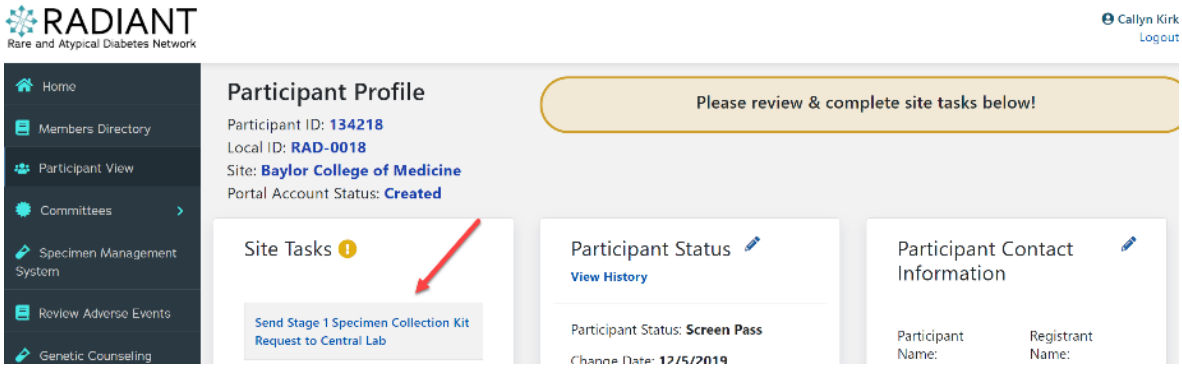
1. Login to the RADIANT Members Website, navigate to the Participant Profile, and review the participant's questionnaire responses.
2. Confirm the participant is eligible and would be willing to do WGS.
    - If Ineligible, update the participant's status in the Participant Profile to Ineligible.
3. Confirm the participant's address displayed in the Participant Profile is correct.
4. Submit the Stage 1 Specimen Collection Kit Shipment Request in the Participant Profile.

Stage 1 Questionnaire is reviewed for completeness

If any responses are missing or contradictory, staff should reach out to the participant to obtain clarification and update the questionnaire accordingly. Site staff must submit the questionnaire at the end of Section 5 to save the newly entered information. Any updates/changes to the questionnaire by the study staff must be appropriately documented – the conversation with the participant must be recorded in the Contact Log and the update/change should be documented in a local Note To File.

Send kit request to Central Lab

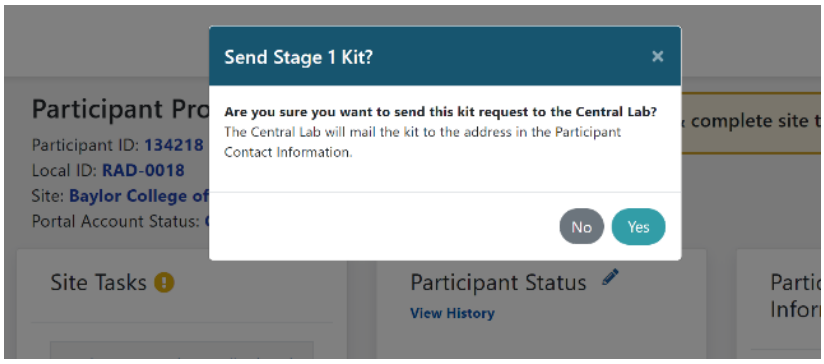
1. Study staff at the participant's assigned site will navigate to the Participant Profile (section 13.3.6) and double check the address of the participant for any typos. Please note that the Central Lab is not able to send kits to PO boxes, so if a PO box is written in for their address, staff must reach out to the participant to request a physical mailing address. This physical mailing address should be used to replace the PO box by selecting the pencil 'edit' icon in the Participant Contact Information tab, and then entering the physical mailing address information in the address section.
2. If the address looks correct, then click the site task "Send Stage 1 Specimen Collection Kit Request to Central Lab".



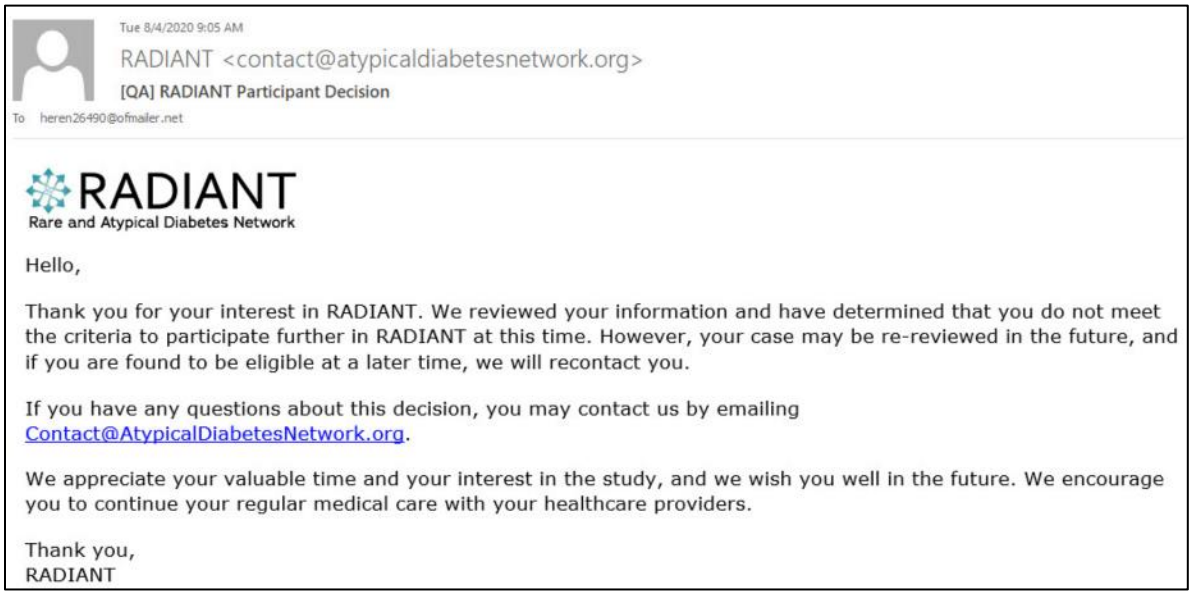
3. Select whether the kit should be a venipuncture kit or capillary collection kit. (This feature will be available once capillary collection kits are implemented for Stage 1.)

- Note: Venipuncture kit is preferrable. Capillary collection kits should only be offered if the participant is not able to complete the venipuncture.

4. A pop-up box will open confirming you want to submit an electronic kit request to the Central Lab. Example below. Click “Yes” to proceed with submitting the request. The Central Lab will then prepare and send the kit to the participant.



5. If the participant is not eligible for any reason, the Project Manager will update the participant status to “Ineligible” in the Participant Profile and will not submit a kit shipment request. Local sites should not mark participants as ineligible – contact the Project Manager team (radiantteam@atypicaldiabetesnetwork.org) if you have questions or believe one of your participants should be updated to “Ineligible”. An example of an acceptable reason for ineligibility at this step would be if the participant is already known to have a confirmed likely pathogenic/pathogenic variant in a known monogenic diabetes gene. Upon updating the participant status to ineligible, the below email will be automatically sent to the participant:


Tue 8/4/2020 9:05 AM
RADIANT <contact@atypicaldiabetesnetwork.org>
[QA] RADIANT Participant Decision
To heren26490@ofmailer.net

RADIANT
Rare and Atypical Diabetes Network

Hello,

Thank you for your interest in RADIANT. We reviewed your information and have determined that you do not meet the criteria to participate further in RADIANT at this time. However, your case may be re-reviewed in the future, and if you are found to be eligible at a later time, we will recontact you.

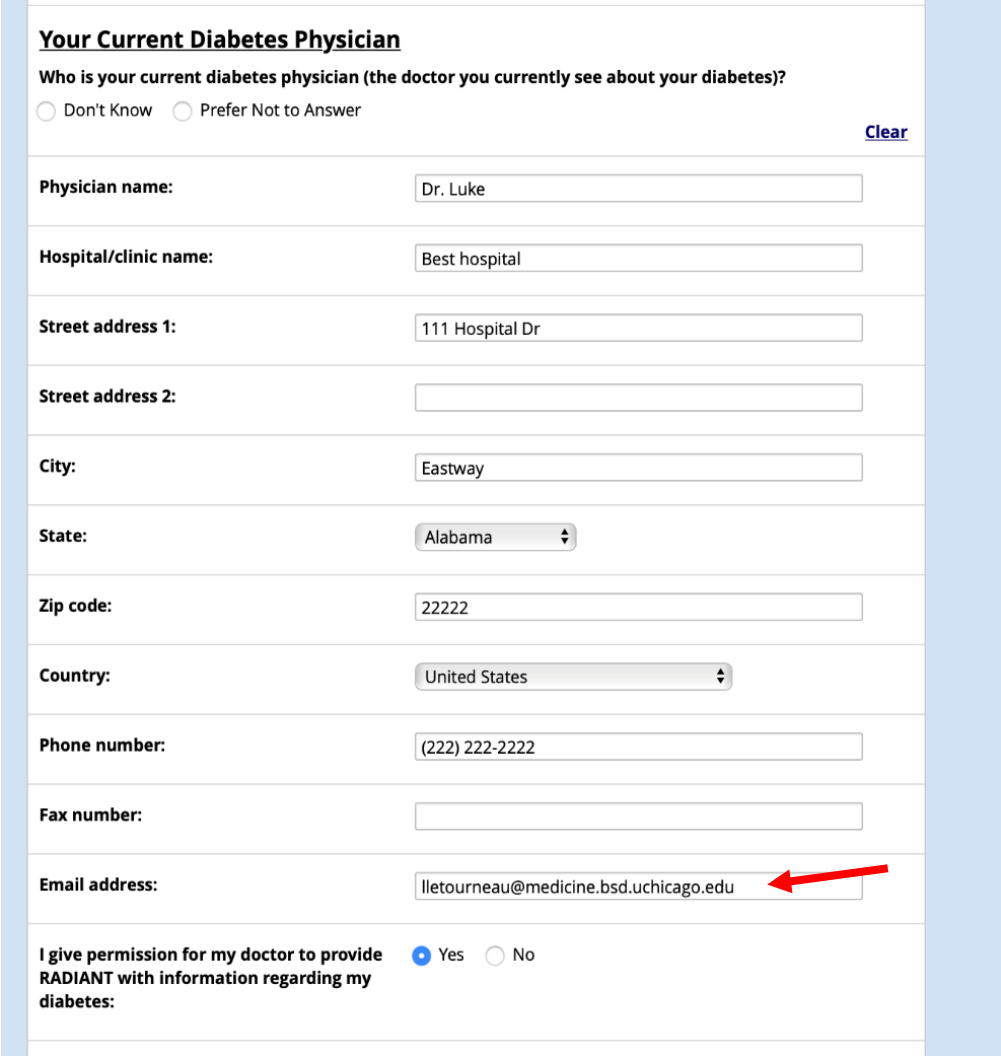
If you have any questions about this decision, you may contact us by emailing Contact@AtypicalDiabetesNetwork.org.

We appreciate your valuable time and your interest in the study, and we wish you well in the future. We encourage you to continue your regular medical care with your healthcare providers.

Thank you,
RADIANT

Project Manager reviews participant decision on treating healthcare provider sharing information and treating healthcare provider email

The Project Manager will check the Section 2 questionnaire to see if the participant allowed their healthcare provider to share information about them, and if they listed an email address for that healthcare provider.



Your Current Diabetes Physician

Who is your current diabetes physician (the doctor you currently see about your diabetes)?

Don't Know Prefer Not to Answer

Clear

Physician name:	Dr. Luke
Hospital/clinic name:	Best hospital
Street address 1:	111 Hospital Dr
Street address 2:	
City:	Eastway
State:	Alabama
Zip code:	22222
Country:	United States
Phone number:	(222) 222-2222
Fax number:	
Email address:	lletourneau@medicine.bsd.uchicago.edu
I give permission for my doctor to provide RADIANT with information regarding my diabetes:	Yes No

- If an email address was listed, and if the participant completed a medical record release form, an automated email will be sent to the healthcare provider requesting the provider to complete a survey about the participant (Section 4.2.9) and no further action is needed (Note: If the email address is added after the initial submission of the questionnaires, an automated email will not be sent. Sites should email the project manager team if an email address is added after initial questionnaire submission.)
- If the participant allowed their healthcare provider to share information, but no email address was entered for the healthcare provider, the Project Manager/Administrative Core staff will:
  a) Fax template treating healthcare provider letter (available on Members Website) to treating healthcare provider's office
  b) If provider emails RADIANT to provide their email address for this survey, Project Manager/Administrative Core staff should email a request to the DCC to send the treating healthcare provider email to this email address. Please include the following information in the request to the DCC: Participant ID, Local ID, treating healthcare provider email address.
  c) Completion of the treating healthcare provider survey is not required prior to adjudication reviewer assignment

Project Manager reviews medical record release form

If the participant completed a medical record release form, then the standardized medical record request process will proceed by Baylor/Chicago (Section 4.2.10). If they did not complete a medical record release form, no further action is required.

4.2.7 SAMPLE COLLECTION FOR AUTOANTIBODIES#

Sample collection for autoantibodies in Stage 1 can be done via venipuncture or capillary collection (starting in Spring/Summer 2023)*. Venipuncture is preferred. Capillary collection may be offered when venipuncture is not feasible (e.g. if participant does not live near a Quest or RADIANT study site to complete the blood draw, or if participant is unable to go to a Quest during regular hours due to work or transportation barriers). More information on each method can be found in the sections that follow.

- All RADIANT participants must have Stage 1 sample collection for autoantibodies. Historical autoantibody results may not be used in place of RADIANT testing.

The DCC will send an announcement when capillary collection is available. Please email radiantteam@atypicaldiabetesnetwork.org to confirm capillary collection is available before offering it to any participants.

4.2.7.1 Selecting Type of Stage 1 Sample Collection Kit for Shipment

The site will select the type of Stage 1 sample collection kit while they are completing the kit request task. Please see Section 4.2.6, "*Send kit request to Central Lab",* for more information. The Central Lab will prepare and ship the type of kit that is requested.

4.2.7.2 Stage 1 Sample Collection by Venipuncture

A venipuncture sample collection kit, including a Stage 1 instruction letter (can be found on Members Website), will be mailed by the RADIANT Central Lab to the participant's home.

The venipuncture sample may be drawn at Quest Diagnostics, another lab, or a local clinical site. **However**, it is preferable for participants to go to Quest as all costs associated with the sample collection at Quest will be paid for by RADIANT. If the sample is drawn at another lab or a local RADIANT clinical site, RADIANT will not be able to reimburse for any costs associated with the sample collection (phlebotomy costs).

If a participant must come to a local clinical site for their Stage 1 draw, study coordinators must go over the following illness instructions with the participant prior to the visit:

a) If you feel sick during the 7 days prior to your Stage 1 sample collection, please call me to reschedule this visit. Feeling sick includes cold, flu, fever, vomiting, diarrhea, or any physical stress. This also includes chills, cough, shortness of breath, difficulty breathing, fatigue, muscle or body aches, headache, recent loss of taste or smell, sore throat, congestion, or nausea.

Sites must also follow any local institutional guidelines for screening participants for COVID-19 symptoms prior to an in-person visit. Sites should also follow any other local COVID-19 procedures such as mandatory masking, temperature checks, etc.

It will take the Central Lab approximately 2 days for a kit to be prepared, sent, and received by the participant. Local study coordinators need to give at least 7 days between requesting kit and having a visit for Stage 1 sample collection.

Full instructions for participants on how to schedule at Quest will be included in their Stage 1 and Stage 2 (if remote visit) collection kit. Stage 1 and Stage 2 Quest scheduling tips include:

- Participant should not throw away any part of the box/kit that they receive, including the outer cardboard box and styrofoam box that the kit comes in. Quest will need all of these materials to ship the samples back to the Central Lab.
- Appointments at Quest can be scheduled over the phone (866-697-8378) or online (www.questdiagnostics.com) – see below for online appointment scheduling steps
- Stage 1 and Stage 2 Quest appointments must be scheduled for Monday, Tuesday, Wednesday, or Thursday. Quest Diagnostics sites have different cut-off times for FedEx pick-ups. Therefore, we recommend participants schedule an appointment *as early in the day as possible*, and before 12:00pm local time.
- Appointments must be made at a "Quest Diagnostics" site, not a contract or affiliate site, such as FastMed or Walmart Pharmacy.
- Information on COVID-19 precautions currently in place at Quest: https://www.questdiagnostics.com/home/Covid-19/Patients/PeaceOfMind/
- Online appointment scheduling steps:
    - Go to https://www.questdiagnostics.com/home/. Click on 'Make an Appointment' at the top right of the screen. On the next page, select the 'Schedule an appointment' green button.
    - For 'Who is sending you for testing?' - Choose MEDICAL PROFESSIONAL.
    - For 'What testing do you need?' - Choose ALL OTHER TESTS.
    - Do not provide medical insurance information. RADIANT pays for this test.
    - Choose an appointment time on a Mon/Tues/Wed/Thurs that is **as early as possible (and no later than 12:00pm local time)** at a 'Quest Diagnostics' site (not a contract or affiliate site, such as FastMed or Walmart Pharmacy). **We recommend the earliest available appointment time.**
- Preparing for visit
    - Participants do not need to fast for either the Stage 1 or Stage 2 Quest visit
    - Cool pack that was in the box must be frozen and taken frozen to Quest
    - Participant should remove any used shipping labels from the outer box before they take the box to Quest
    - Participants should bring the box (both outer cardboard and inner Styrofoam) and collection kit, frozen pack, and Quest instructions envelope to the visit

The participant will bring their kit to a local Quest Diagnostics lab (or another lab or local RADIANT clinical site, if needed) for a blood draw for diabetes autoantibodies.

Samples will be shipped to the Central Lab. All participants will be tested for GAD65. If GAD65 is negative, participants will be tested for IA2 and ZnT8.

Additional details on the collection, processing, and shipment of venipuncture samples in Stage 1 can be found in Appendix 3 (Stage 1 Specimen Collection & Processing MOP).

Quest Diagnostics has also been provided with specimen collection instructions.

4.2.7.3 Stage 1 Sample Collection by Capillary Kit

If a participant is unable to complete the Stage 1 sample collection via venipuncture, the participant may be invited to complete the sample collection via capillary collection*. If the participant is willing to complete the sample collection via capillary collection, the study staff will submit a request in the RADIANT Members Website Participant Profile to send a capillary collection kit to the participant.

PLEASE NOTE: Capillary collection can be challenging and, if an appropriate volume is not collected, all the Stage 1 antibodies may not be able to be tested. Given this, participants should be informed on the capillary collection process (such as sharing the instructional materials or video) prior to sending

them a capillary collection kit. Capillary collection is not recommended for very young children. Please email radiantteam@atypicaldiabetesnetwork.org if you have questions on this process.

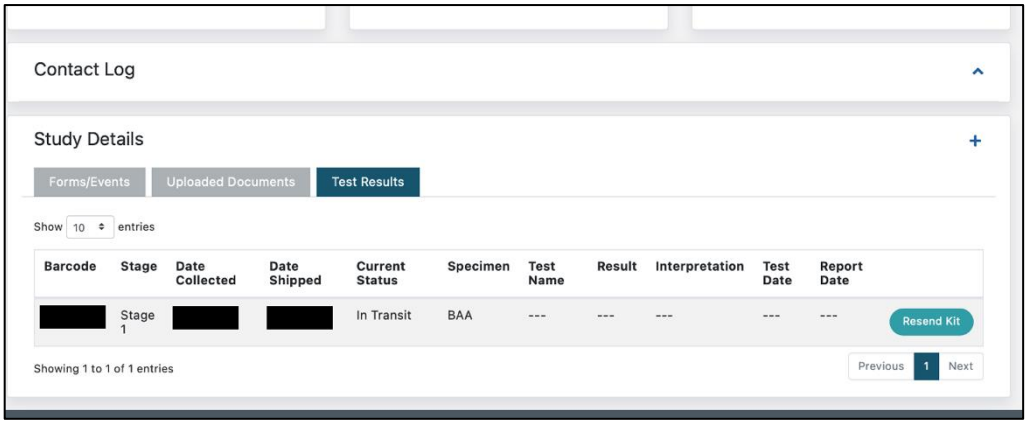
*The DCC will send an announcement when capillary collection is available. Please email radiantteam@atypicaldiabetesnetwork.org to confirm capillary collection is available before offering it to any participants.

Additional details on the collection, processing, and shipment of capillary samples in Stage 1 can be found in Appendix 3 (Stage 1 Specimen Collection & Processing MOP).

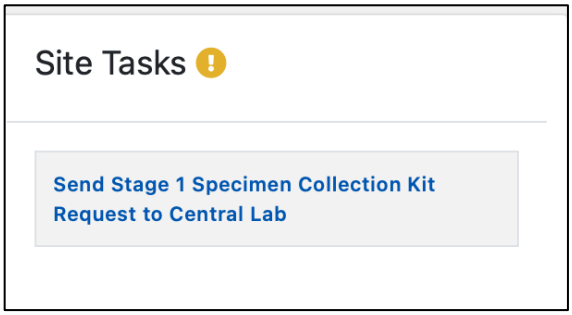
4.2.7.4 Requesting Replacement Stage 1 Sample Collection Kit

If a participant requires a replacement venipuncture or capillary kit, or if a participant would prefer a different type of kit, following the steps below:

1. Navigate to the participant's Profile in the RADIANT Members Website. Under 'Study Details', select the 'Test Results' tab.



2. Select the 'Resend Kit' button at the far right of the Stage 1 row. You may need to scroll to the right on your screen to see this button.
3. Once the page refreshes, go back to Site Tasks and select Send Stage 1 kit request. From here, you can select whether a venipuncture kit or capillary kit should be sent.



4.2.8 RETURN OF AUTOANTIBODY RESULTS

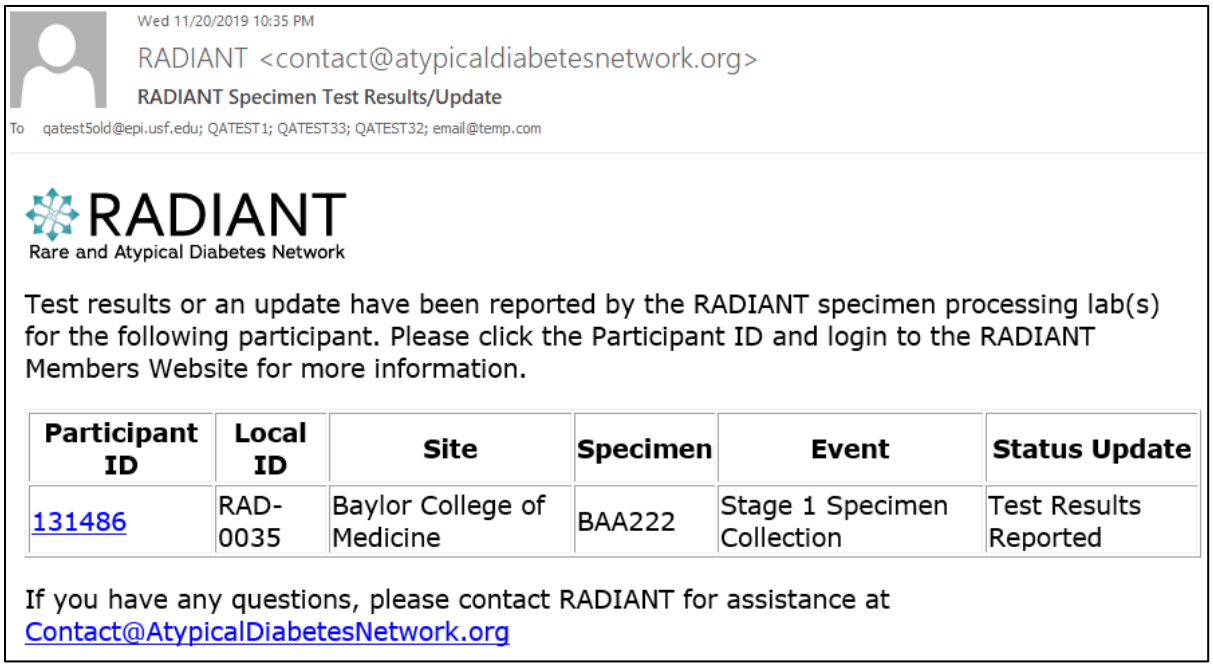
Results from the RADIANT Central Lab will be returned to the DCC. Results are typically returned 7-10 business days after sample receipt.

NEGATIVE REPORTING CUTOFFS FOR STAGE 1 AUTOANTIBODY RESULTS FROM UF CENTRAL LAB:

GADA <5
IA-2A <7.5
ZnT8A <15

Results may be viewed by the RADIANT Study Team on the Participant Profile in the RADIANT Members Website (Section 13.3.6). An automated email will be sent to the Study Team when test results are reported by the lab and available to view in the RADIANT Members Website.

Test Results Email Notification to Study Team:



Wed 11/20/2019 10:35 PM

RADIANT <contact@atypicaldiabetesnetwork.org>

RADIANT Specimen Test Results/Update

To qatest5old@epi.usf.edu; QATEST1; QATEST33; QATEST32; email@temp.com

RADIANT
Rare and Atypical Diabetes Network

Test results or an update have been reported by the RADIANT specimen processing lab(s) for the following participant. Please click the Participant ID and login to the RADIANT Members Website for more information.

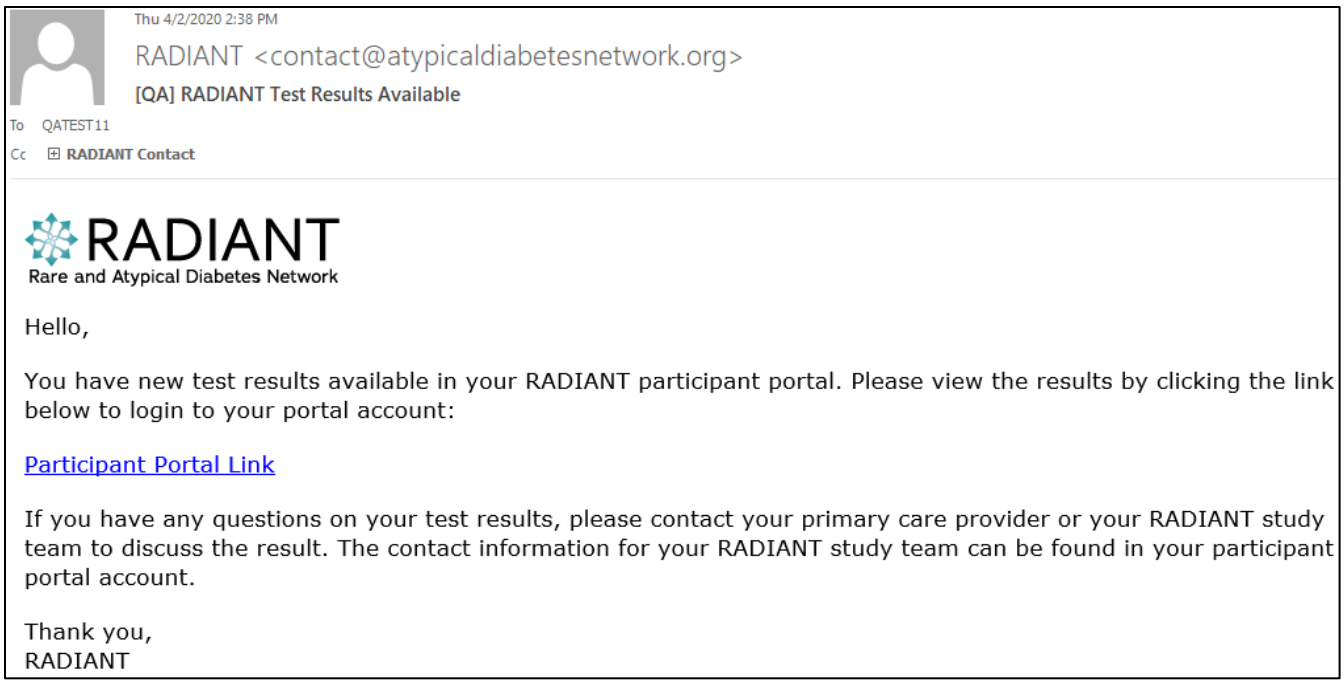
Participant ID	Local ID	Site	Specimen	Event	Status Update
131486	RAD-0035	Baylor College of Medicine	BAA222	Stage 1 Specimen Collection	Test Results Reported

If you have any questions, please contact RADIANT for assistance at Contact@AtypicalDiabetesNetwork.org

All lab results to participants are delayed by 24 hours. After 24 hours, participants will be notified via email (see below) that their results are ready and they may view them in their Participant Portal account (if they chose to receive results in their Stage 1 consent form). Results will be reported with a reference range and interpretation.

Study staff are **not** required to follow up with participants about autoantibody results because there are no 'critical values' for this part of RADIANT. If participants have questions, they will be directed to the general RADIANT contact email (contact@atypicaldiabetesnetwork.org or radiantteam@atypicaldiabetesnetwork.org).

Test Results Automated Email Notification to Participants:



Thu 4/2/2020 2:38 PM

RADIANT <contact@atypicaldiabetesnetwork.org>

[QA] RADIANT Test Results Available

To QATEST11

Cc RADIANT Contact

RADIANT
Rare and Atypical Diabetes Network

Hello,

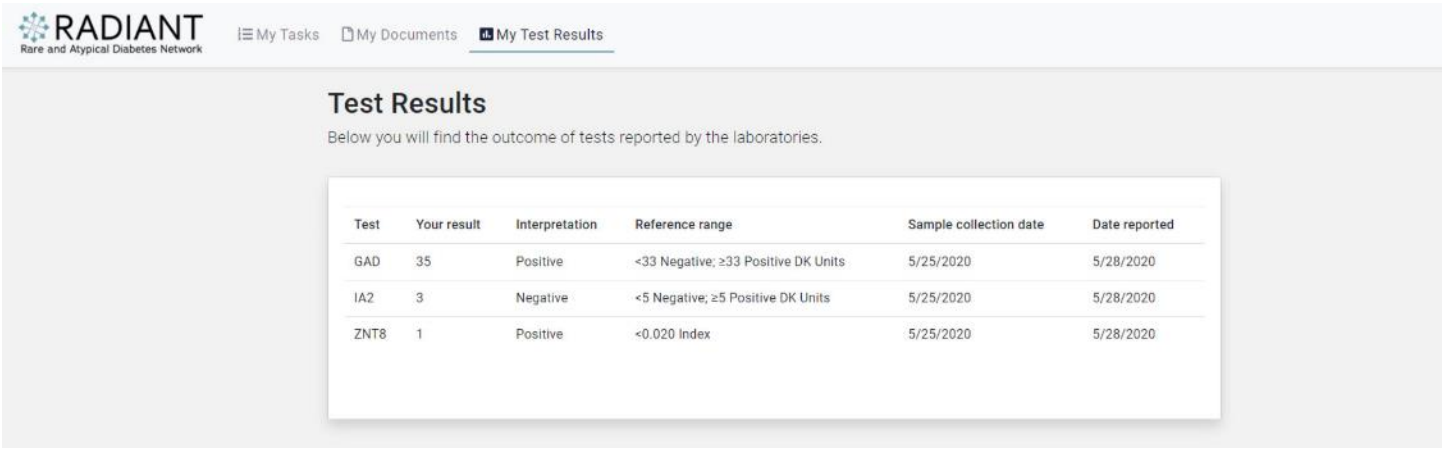
You have new test results available in your RADIANT participant portal. Please view the results by clicking the link below to login to your portal account:

Participant Portal Link

If you have any questions on your test results, please contact your primary care provider or your RADIANT study team to discuss the result. The contact information for your RADIANT study team can be found in your participant portal account.

Thank you,
RADIANT

Example of autoantibody test results displayed in the Participant Portal:

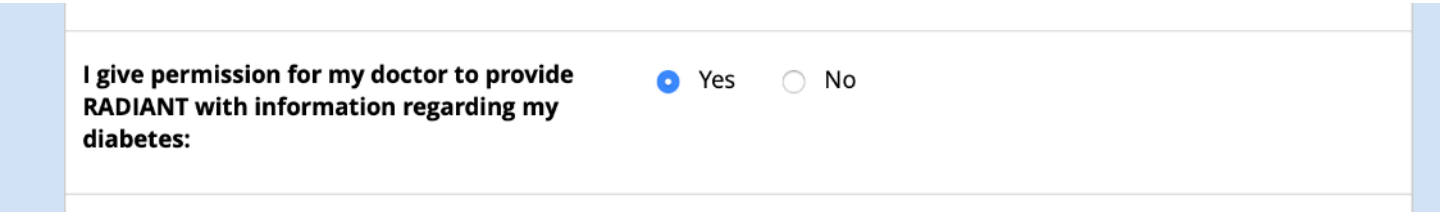


Project Managers will review participant consent and coordinate results to provider

1. The Project Manager will review the participant's Stage 1 consent form to determine whether the participant consented for results to be shared with their healthcare provider.
2. If they did, the Project Manager/Administrative Core staff will send a copy of the test result to the healthcare provider that is listed:
    a) Fax template healthcare provider results sharing letter (available on Members Website) to healthcare provider's office
    b) Project Manager/Administrative Core staff will document this action in the Contact Log

4.2.9 TREATING HEALTHCARE PROVIDER EMAIL AND QUESTIONNAIRE

In Section 2 of the questionnaire, the participant is asked for information about the healthcare provider who is currently taking care of their diabetes. They are also asked if they give this healthcare provider permission to provide RADIANT with information regarding their diabetes:



If they say yes, enter their healthcare provider's email address, and complete their medical record release form (Section 4.2.10), an email will automatically be sent to that healthcare provider to ask for additional information about this participant:

Email sent to treating healthcare provider

[UAT] RADIANT Study Request for Patient Diabetes Records

RADIANT <contact@atypicaldiabetesnetwork.org> Today at 8:54 AM
To: lletourneau@uchicago.edu

Completed on Wednesday, August 12, 2020.

RADIANT
Rare and Atypical Diabetes Network

Hello,

Your patient has given permission for us to contact you regarding their participation in a research study. The Rare and Atypical Diabetes Network (RADIANT) aims to identify and study individuals and families with rare and uncharacterized forms of diabetes. This study is funded through the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

To aid the research team in determining whether your patient has an uncharacterized form of diabetes we would like for you, as their treating physician, to provide some additional information regarding their diabetes history. Providing this information should only take 5 minutes to complete.

Next Steps:

1. Please click this link to take you to a secure page to provide information to RADIANT: Treating Physician Questionnaire
2. Please enter the patient's local code which is provided below. Please enter the patient's date of birth to confirm you are this patient's treating physician.
3. To verify the patient's medical release form please select "Download Medical Release Form".
4. Once you have verified the completed release form please select "Proceed to Study Questionnaire".
5. Please summarize why you think this patient has an unknown form of diabetes. There will also be a space to upload any test results or medical records that you think will aid the research team in determining whether this participant is eligible for this study. Once you have uploaded any documents please click "Submit".
6. If you need to upload any additional documents after submitting the form, you can access the link above and select "Upload Additional Documents" at any time.

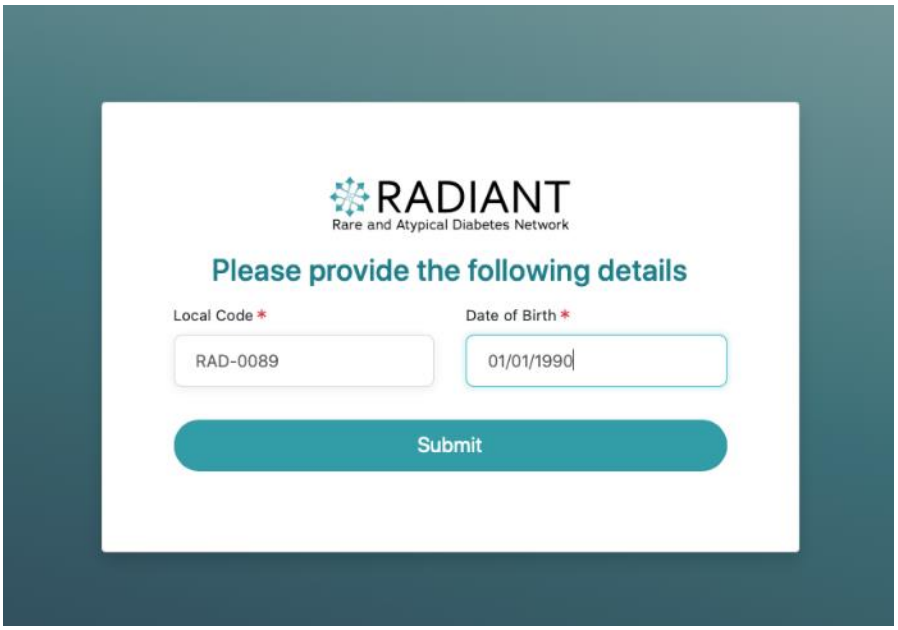
Local Code: RAD-0089
Participant Name: TestLF TestLF

For additional information regarding the RADIANT study please visit https://www-uat.atypicaldiabetesnetwork.org/

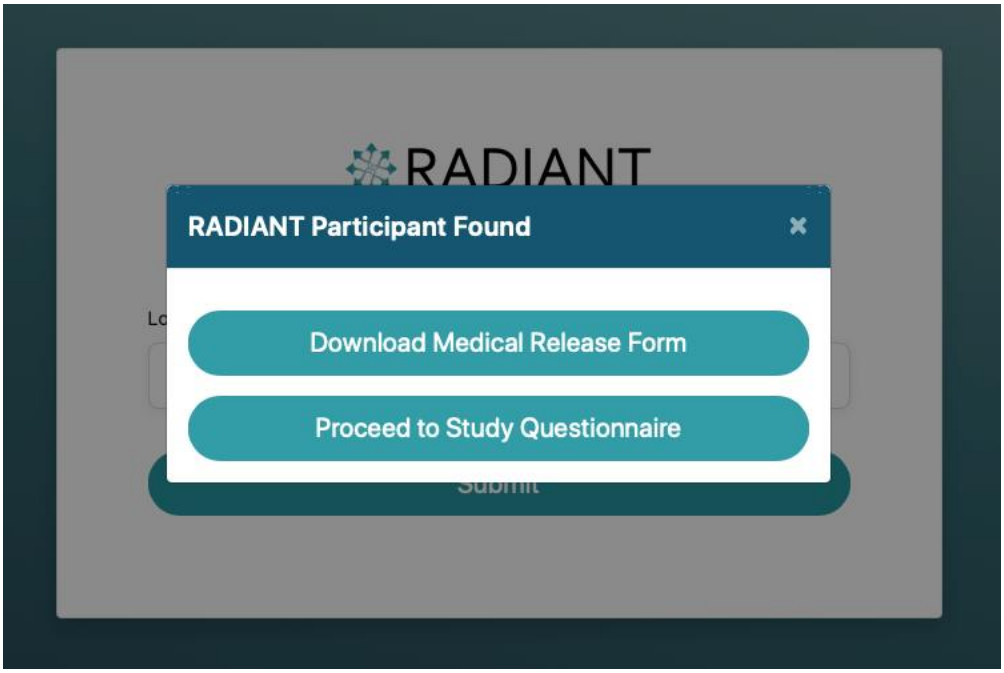
Thank you for providing the RADIANT team with additional information. If you have any additional questions please contact Contact@AtypicalDiabetesNetwork.org.

Thank you,
RADIANT

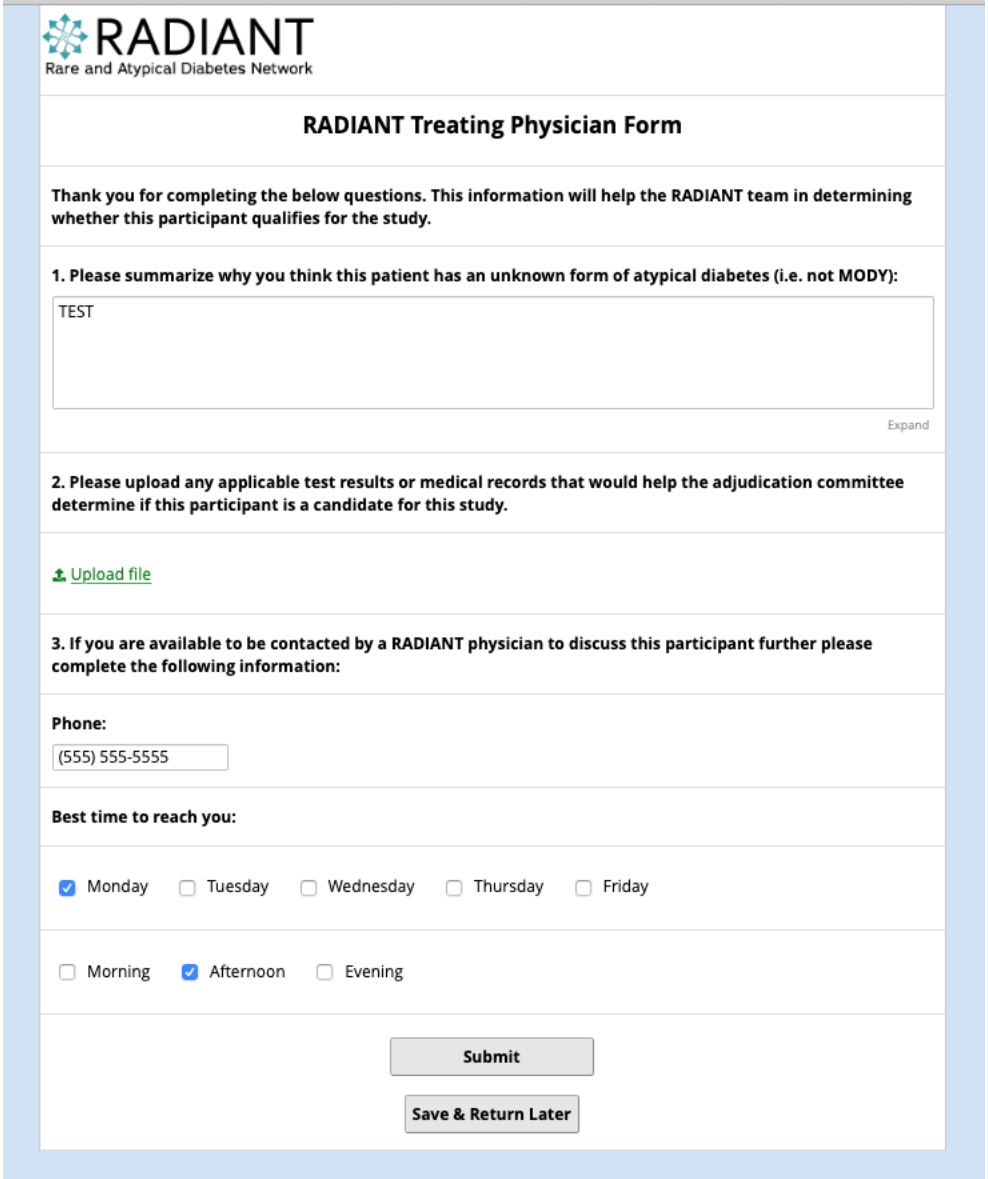
After the healthcare provider clicks on 'Treating Physician Questionnaire' in the email above, they will be asked to verify the participant's identity by entering their Local Code (found in email) and date of birth.



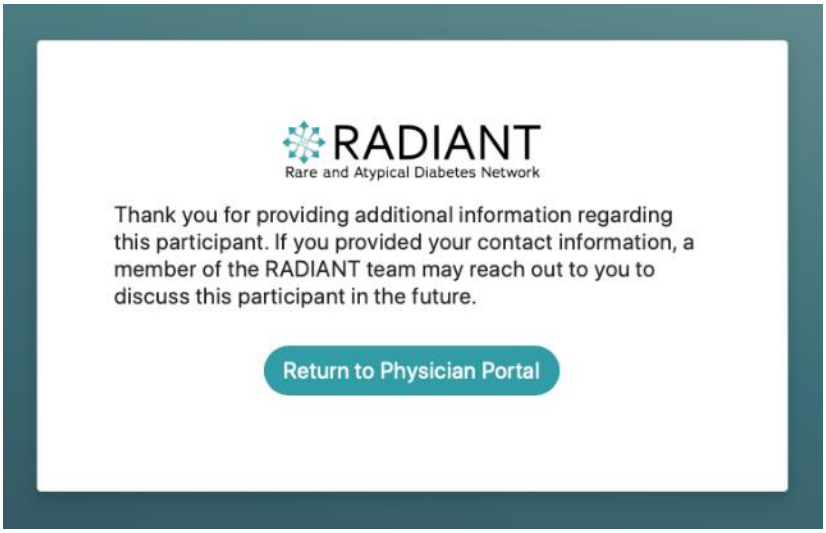
The healthcare provider may view the full medical record release form if needed, and they can proceed to the study questionnaire.



Treating healthcare provider questionnaire:
(If they would like to be contacted by RADIANT, Administrative Core Project Managers will connect with an Adjudication Committee member to organize this call.)



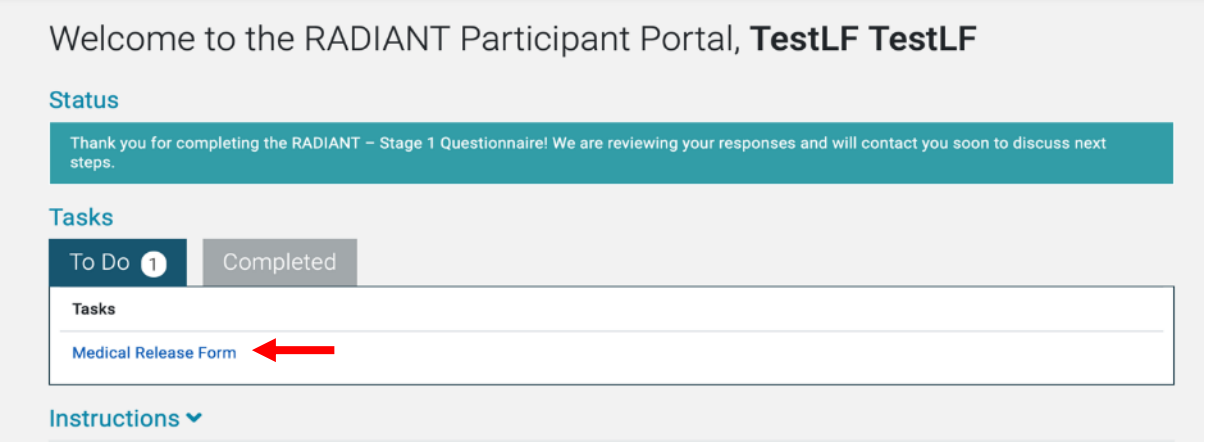
After they click 'Submit' on the questionnaire, they will be shown a thank you message:

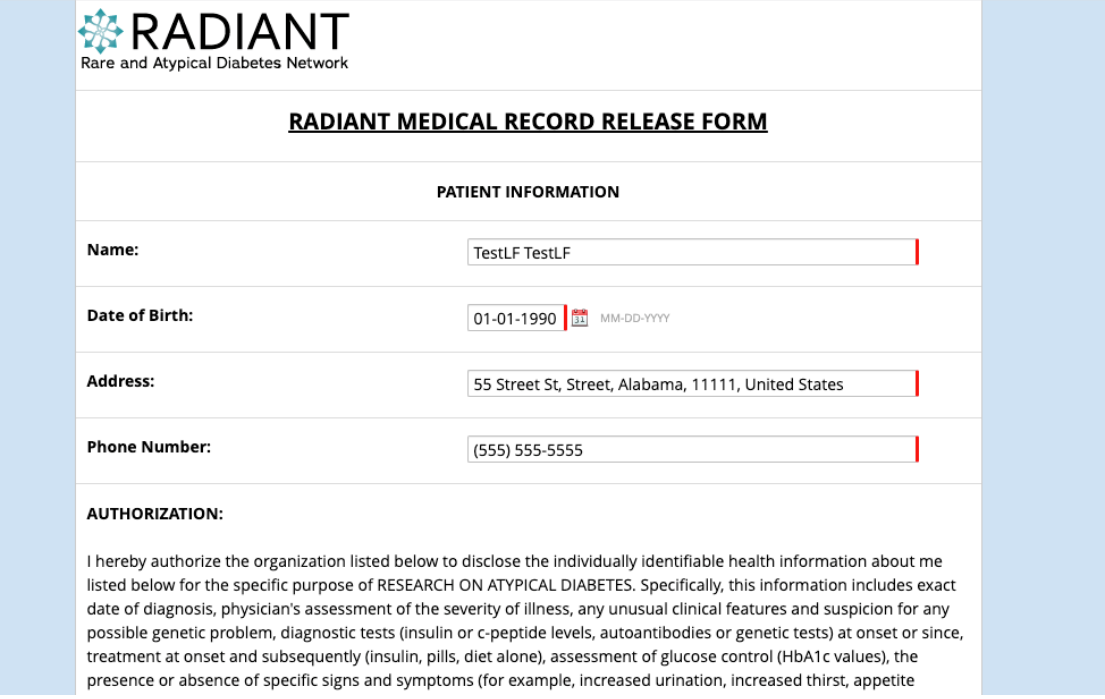


If a provider email address is not listed, the Administrative Core staff will request this via template letter fax as noted in Section 4.2.6. Completion of the treating healthcare provider survey is not required prior to adjudication reviewer assignment.

4.2.10 MEDICAL RECORD RELEASE FORM & STANDARDIZED MEDICAL RECORD REQUESTS

Participants will be asked in the Stage 1 Questionnaire (Section 2) if they give permission for their healthcare provider to provide RADIANT with information about their diabetes. If they respond “Yes”, they will be asked to complete an online medical record release form in the Participant Portal. The release form will appear in the participant To Do list on their Participant Portal homepage after they complete questionnaire sections 2-5:




RADIANT
Rare and Atypical Diabetes Network

RADIANT MEDICAL RECORD RELEASE FORM

PATIENT INFORMATION

Name:	TestLF TestLF
Date of Birth:	01-01-1990 MM-DD-YYYY
Address:	55 Street St, Street, Alabama, 11111, United States
Phone Number:	(555) 555-5555

AUTHORIZATION:

I hereby authorize the organization listed below to disclose the individually identifiable health information about me listed below for the specific purpose of RESEARCH ON ATYPICAL DIABETES. Specifically, this information includes exact date of diagnosis, physician's assessment of the severity of illness, any unusual clinical features and suspicion for any possible genetic problem, diagnostic tests (insulin or c-peptide levels, autoantibodies or genetic tests) at onset or since, treatment at onset and subsequently (insulin, pills, diet alone), assessment of glucose control (HbA1c values), the presence or absence of specific signs and symptoms (for example, increased urination, increased thirst, appetite

Participants who complete a medical record release form will undergo a standardized medical record request process which is separate from the information that may be provided by their treating healthcare provider (Section 4.2.9). These requests will be processed by staff at the Administrative Cores.

The following medical records will be requested:

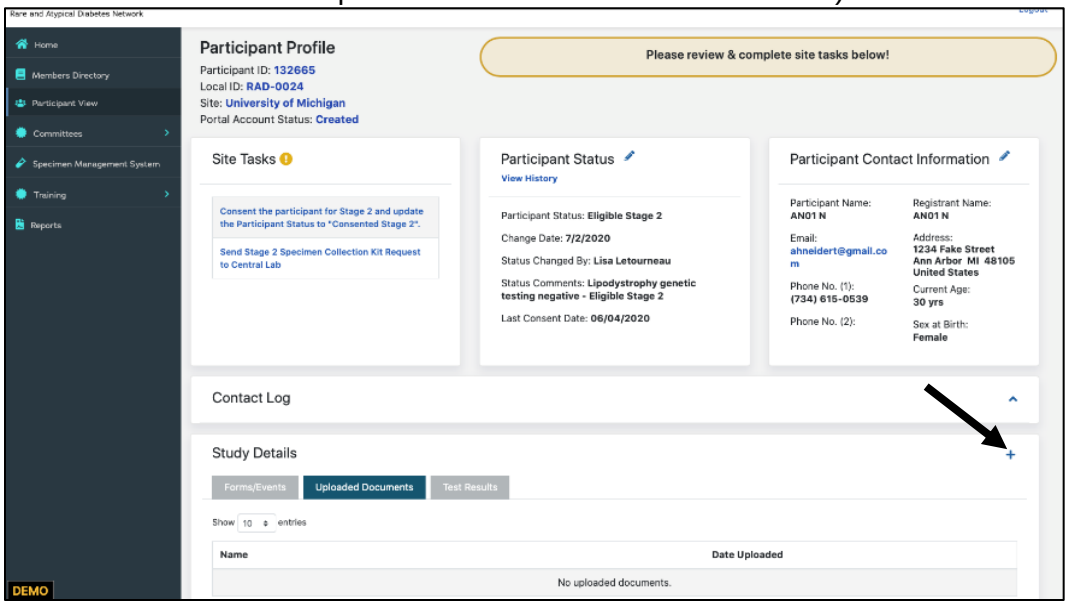
1. Diabetes diagnosis record (hospitalization record, if applicable, with diagnosis labs)
2. Last 3 clinic notes from endo/DM provider (with labs)

3. The following blood tests from any time: diabetes autoantibodies (ex: glutamic acid decarboxylase antibody (GAD65), islet antigen 2 antibody (IA-2), islet cell antibody, insulin antibody, zinc transporter 8 antibody (ZnT8)), celiac antibodies (ex: tissue transglutaminase antibody (tTG), endomysial antibody (EMA), deamidated gliadin peptide antibody (DGP)), thyroid antibodies (ex: thyroid peroxidase antibody (TPO), thyroglobulin antibody (TGAb), thyrotropin receptor blocking antibody (TSHRAb), thyroid-stimulating immunoglobulin (TSI), thyrotropin-binding inhibitory immunoglobulin (TBII), and/or anti-nuclear antibody)
4. Any genetic testing previously performed related to diabetes (monogenic diabetes, lipodystrophy, syndromic diabetes, mitochondrial diabetes)

Administrative Core staff will be responsible for requesting these records. They will request the records by:

1. Completing the medical record request template letter (found on Members Website) and faxing this, along with the completed medical record release form, to the hospital/clinic indicated on the medical record release form.
    - This request should be sent directly to the Medical Records Department, not to the treating healthcare provider.
2. The original request, as well as each follow-up to the Medical Records Department, should be documented in the Contact Log. Standardized medical records do not need to be requested a certain number of times or received prior to assigning cases to adjudication reviewers.
3. Administrative Core staff will follow up on requests up to 3 times. This limit is put in place so study processes are not slowed down by waiting for medical records.

Once records are received, they will be uploaded via the Participant Profile (see screenshots below and section 13.3.6 – How to Upload Documents for additional details):



This medical record release form may also be used later in Stage 1-3 if the Adjudication Committee and/or Discovery Team requests additional records for a participant.

Staff must follow all local guidelines on appropriate storage of Protected Health Information, such as deleting medical records from their devices once they are uploaded to the Participant Profile.

4.2.11 DIABETES AUTOANTIBODY POSITIVE CASES

Once participants have completed all of the questionnaire sections and their diabetes autoantibody results have been returned by the Central Lab, Project Managers will briefly review any case who is found to be antibody positive.

The purpose of this review is to screen out participants who are very likely to have typical type 1 diabetes and thus are not eligible for RADIANT.

The following general guidelines will be employed:

- If multiple diabetes autoantibodies are positive (RADIANT Ab or previously done Ab), participant status will be changed to 'ineligible' (section 13.3.6 – How to Edit Participant Status)
    - Project Managers will document rationale for marking participant as ineligible in the status change comment box.
- If GAD65 is positive and participant does not have any additional interesting features, participant status will be changed to 'ineligible' (section 13.3.6 – How to Edit Participant Status)
    - Project Managers will document rationale for marking participant as ineligible in the status change comment box.
- If participant is GAD65 positive but has interesting features (such as a linear family history), they should proceed to Adjudication review

This process will be re-evaluated at regular intervals and procedural changes may be employed if needed.

4.2.12 ADJUDICATION COMMITTEE REVIEW

After the questionnaire is completed and the antibody results are received, the RADIANT Administrative Core Project Managers will assign the case for Adjudication Review.

Three groups of adjudicators will serve in parallel (Group A, B, and C). Each group will meet once per month via conference call. Each group will review approximately 8-12 cases per call.

The Stage 1 data will be assembled electronically at the Data Coordinating Center and shared with the Adjudication Committee via the Adjudication Committee Dashboard in the RADIANT Members Website (see section 4.2.12). The Adjudication Committee will review the participant's Stage 1 data and select candidates to progress to Stage 2 of the study for whole genome sequencing (WGS).

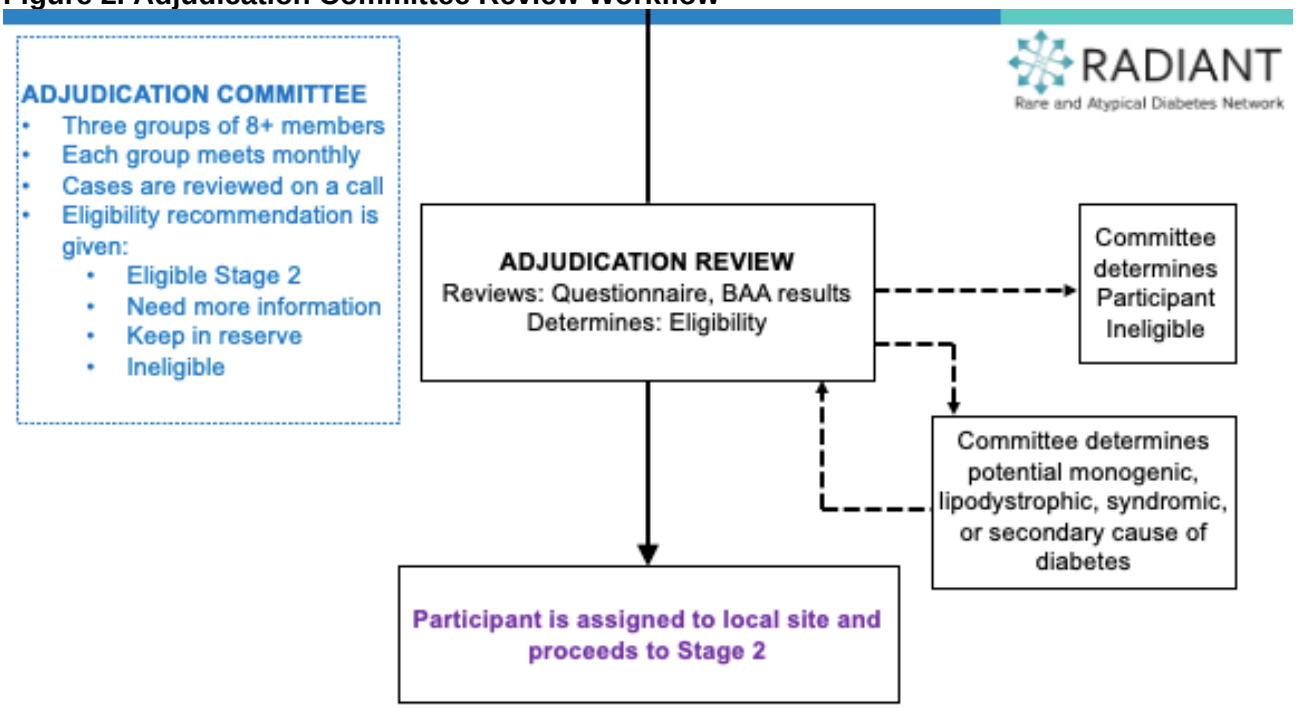
To assist with their review, the Adjudication Committee may also request additional information from the participant's referring Clinical Center, atypical diabetes/syndromic diabetes registry, or diabetes cohort/database for additional information. Participants will be asked to complete a medical record release form in Stage 1 that can be utilized to acquire additional information, if needed (see section 4.2.10).

Cases with incomplete questionnaires or other pre-adjudication data

RADIANT Administrative Core Project Managers will review cases that are missing questionnaire data, antibody data, or other pre-adjudication data on a monthly basis. If the case appears to be interesting with the information provided, they will ask the Steering Committee member who chairs the group scheduled to receive this case to give a preliminary impression of the case. If the Steering Committee member agrees it is ready for adjudication, even with the missing data, it may be passed along for adjudication review.

The Adjudication Committee structure will be re-evaluated annually to determine if additional members are needed, if call frequency schedules should change, or if other adjustments need to be made.

Figure 2. Adjudication Committee Review Workflow



4.2.12.1 Role of the Adjudicator

Each case will be assigned to two reviewers within the same adjudication group. When reviewers are assigned, a call date for reviewing the case will also be assigned. The reviewers will receive an automated email when they are assigned a case for review.

Prior to the Adjudication call: Prior to the call, the reviewer is responsible for reviewing the case and completing the adjudication form via the Adjudication Committee Dashboard in the RADIANT Members Website. If the case review is not completed in the Members Website 48 hours prior to the call, an automated reminder email will be sent to the reviewer. The final step on the reviewer's form is to provide a recommendation for the case – Eligible Stage 2, Keep In Reserve, Need More Information or Ineligible. Each reviewer must submit their final recommendation before they can see the recommendation of the other person reviewing the case. Once submitted, adjudicators cannot edit their review until the 2nd reviewer submits their review. This will help to reduce bias.

- Please see Section 4.2.12.3 for step-by-step instructions on how to use the adjudication reviewer dashboard

During the call:

1. Project manager will display the participant information on the screen (Members Website – auto-generated report + participant record).
2. Primary reviewer will give a brief summary of case (<2-minute summary). Secondary reviewer will have a chance to add any pertinent information. Primary reviewer will describe their final recommendation and reasoning. Secondary reviewer will do the same.
3. The discussion will open to the full group for comments.
4. Discuss to majority agreement.

5. Project manager will record final decision and any pertinent notes on screen (Members Website).
6. Move on to next case.

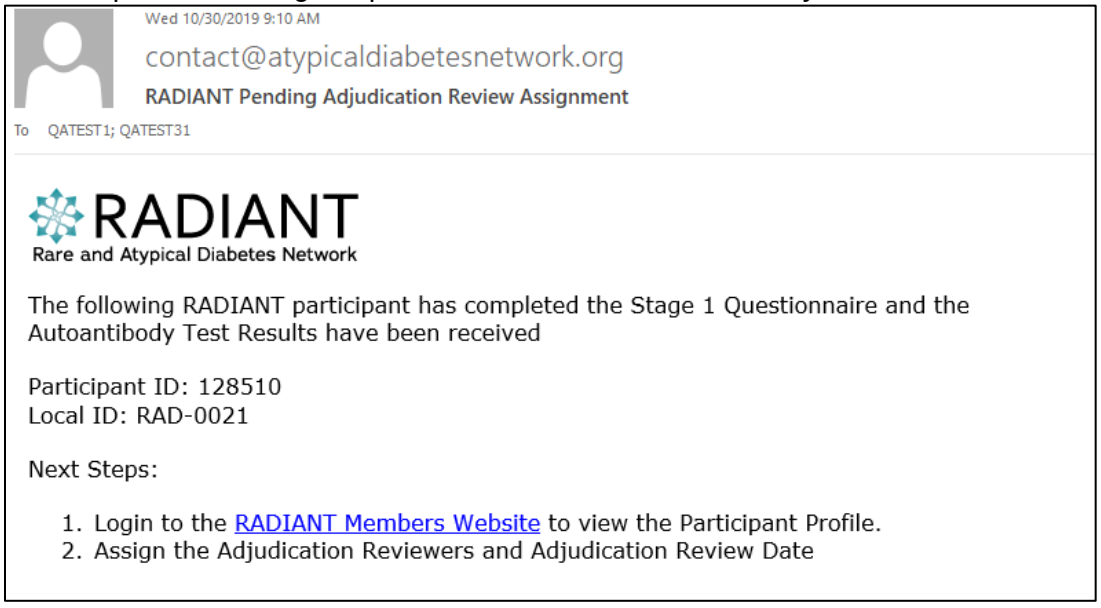
- Group discussion, even if minimal, will occur for all cases.
- If both adjudicators chose the same final recommendation, but others on the call disagree, the group should re-discuss until a majority agreement is reached.

Reviewers are expected to make every effort to attend their assigned calls. If reviewers are unable to attend calls, the following guidelines will be followed:

- If the Project Manager is aware of the absence prior to case assignment (typically 7 days prior to call), no cases will be assigned to the reviewer who will be absent.
- If the reviewer notifies Project Manager of their absence after a case has been assigned, but before they have completed the review, the Project Manager may attempt to assign the case to someone else in the group if there is sufficient time ahead of the call. If reassignment is not possible, case may be pushed to following month's call.
- If a reviewer cannot attend the call but their review has been submitted in the Members Website…
  - …if there is reviewer concordance, group discussion may occur in the absence of the reviewer.
  - …if there is NOT reviewer concordance:
    - The two reviewers may discuss among themselves prior to the call and come to a concordant decision, in which case the group discussion may occur in the absence of the reviewer.
      - If the above is not possible, the case discussion may be moved to email or pushed to the following month's call.

4.2.12.2 Reviewer Assignment by Administrative Core Project Managers

The Administrative Core Project Managers will receive an automated email from the DCC when a participant has completed the Stage 1 questionnaire and the autoantibody test results have been received:



Wed 10/30/2019 9:10 AM

contact@atypicaldiabetesnetwork.org

RADIANT Pending Adjudication Review Assignment

To QATEST1; QATEST31

RADIANT
Rare and Atypical Diabetes Network

The following RADIANT participant has completed the Stage 1 Questionnaire and the Autoantibody Test Results have been received

Participant ID: 128510
Local ID: RAD-0021

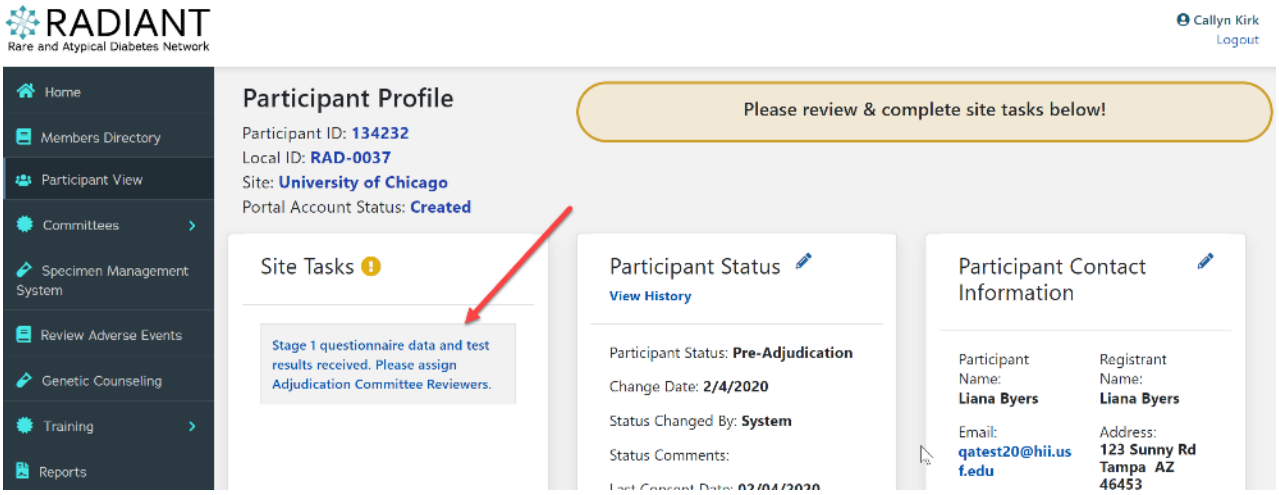
Next Steps:

1. Login to the RADIANT Members Website to view the Participant Profile.
2. Assign the Adjudication Reviewers and Adjudication Review Date

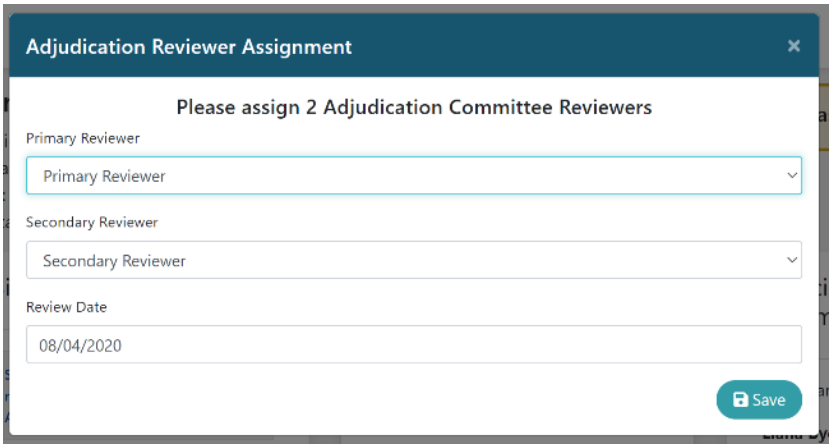
The Administrative Core Project Managers will then follow the steps below to assign Adjudication Reviewers to the case:

- Login to the RADIANT Members Website.
- Navigate to the Participant Profile (see section 13.3.6).

- Click on the site task to assign Adjudication Committee Reviewers.



- The Adjudication Reviewer Assignment module will open. Select the Primary Reviewer, Secondary Reviewer, and Review Date. The primary reviewer and secondary reviewer must be within the same adjudication group.



Every effort will be made to assign cases to the 'best match' reviewers without delaying participant progress through the study:

- If an adjudication committee member referred the participant, or is their current HCP, every effort will be made for the case to be assigned to that group, but two other members of that group will serve as reviewers. This will allow the referring/HCP adjudicator to provide input on the case if needed, but not serve as their formal reviewer.
    - The Adjudication Committee member would need to be listed by the participant for one of the following questions:
        - "How did you hear about RADIANT?" → "My doctor or diabetes provider told me about this study" (On Stage 1 questionnaire, Section 1)
        - "Who is your current diabetes physician?" (On Stage 1 questionnaire, Section 2)
        - "Are there any other physicians who help you with your diabetes management?" (On Stage 1 questionnaire, Section 2)
    - Please note: RADIANT members may only provide information (verbal or written) about a case if they have permission to do so – such as a RADIANT medical record release form, signed consent form from another study allowing for data sharing, or other documented agreement by the participant.

- If a participant comes from an existing atypical diabetes registry, the case will be assigned to a group which includes a PI from that registry
    - If a participant comes from an atypical diabetes registry AND lists an Adjudication Committee member as their current HCP/referral HCP, priority will be given to the group with their current HCP/referral HCP
    - The atypical registry would need to be listed by the participant for the following question:
        - "How did you hear about RADIANT?" → "I heard through my involvement in an existing research study" (On Stage 1 questionnaire, Section 1)
    - Please note: Information (verbal or written) from these registries should only be shared if they have a signed consent form allowing for data sharing.
- Project Managers will attempt to assign pediatric cases to pediatricians in the Adjudication Committee.
- Cases that are likely monogenic, lipodystrophic, or syndromic will be prioritized for Adjudication Committee members who have expertise in those areas (Section 4.2.12.5).

2. Adjudication reviewer assignment is complete. The assigned Adjudication reviewers will receive an email notification notifying them that they have been assigned a case for review:

Wed 10/30/2019 1:38 PM

contact@atypicaldiabetesnetwork.org

RADIANT Adjudication Review Assignment

To Lili Wurmser; QATEST31

RADIANT
Rare and Atypical Diabetes Network

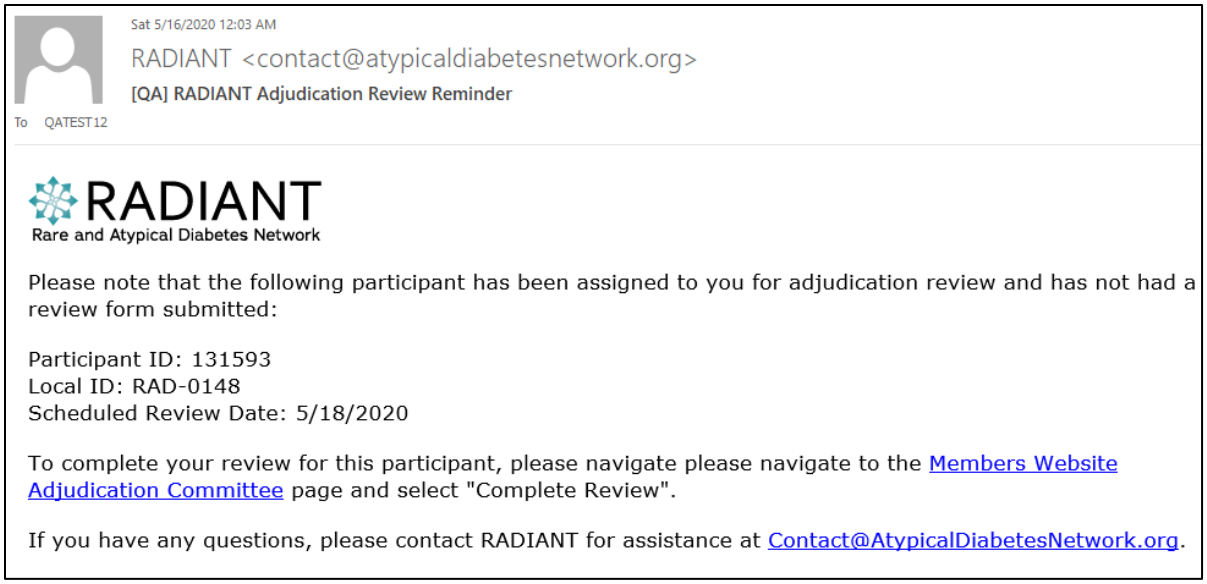
You have been assigned a RADIANT Participant for Adjudication Review.

Participant ID: 128510
Local ID: RAD-0021

Please navigate to the Members Website Adjudication Committee page to review participant details.

If you have any questions, please contact RADIANT for assistance at Contact@AtypicalDiabetesNetwork.org

The assigned Adjudication reviewers will receive a reminder email 48 hours before the case's assigned call if they have not completed their review by that time:



Sat 5/16/2020 12:03 AM

RADIANT <contact@atypicaldiabetesnetwork.org>

[QA] RADIANT Adjudication Review Reminder

To QATEST12

RADIANT
Rare and Atypical Diabetes Network

Please note that the following participant has been assigned to you for adjudication review and has not had a review form submitted:

Participant ID: 131593
Local ID: RAD-0148
Scheduled Review Date: 5/18/2020

To complete your review for this participant, please navigate please navigate to the Members Website Adjudication Committee page and select "Complete Review".

If you have any questions, please contact RADIANT for assistance at Contact@AtypicalDiabetesNetwork.org.

4.2.12.3 Reviewer Instructions – Using the Adjudication Dashboard

Once a participant has been assigned to a reviewer, the reviewer will receive an email notification notifying them that they have been assigned a case for review:

Wed 10/30/2019 1:38 PM

contact@atypicaldiabetesnetwork.org

RADIANT Adjudication Review Assignment

To Lili Wurmser; QATEST31

RADIANT
Rare and Atypical Diabetes Network

You have been assigned a RADIANT Participant for Adjudication Review.

Participant ID: 128510
Local ID: RAD-0021

Please navigate to the Members Website Adjudication Committee page to review participant details.

If you have any questions, please contact RADIANT for assistance at Contact@AtypicalDiabetesNetwork.org

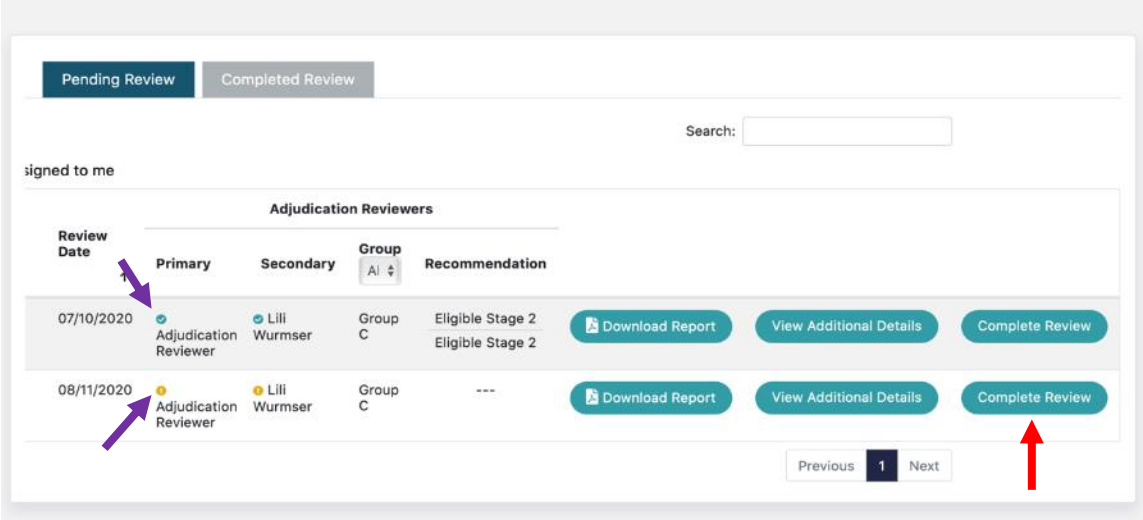
Upon receiving this email notification, the reviewer should follow the steps below:

1. Click the link in the email and login to the Members Website

   OR

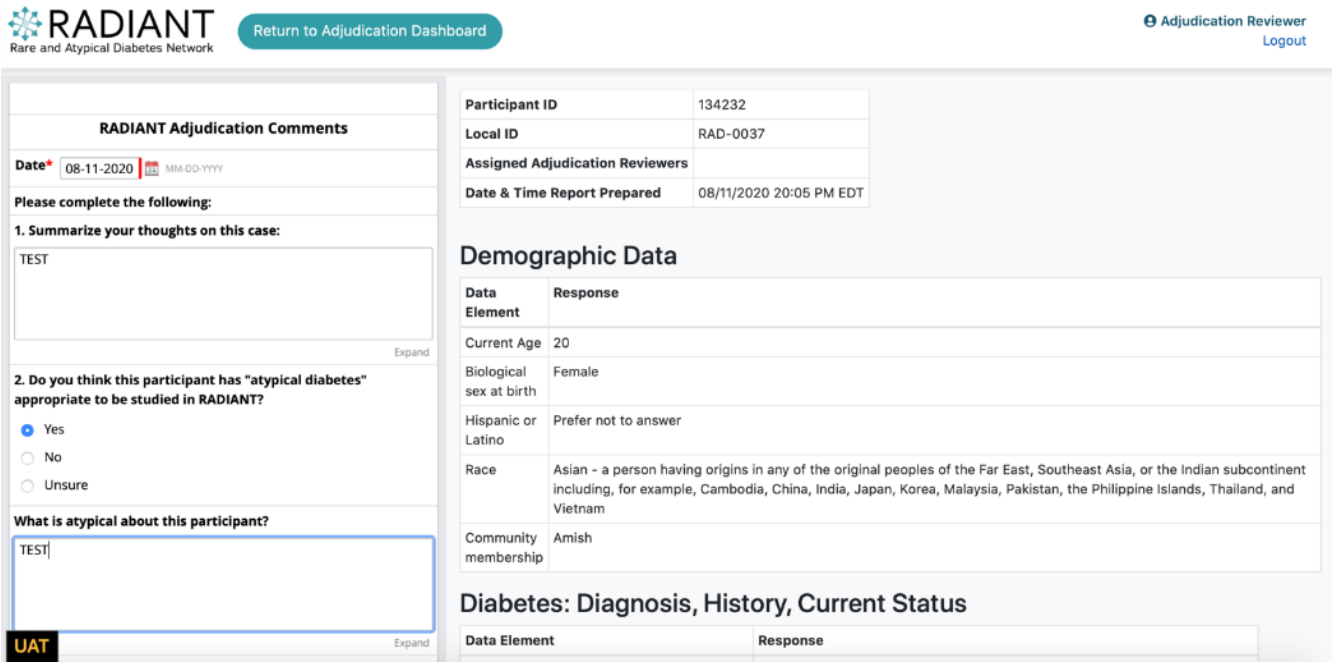
   Go to https://members.atypicaldiabetesnetwork.org/, login, and select ‘Committees’ then ‘Adjudication’ on the left side of the screen

2. Cases that are awaiting adjudication will appear under the ‘Pending Review’ tab in the Adjudication Dashboard. Primary and secondary reviewer names are noted for each participant. Cases that have a yellow exclamation point still need to be reviewed by the assigned reviewer (second row in screenshot below). Once a reviewer completes their review, the icon will turn to a green check mark (first row in screenshot below).



3. Click on ‘Complete Review’ to begin the reviewer process. You may need to scroll to the right to see the ‘Complete Review’ button.

4. Next, you will see a side-by-side screen. The left side contains the reviewer survey. This is what the reviewer will complete to document their impressions and final eligibility recommendation. The right side contains the auto-generated report, which provides a subset of information about the participant. Be sure to scroll down on both the left and right side to see the full screens. The reviewer survey ‘submit’ button is at the bottom of the left side of the screen.

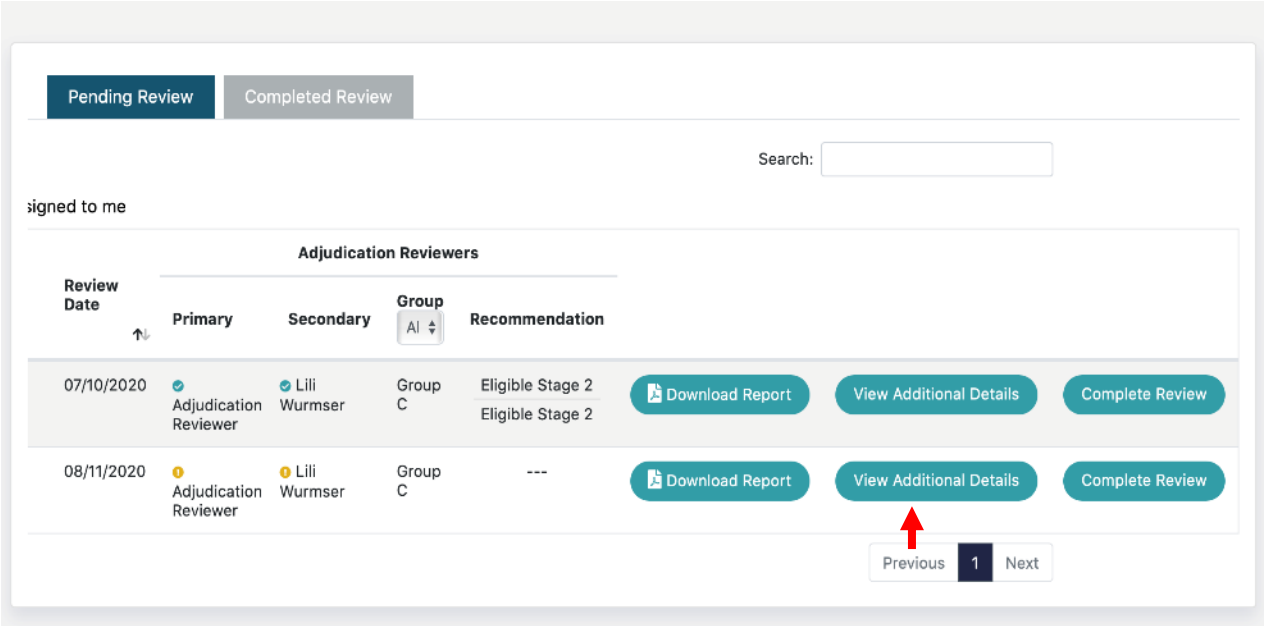


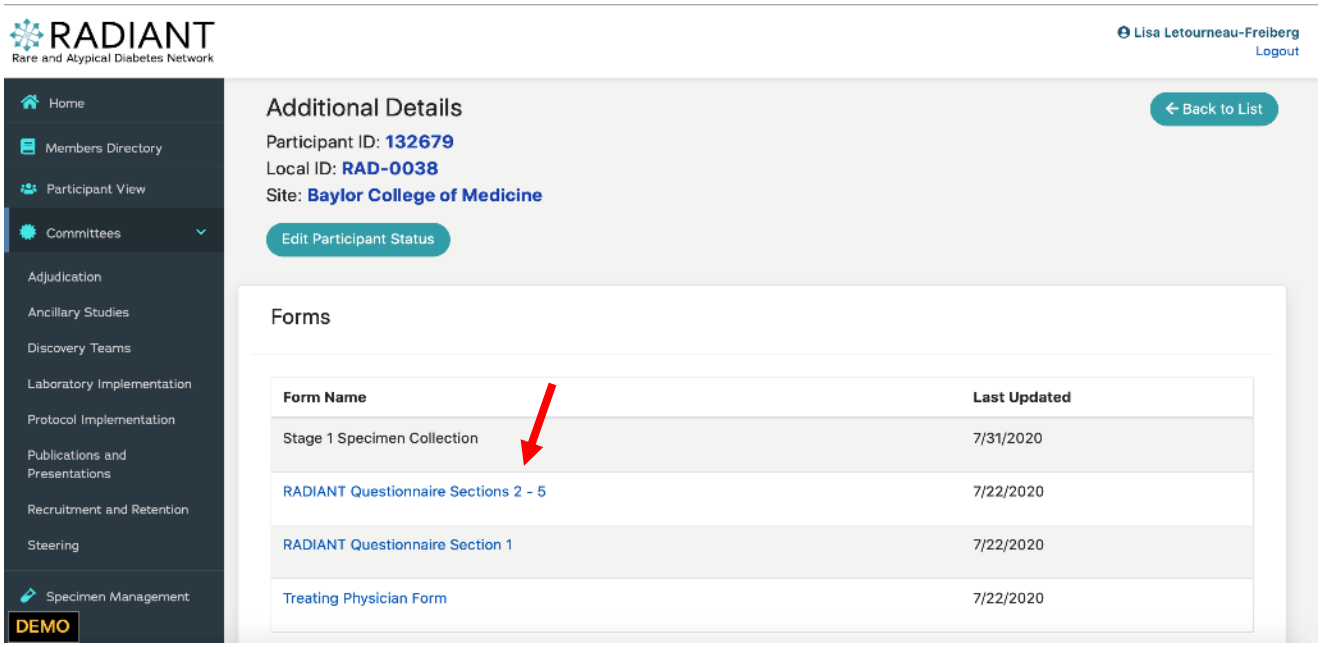
The purpose of this review is to determine if the participant is atypical and meets eligibility criteria for RADIANT. Key areas to assess may be:

- Diabetes diagnosis
  - Dx ≤30 years old
  - Non-obese BMI at diagnosis in “T2D”
  - Pre-pubertal at diagnosis of “T2D”
- DKA history
  - Has never been in DKA in “T1D”

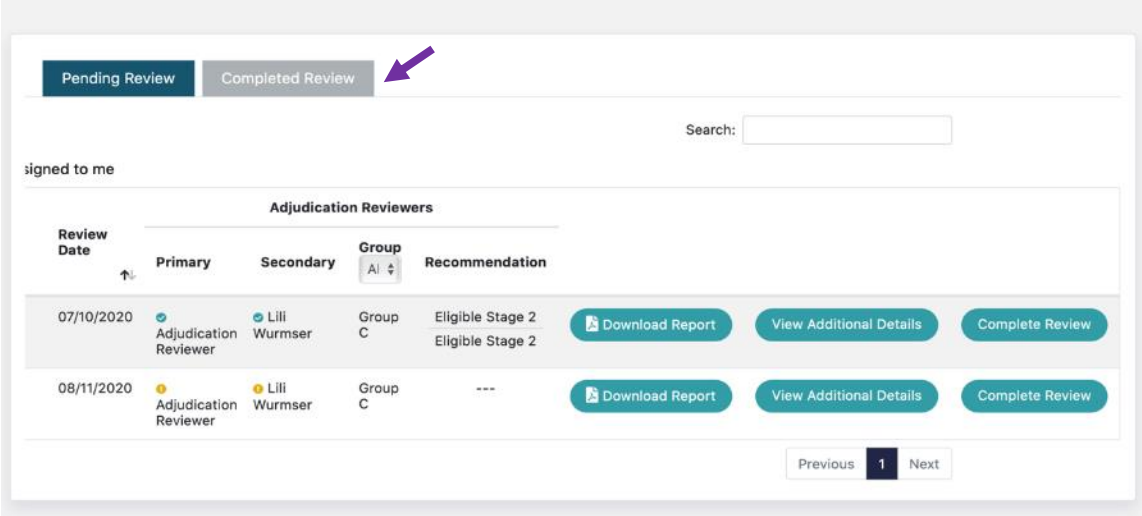
    - Has gone more than 1-2 weeks without medications and still not had ketosis/DKA in “T1D”
- Laboratory values
    - Diabetes autoantibody negative
    - C-peptide positive (>0.2 nmol/L three years or more after diagnosis of “T1D”)
    - Lack of metabolic syndrome features (e.g. normal lipids) in “T2D”
    - Extremely high insulin levels
    - Interesting AB group
        - A-B-
        - A-B+ with unprovoked DKA at initial presentation
        - A-B+ of pre-pubertal onset
- Medications
    - Low insulin requirements (<0.5 units/kg/day) for a long period of time (e.g., >3 years) and no obvious explanation (e.g., very low carbohydrate) in “T1D”
- Blood glucose patterns
    - Cyclical hyperglycemia with periods of remission or with hypoglycemia (not secondary to insulin administration)
- Other medical problems
    - Myopathy
    - Hearing deficits
    - Lipodystrophy
    - PCOS in a lean individual
    - History of GDM when lean
    - Insulin resistance when lean
- Family history
    - Linear family history of people with diabetes dx ≤30 years old
    - Family history of lipodystrophy
    - Family history of other unusual medical condition
- Other clinical features that the adjudicator deems to be ‘atypical’

5. To see additional details about the participant, including the entire Stage 1 questionnaire, any medical records that may have been collected, or any additional documents the participant uploaded, click on ‘Return to Adjudication Dashboard’ (top left of page, next to logo), then click ‘View Additional Details’.





6. Once both reviewers have completed their review, their recommendations will appear in the dashboard table. Reviewers may go back to their review prior to the scheduled adjudication call by clicking on 'Completed Review'. Reviewers may only edit their original submission after the 2nd reviewer submits their review.



4.2.12.4 Documenting and Acting On Adjudication Committee Eligibility Decision

During the adjudication group calls, the committee members will discuss each case and come to a consensus on a final eligibility decision. Administrative Core Project Managers will document this final decision for each case in the RADIANT Members Website as well as any pertinent notes regarding the case.

These recommendation options are:

- Eligible Stage 2 (move on to Stage 2/WGS)
- Keep in Reserve (lower priority for WGS – can be moved to Stage 2 if funds allow at the end of each year)
- Need more information (specify what information is needed)
- Ineligible (participant is not atypical and should not proceed further)

For participants with the eligibility decision of “Eligible Stage 2”, Administrative Core Project Managers will update the participant status to “Eligible Stage 2” (Section 13.3.6) and update the participant’s assigned clinical site to one of the local sites in the RADIANT Members Website (see section 5.2.2). Local sites will receive an email notifying them that a participant has been assigned to their site, and the local sites will initiate processes to proceed with Stage 2.

For participants with the eligibility decision of “Keep in reserve”, Administrative Core Project Managers will update the participant status (Section 13.3.6). This list of cases will be reviewed at regular intervals and, if funds allow, participants may then be updated to “Accept” and proceed to Stage 2.

For participants with the eligibility decision of “Need more information”, Administrative Core Project Managers will update the participant status (Section 13.3.6) and select “Need more information” for the final recommendation and document in the comment box what additional information has been requested by the group. Administrative Cores (Baylor and Chicago) will coordinate “Need more information” requests for participants assigned to their sites. They may request assistance from local sites in following up with participants for “Need More Information” requests.

If the participant is likely to have a monogenic, lipodystrophic, or syndromic form of diabetes, they will follow the instructions in Section 4.2.12.5.

If additional medical records are requested, the Project Manager will document which records are requested in the comment box and inform the Administrative Core that is overseeing this participant. Obtaining the additional information will be the responsibility of the Administrative Core. Administrative Core staff will inform the Project Manager and primary reviewer when the requested information is available, and the adjudication review will proceed at a subsequent adjudication group meeting.

Cases where information (including medical records) is not available
Administrative Core staff will attempt to obtain the requested additional information at least 3 times (see Section 4.2.10). If they are unable to obtain the information after 3 attempts, the adjudication group will be encouraged to make a decision with the information available. If there is a sense of atypicality, but no confirmed medical records to exclude other potential diagnoses, the participant status will be updated to ‘Keep in Reserve’.

For participants with the eligibility decision of “Ineligible”, Administrative Core Project Managers will update the participant status to “Ineligible” (Section 13.3.6) and document the reason the participant is ineligible (including the type of diabetes they are most likely to have).

4.2.12.5 Process for likely monogenic, lipodystrophic, and syndromic diabetes cases

Pre-adjudication genetic variant data entry: For participants who have listed specific variant(s) in known monogenic diabetes genes in their questionnaire (Section 4 – Monogenic DM/mitochondrial/lipodystrophy sections), Administrative Core Project Managers will work with genetic experts at the University of Maryland and/or University of Chicago to request information on any genetic variants listed (check Monogenic Diabetes Expert Panel (MDEP) database; if not in MDEP database, circulate variant to MDEP email list (and others who may have data) to ascertain case data from existing registries, clinics, and labs, and utilize data available along with other evidence (allele frequency, previous reports in literature, functional data, prediction software, evolutionary conservation) that can be used as input for classification by ACMG/AMP guidelines, using MDEP or other panel gene-specific rules when available. This will include variants of any pathogenicity level (including variants of uncertain significance). This information will be summarized and entered by the Project Managers in the Adjudication Dashboard for members of the adjudication group to view.

Assigning reviewers: Project Managers will make every attempt to assign the case to at least 1 person who has been listed as an expert in this area (a list of current expert reviewers can be found below).

During adjudication group discussion: Geneticists on each adjudication group will provide any additional guidance needed regarding interpretation of genetic variants. If the adjudication group members agree that the

participant under review is likely to have monogenic, lipodystrophic, or syndromic diabetes, the Administrative Core Project Managers will update the participant's status to "Needs more information" in the RADIANT Members Website while the below steps occur.

Letter and call to participant: One adjudication group member (or another RADIANT investigator, if needed) will volunteer to set up a phone call with the participant. A table of adjudication members who are experts in these areas and have volunteered to hold these calls can be found below. The participant may include their HCP on the call as well, if they would like to (including if their HCP is a RADIANT investigator).

An email or letter will be sent to the participant to inform them that we'd like to schedule a call. An Administrative Core Project Manager will send this letter (Appendix 2) and copy the adjudication group member who volunteered to speak with the participant.

The adjudication group member will discuss the following on the phone call:

1. Gather any remaining data RADIANT may need for this participant (e.g. missing date of diagnosis)
2. Explain why the Adjudication Committee thinks this participant may have monogenic, lipodystrophic, or syndromic DM
3. Describe what clinical tests would be clinically recommended to investigate this (these will NOT be covered by RADIANT)
4. Provide guidance on how to obtain those clinical tests, if needed (helping guide on how to get genetic testing, for example)
5. Explain what to do once participant has the results of these additional tests. Participants should return to the Adjudication Committee once these results are ready for re-discussion and adjudication.
    a. If the results are indicative of a known and previously characterized form of monogenic, lipodystrophic, or syndromic DM, the participant may not be eligible for RADIANT, but other research studies could be a possibility.
    b. If the results do not indicate a known and previously characterized form of monogenic, lipodystrophic, or syndromic diabetes, the participant may be eligible to continue to Stage 2.

Participants will also be provided with a 'tear sheet' for the suspected form of diabetes following the call. This will provide more detailed information on the suspected type of diabetes as well as pertinent testing information, such as how to obtain genetic testing outside of RADIANT.

The participant is not obligated to have these additional clinical tests performed and may still be considered for progression to Stage 2 of RADIANT if they are unable to get these tests performed.

Resources for investigators when speaking with participants about monogenic diabetes testing:

	IRB-approved document?	**Location of resource**
00. RADIANT process for participants with likely monogenic diabetes	No – don't share with participants	Google Drive folder linked here
02. Options for obtaining genetic testing	No – don't share with participants	Google Drive folder linked here
03. Other Helpful Resources	No – don't share with participants	Google Drive folder linked here
Likely monogenic, lipodystrophy, syndromic letter – this is what Project Managers send to participant when setting up phone call	Yes – this may be sent to participants using template	Appendix 2 of this MOP or Central IRB Approval Letters & Documents > Approval 07-13-20 > Zipped file > Other Approved Documents > RADIANT likely monogenic lipo syndromic letter 20200520
RADIANT Monogenic DM Testing 101 tear sheet	Yes – this may be sent to participants	Central IRB Approval Letters & Documents > Approval 07-13-20 > Zipped file > Other

		Approved Documents > RADIANT Monogenic DM Testing 101 tear sheet 20200520
RADIANT Lipodystrophy Testing 101 tear sheet	Yes – this may be sent to participants	Central IRB Approval Letters & Documents > Approval 07-13-20 > Zipped file > Other Approved Documents > RADIANT Lipodystrophy Testing 101 tear sheet 20200520
Phone script for RADIANT investigators to use when speaking to participants about likely monogenic diabetes	Yes – this may be used on participant phone calls	Central IRB Approval Letters & Documents > Approval 09-22-21 > RADIANT_likely MDM_phone script_V20210709
Follow-up email template for RADIANT investigators to send to participants after phone call	Yes – this may be sent to participants using template	Central IRB Approval Letters & Documents > Approval 09-22-21 > RADIANT_likely MDM_follow up email template_V20210709
Process for patient-initiated ordering through Invitae-Genome Medical	Yes – this may be shared with participants	Central IRB Approval Letters & Documents > Approval 09-22-21 > Process for pt initiated ordering Invitae GenomeMed 20210331
FAQ on GINA & insurance for RADIANT site staff	No – don't share with participants	Study Documents > Manual of Procedures > Stage 1 and Stage 2 MOP and Resources > Consenting Resources > 03. FAQ on GINA & Insurance for RADIANT Site Staff V20210712

Re-adjudication: Once the additional test results are returned, the case will be re-reviewed on an adjudication group call.

The following expert Adjudication Committee members are available to speak with participants for the following categories (as of 02/15/22). Other Adjudication Committee members may also volunteer to speak with participants, as desired:

Monogenic DM	Lipodystrophy	Syndromic, Wolfram
Liana Billings	Janet McGill	Janet McGill
Siri Greeley	Elif Oral	Steve Stone
Rochelle Naylor	Ashok Balasubramanyam	Fumi Urano
Lou Philipson		
Toni Pollin		
Miriam Udler		

4.2.12.6 Process for likely secondary diabetes cases

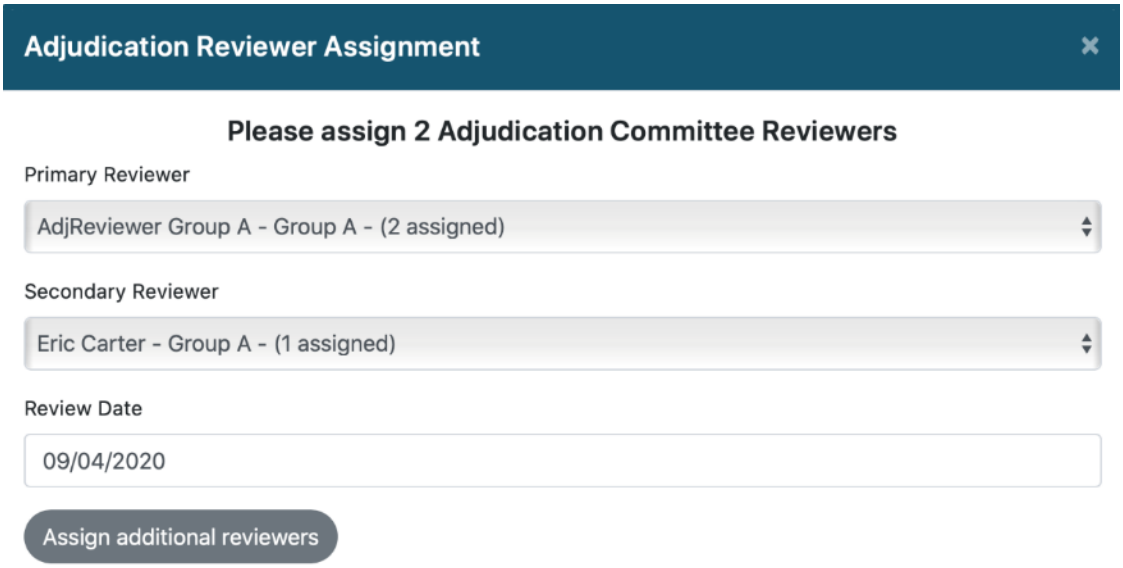
If the adjudication group determines that a case is likely to have a secondary form of diabetes requiring additional testing, they will use the same process as the likely monogenic, lipodystrophic, and syndromic diabetes cases above (section 4.2.12.5). The primary reviewer will call the participant to discuss the impression of the Adjudication Committee.

4.2.12.7 Consistency control cases (CCC) process

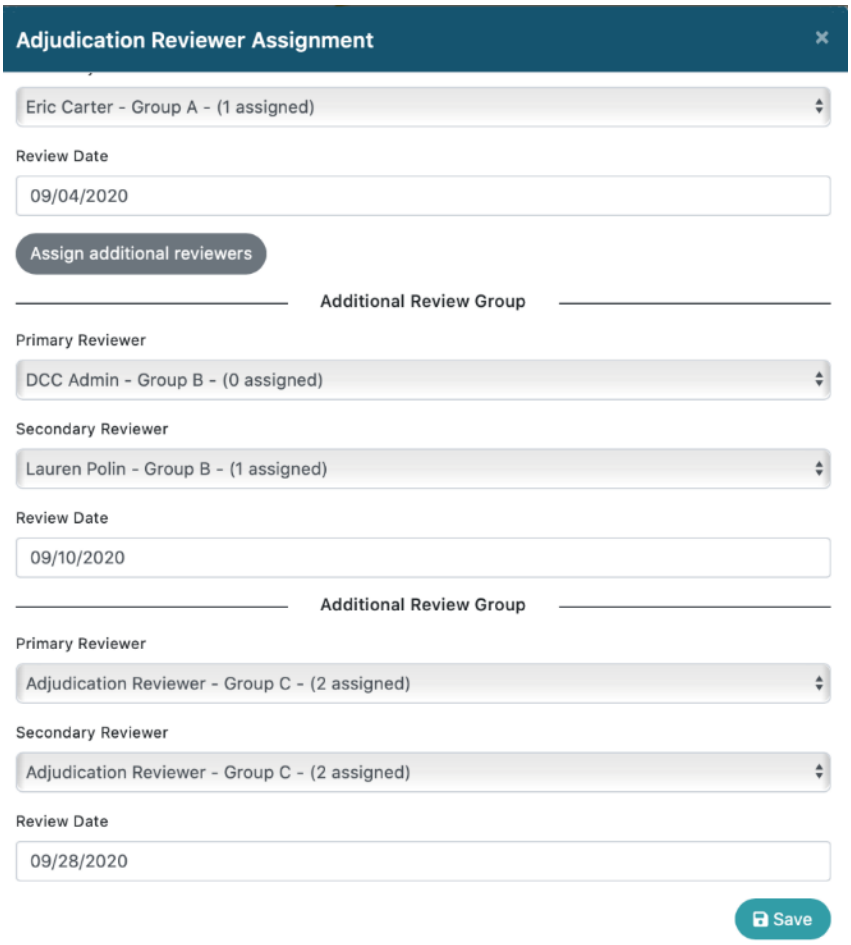
A small fraction of cases (1-3 per monthly meeting) will be reviewed by all three adjudication groups in a blinded fashion, with one group designated as the "decision" group upon which the adjudication of that case will proceed. This will generate a database of several cases per year that can be reviewed for uniformity of adjudication procedures.

On a regular basis, the three adjudication groups will convene and go over the CCC reviews for that period, sharing their adjudication procedures and concentrating on the adjudication decisions that might have diverged, to resolve differences and harmonize procedures. If the face-to-face meeting does not take place on the expected biannual schedule, the meeting will happen by *ad hoc* conference call.

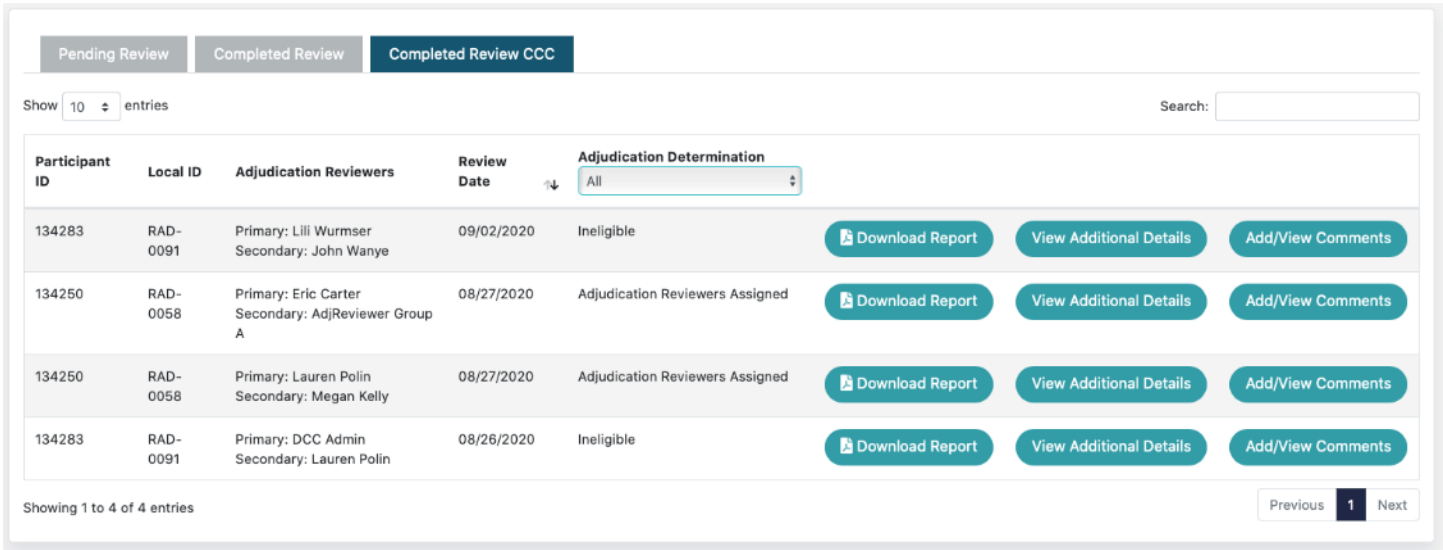
1. Administrative Core Project Managers will choose one case per month to assign to all three groups with one group designated as the “decision” group. The “decision” group will rotate each month. When the case is selected, the Project Manager will assign reviewers. The “decision” group reviewers will be assigned first as shown below. In this example, Group A is the “decision” group.



2. The Project Manager will click “Assign additional reviewers” to assign the non-decision group reviewers (in this example, Groups B and C).



3. The adjudication group calls will proceed as usual. The reviewers will not know their case is a 'CCC' until the conclusion of the discussion for that case. In the "decision" group, the case will be adjudicated as usual and once completed, will move into the 'Completed review' tab. In the non-decision groups, once completed, the case will move into the 'Completed Review CCC' tab.



4.2.12.8 Guidelines for manual review of screen fail cases

Once approximately 10 screen fail cases have accumulated, or every 6 months (whichever comes first), a manual review of screen fail cases will take place. A reviewer, or group of reviewers called the Screen Fail Manual Review Committee, will go through screen fail cases to determine if they may be interesting enough to proceed in RADIANT.

Possible case decisions are:

- Leave as screen fail: the committee feels the screen fail was appropriate
- Need More Information (NMI): screen fail cases may be recontacted if necessary to gather additional information, then be re-reviewed by email or on a future call
- Change to screen pass: the committee feels the case is interesting enough to proceed to next step of RADIANT Stage 1 – including remaining questionnaire sections, antibody testing, and potentially full adjudication review
    - Changing participant status from screen fail to screen pass: If a participant needs to be changed from screen fail to screen pass, the Project Manager will email DCC staff to ask for this change in status. The DCC will then push out the Participant Portal set-up email.

Documenting Screen Fail Manual Review Committee decisions: A Project Manager will document the decision for each case in the Participant's Profile, such as by uploading a Word document with notes on the decision.

Screen Fail Manual Review Committee membership: Adjudication Committee members may volunteer to serve on the manual review team. Cases will be assigned to reviewers by a Project Manager via email. Each case will be reviewed by at least two committee members. A meeting will be scheduled between the manual reviewers and at least one Adjudication Committee co-chair.

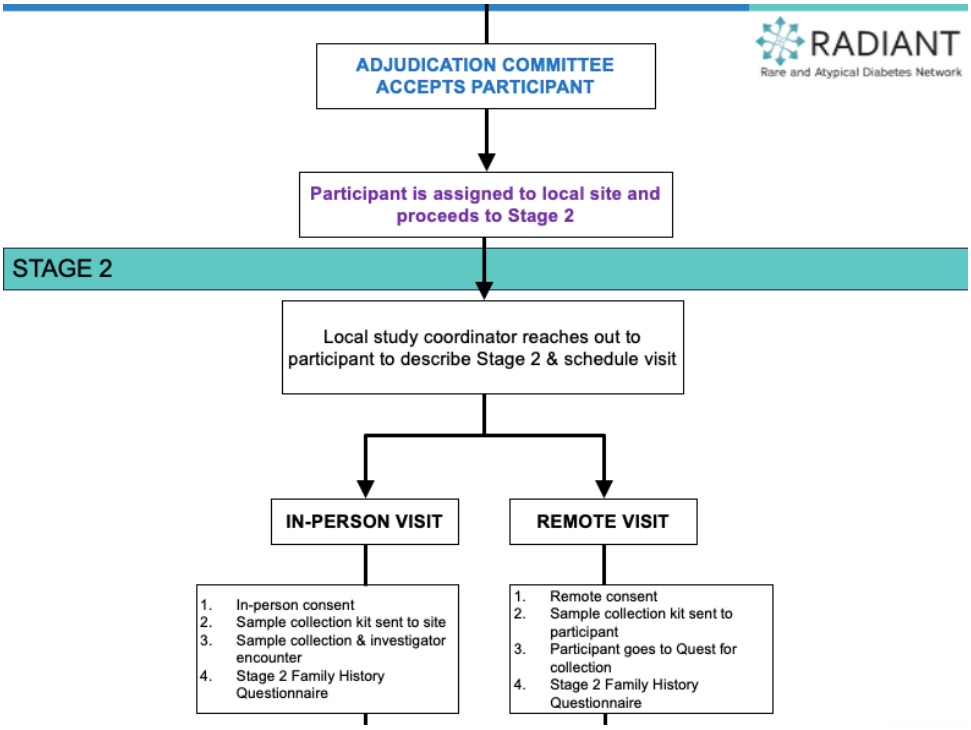
Volunteers for manual review team (as of 03/09/23):
Toni Pollin
Fumi Urano
Maria Redondo

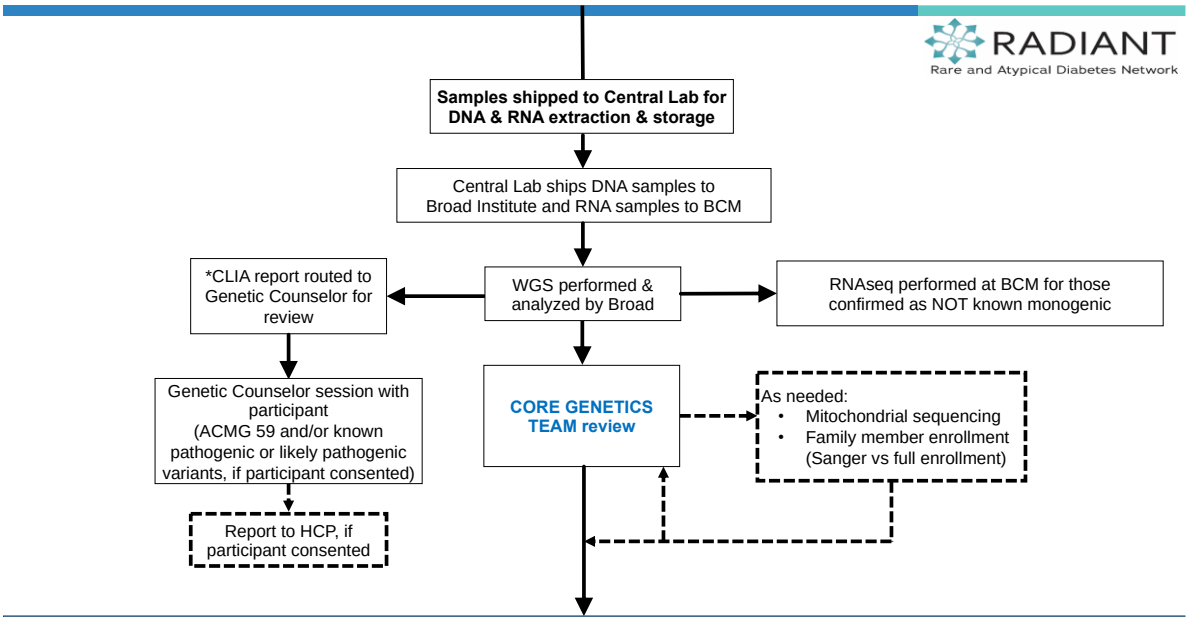
5 STAGE 2 PROCEDURES

5.1 STAGE 2 OVERVIEW#

Participants accepted by the Adjudication Committee will continue to Stage 2. Stage 2 activities include: sample collection for DNA and RNA, whole genome sequencing, optional investigator encounter, Stage 2 Family History Questionnaire, sample storage in the RADIANT Biobank (DNA and RNA storage), and collection of samples for the NIDDK Repository (DNA and RNA). RNA sequencing will be performed on participants who do not carry known genetic variants after completion of WGS.

Figure 3. RADIANT Stage 2 Workflow
Abbreviations in Stage 2 Workflow figure: BCM – Baylor College of Medicine, WGS – whole genome sequencing, HCP – healthcare provider





5.1.1 RUNNING STAGE 2 AND S3SV IN PARALLEL

Stage 2 and S3SV may be run in parallel. This option will expedite the participant's progress in the study by allowing the participant to proceed with scheduling and completing the S3SV while WGS is in progress. This option will also allow the flexibility for Stage 2 procedures and S3SV procedures to be completed during the same in-person visit, if it is not possible for the participant to complete Stage 2 remotely. Please see the S3SV MOP, Section 16, for full information.

5.2 STAGE 2 PROCEDURES

5.2.1 STAFF RESPONSIBILITIES – STAGE 2#

The following table indicates which RADIANT staff are responsible for procedures in Stage 2:

Procedure	RADIANT staff responsible	Notes
Documenting any participant communications in the Contact Log section of the Participant Profile	Local site staff or Administrative Core staff, as needed	
Contacting participants who are transferred to local site to continue on in Stage 2	Local site staff	
Stage 2 consent (remote or in-person)	Local site staff	
Stage 2 remote visit	Quest staff	
Stage 2 in-person visit – collection, processing, shipment of samples	Local site staff	It will take the Central Lab approximately 2 days for a kit to be prepared, sent, and received by the participant or local study site. Local study coordinators need to give at least 7 days between requesting kit and having a visit for Stage 2 sample collection.
Stage 2 in-person visit – investigator encounter	Local site investigator	Local site study coordinator can complete if investigator unavailable
Stage 2 Family History Questionnaire	Participant	Local site study coordinator should follow up with participant to complete this questionnaire in their Participant Portal account if incomplete
Stage 2 genetic testing results sharing	RADIANT Genetic Counselor	
Faxing genetic testing report to participant's healthcare provider *(If they requested report to be shared on Stage 2 consent form)*	Local site staff	

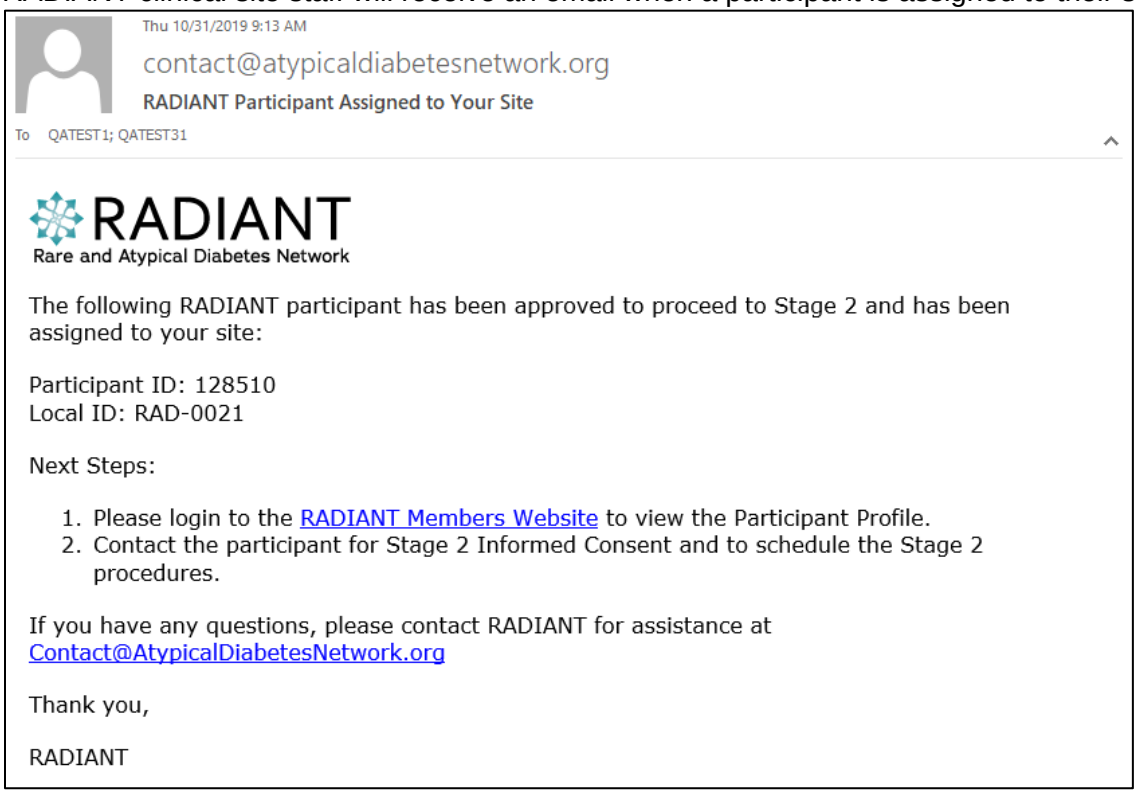
5.2.2 PARTICIPANT ASSIGNED TO RADIANT CLINICAL SITE FOR STAGE 2#

As described in the Adjudication procedures above, after a participant is accepted by the Adjudication committee for continuation to Stage 2 of the study, the Administrative Core Project Manager will assign the participant to a RADIANT clinical site for Stage 2.

Project Managers will make every effort to assign participants to the site they chose in the Stage 1 questionnaire. If a Spanish-speaking participant chooses a preferred site for Stage 2 that doesn't accommodate Spanish-speaking participants, staff at Baylor/Chicago will call the participant to explain that the

situation and assist the participant in choosing a different site that can accommodate Spanish-speaking participants. The participant may be assigned to a Spanish-speaking site that is not near their home but may still complete a remote Stage 2 visit at a Quest near their home.

RADIANT clinical site staff will receive an email when a participant is assigned to their site for Stage 2:



Thu 10/31/2019 9:13 AM

contact@atypicaldiabetesnetwork.org

RADIANT Participant Assigned to Your Site

To QATEST1; QATEST31

RADIANT
Rare and Atypical Diabetes Network

The following RADIANT participant has been approved to proceed to Stage 2 and has been assigned to your site:

Participant ID: 128510
Local ID: RAD-0021

Next Steps:

1. Please login to the RADIANT Members Website to view the Participant Profile.
2. Contact the participant for Stage 2 Informed Consent and to schedule the Stage 2 procedures.

If you have any questions, please contact RADIANT for assistance at Contact@AtypicalDiabetesNetwork.org

Thank you,

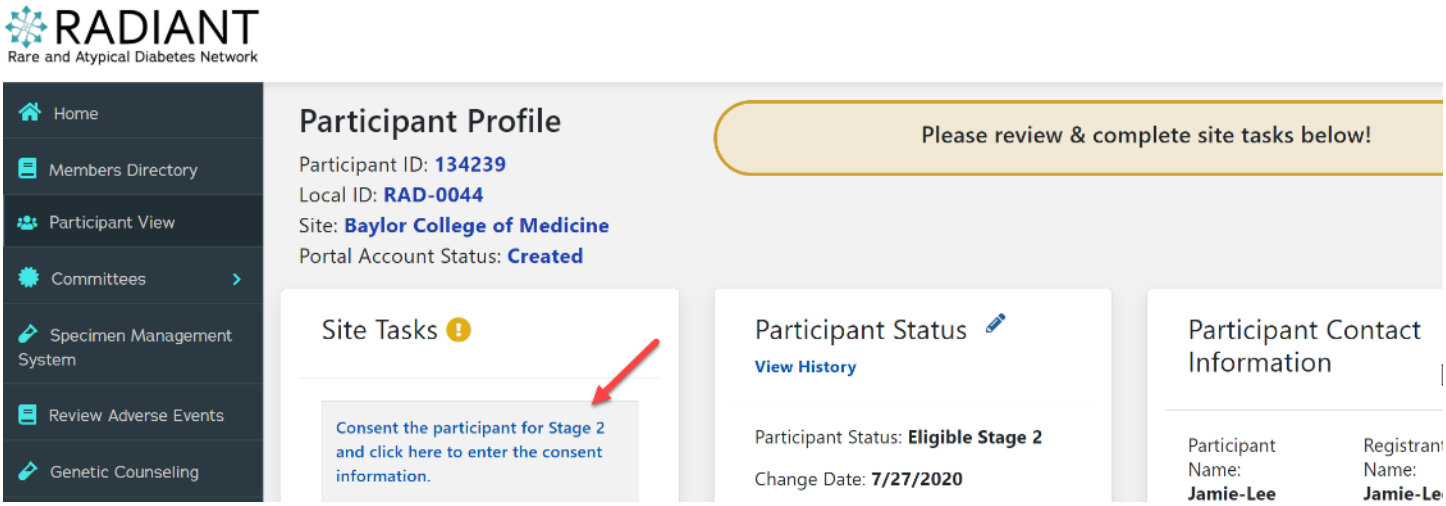
RADIANT

Procedure for local site staff upon receiving this notification email:

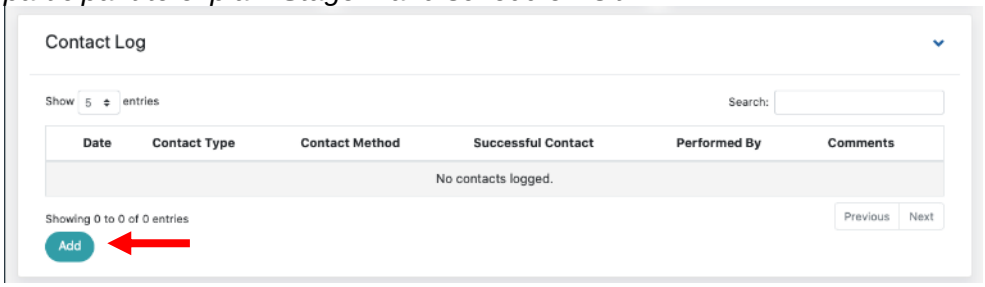
1. Login to the RADIANT Members Website and navigate to the Participant Profile (section 13.3.6)
2. Review the “Site Tasks” list (see screenshot below)
3. Contact the participant to let them know they are eligible for Stage 2
4. Ensure participant is not pregnant at this time.
    1. Pregnant participants are not able to participate in RADIANT. If participant is pregnant, mark them as ‘Withdrawn’ with reason for withdrawing as ‘Pregnancy’. If the participant would like to continue in the study when they are no longer pregnant, they can reach back out to the study site, and the site staff should email radiantteam@atypicaldiabetesnetwork.org to request that the participant status be reverted from Withdrawn back to active status.
5. Assess whether the participant is able to come to the clinic for an in-person visit.
6. Document this conversation in the Participant Profile under Contact Log (see screenshots below and section 13.3.6)
7. Continue with in-person or remote procedures as noted in Sections 5.2.3 or 5.2.4.

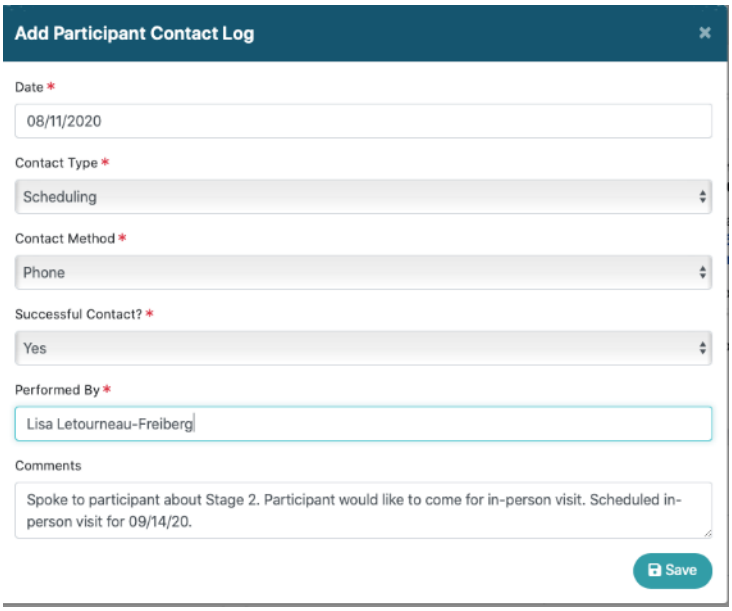
It is preferred to have the participant come for an in-person visit for Stage 2 (Section 5.2.3). If participants are unable to come for an in-person visit in Stage 2, remote participation instructions can be found in Section 5.2.4.

Site Tasks list at beginning of Stage 2:



Scroll down on the Participant Profile, to view the Contact Log section and document the contact made with participant to explain Stage 2 and schedule visit





5.2.3 STAGE 2 IN-PERSON VISIT PROCEDURE#

RADIANT site staff should work with the participant to schedule an in-person visit. Stage 2 visits may be scheduled Monday-Thursday. Samples may only be shipped Monday-Thursday. Samples must be shipped on the day of collection.

Be mindful of scheduling around holidays. See the Stage 2 Central Lab MOP for full information on scheduling near holidays.

When scheduling the Stage 2 in-person visit with the participant, study coordinators must go over the following illness instructions:

1. If you feel sick during the 7 days prior to your Stage 2 in-person visit, please call me to reschedule this visit. Feeling sick includes cold, flu, fever, vomiting, diarrhea, or any physical stress. This also includes chills, cough, shortness of breath, difficulty breathing, fatigue, muscle or body aches, headache, recent loss of taste or smell, sore throat, congestion, or nausea.

Sites must also follow any local institutional guidelines for screening participants for COVID-19 symptoms prior to an in-person visit. Sites should also follow any other local COVID-19 procedures such as mandatory masking, temperature checks, etc.

Participants who are currently pregnant are unable to participate in the study. See section 5.2.2 for more information.

It will take the Central Lab approximately 2 days for a kit to be prepared, sent, and received by the site. Local study coordinators need to give at least 7 days between requesting kit and having a visit for Stage 2 sample collection.

*Study coordinators must send the participant the Stage 2 visit clinical site instruction letter (can be found on Members Website) when they schedule a Stage 2 in-person visit.

5.2.3.1 Stage 2 In-Person Informed Consent and Assent Process#

For any participants coming for an in-person visit, informed consent/assent should be completed in person at the beginning of the visit.

It is helpful to email or mail the participant a copy of the Stage 2 consent form prior to the in-person visit so they can review it ahead of time.

* The Stage 2 consent process is very important to RADIANT as it contains complicated information about whole genome sequencing (WGS). Study staff are encouraged to use the annotated Stage 2 consent resource to help guide them through the Stage 2 consent process (can be found on the Members Website).*

Please note: There are several videos that participants are required to view either prior to or during the consent process to ensure they understand genetic testing and the types of information it may (or may not) provide. These are linked in the annotated Stage 2 consent resource and are available on the RADIANT public website at: https://www.atypicaldiabetesnetwork.org/genetictesting.

The participant must provide informed consent and assent (if applicable – ages 7-17 years old) for the Stage 2 Procedures before any Stage 2 Procedures occur.

- Forms needed:
  - Forms are based on participant age and RADIANT stage – see Appendix 1
- Instructions:
  1. Print out all necessary forms
  2. Meet with participant (and/or caregivers if needed) in a quiet place
  3. Explain what you are asking them to do for this stage of RADIANT and what is contained in the consent form. Show the participant the videos from the annotated consent form if they have not watched them already. Encourage them to ask you any questions they may have as you go through the form. When you finish explaining the form, ask them “what questions do you have for me?” After all questions have been answered, ask “do you want to proceed with participating in this study?”

i. If no → Thank them for coming, check if they need parking validation and update the Participant Status to “Withdrawn” with the reason for withdrawal (ex. did not agree to participate in Stage 2) in the RADIANT Members Website (see section 12.2 – Withdrawals and section 12.3.6 – How To Edit Participant Status). Record this interaction in the Contact Log.
ii. If yes → Proceed

4. Direct the participant to areas where they need to initial and/or sign on the consent/assent forms
5. Sign and date as the consenter on the last page. If your local site requires PI signature, ensure PI has signed as well.
6. Make a copy of the signed consent/assent forms and return the copy to the family
7. Document consent process locally
8. Enter consent information in RADIANT Members Website (see Section 13.3.6.2)
9. Proceed with study procedures for Stage 2 in-person visit

5.2.3.2 Stage 2 Specimen Collection at Clinical Center

After the Stage 2 in-person visit has been scheduled, the site staff must request a specimen collection kit to be sent from the Central Lab to the site. This request is submitted via the RADIANT Members Website (see Section 13.3.6.3). It will take the Central Lab approximately 2 days for a kit to be prepared, sent, and received by the local study site. Local study coordinators need to give at least 7 days between requesting kit and having a visit for Stage 2 sample collection.

*Study coordinators must send the participant the Stage 2 visit clinical site instruction letter (can be found on Members Website) when they schedule a Stage 2 in-person visit.

Blood will be collected for Stage 2 tests per protocol and shipped per protocol to the central RADIANT lab. DNA and RNA will be extracted at the central RADIANT lab.

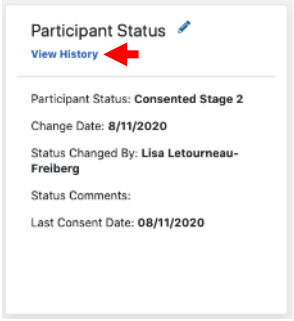
See Appendices 3 and 4 for details on sample collection and shipment.

5.2.3.3 Stage 2 Investigator Encounter#

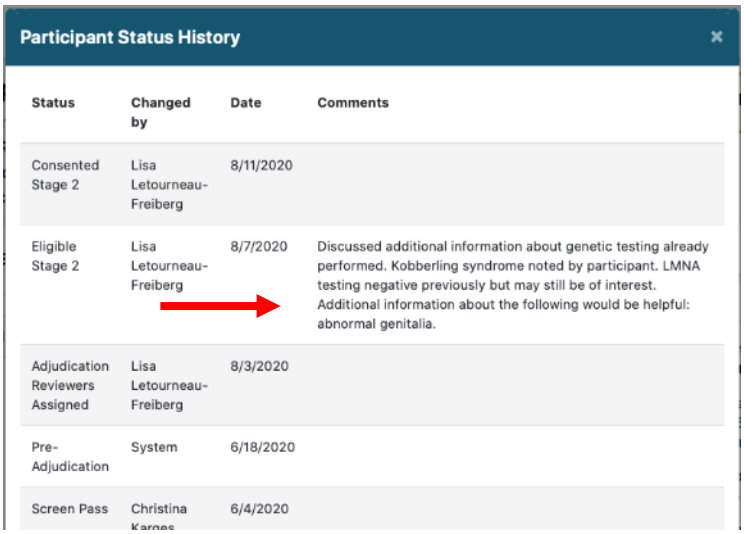
An “investigator encounter” is highly encouraged (but not required) for all in-person Stage 2 visits.

At least one RADIANT investigator or the study coordinator from the local site is encouraged to meet with the participant/family during the Stage 2 visit to accomplish the following:

1. Introduce themselves, other local site staff, and the RADIANT study
2. Answer any questions the participant may have
3. Go over any additional questions the site may have regarding the participant’s questionnaires answers or questions that the Adjudication Committee asked. Questions from the Adjudication Committee are documented in Participant Status – View History section of the Participant Profile on the RADIANT Members Website. Follow the instructions below to check on whether there are any Adjudication Committee questions to be addressed during the visit:
    1. Login to the RADIANT Members Website
    2. Navigate to the Participant Profile (Section 13.3.6)
    3. In the Participant Status section of the profile, click “View History”



4. Review the comments in row for the 'Eligible Stage 2' status



4. Determine if additional medical records need to be requested (If yes, an additional medical record release form may need to be completed. Completing this medical record release form and requesting the medical records is the responsibility of the local site). Medical records may only be requested if an appropriate medical record release form is signed by the participant. The local site will upload any received medical records to the Participant Profile. Staff must follow all local guidelines on appropriate storage of Protected Health Information, such as deleting medical records from their devices once they are uploaded to the Participant Profile.

5. Document any impressions/findings on a local Stage 2 visit notes form. This does not need to be entered into the Members Website.

Site investigators and study coordinators are encouraged to review participant information and questionnaire data PRIOR TO the visit so they are familiar with the participant's history and prepared for the investigator encounter.

5.2.3.4 Stage 2 Compensation#

Participants who come for an in-person visit will either 1) be given pre-paid parking validation passes or 2) be reimbursed for the cost of their parking. Providing participants with a pre-paid parking validation pass is preferred.

Pre-paid passes should be purchased by the local site. The local site should then send this receipt to their respective Administrative Core for reimbursement (see Section 2.3.1 for Administrative Cores). The same reimbursement process should be employed for participants who are reimbursed for the cost of their parking.

5.2.4 STAGE 2 REMOTE VISIT PROCEDURE#

Participants who are currently pregnant are unable to participate in the study. See section 5.2.2 for more information.

If a participant cannot come to a RADIANT Clinical Center for an in-person Stage 2 visit, consent and specimen collection can be obtained remotely per the procedures below.

5.2.4.1 Stage 2 Remote Informed Consent and Assent Process#

If a participant cannot come for an in-person visit for Stage 2, consent will be obtained remotely. The consenting Clinical Center will mail a blank consent/assent form to the participant and schedule a time to discuss the consent either by telephone or if necessary, web-based video or audio call (such as Skype, Webex, FaceTime, etc) to discuss the Stage 2 consent. The participant will be asked to sign the consent and mail it back to the consenting Clinical Center. The participant must provide informed consent and assent (if applicable) for the Stage 2 Procedures before any Stage 2 Procedures occur.

* The Stage 2 consent process is very important to RADIANT as it contains complicated information about whole genome sequencing (WGS). Study staff are encouraged to use the annotated Stage 2 consent resource to help guide them through the Stage 2 consent process (can be found on the Members Website).*

Please note: There are several videos that participants are required to view either prior to or during the consent process to ensure they understand genetic testing and the types of information it may (or may not) provide. These are linked in the annotated Stage 2 consent resource and are available on the RADIANT public website at: https://www.atypicaldiabetesnetwork.org/genetictesting.

A resource with helpful tips on performing remote consent can be found on the Members Website – Study Documents > Manual of Procedures > Stage 1 and Stage 2 MOP and Resources > Consenting Resources > 02. Telephone Consent Process to Obtain a Signed Consent Form

- Forms needed:
    - Forms are based on participant age and RADIANT stage – see Appendix 1
- Instructions:
    1. Discuss with participant if they would like you to mail them hard copies of the consent form ahead of time, or if they have access to a printer and can print them off.
        i. If mail requested – mail consent forms and schedule consent phone call for after the forms arrive
        ii. If print requested – email consent forms and schedule consent phone call
    2. Call participant (and parent/caregivers if needed). If the participant is a child (age 7-17 years old), ask to be put on speakerphone so that you can speak to the child and parent/caregiver at the same time.
    3. Explain what you are asking them to do for this stage of RADIANT and what is contained in the consent form. Show the participant the videos from the annotated consent form if they have not watched them already. Encourage them to ask you any questions they may have as you go through the form. When you finish explaining the form, ask them "what questions do you have for me?" After all questions have been answered, ask "do you want to proceed with participating in this study?"
        iii. If no → Thank them for speaking with you and update the Participant Status to "Withdrawn" with the reason for withdrawal (ex. did not agree to participate in Stage 2) in the RADIANT Members Website (see section 12.2 – Withdrawals and section 12.3.6 – How To Edit Participant Status).
        i. Record this interaction in the Contact Log.
        ii. If yes → Proceed
    4. Direct the participant to areas where they need to initial and/or sign
    5. Document consent process locally
    6. Provide prepaid FedEx label* for participant to mail consent form back to you

7. Once consent is received, consenter signs and dates on the last page. If your local site requires PI signature, ensure PI has signed as well.
8. Make a copy of the signed consent/assent forms and return the copy to the family
9. Enter consent information in RADIANT Members Website (see Section 13.3.6.2)
10. Proceed with remote specimen collection procedures – Participant is responsible for scheduling Quest visit.

*RADIANT FedEx account should only be used for approved RADIANT participant shipments:
Username: radiantstudy
Password: 2*YGaj.Cjedf42

5.2.4.2 Stage 2 Remote Specimen Collection#

Once the signed consent/assent form has been received by the Clinical Center, the local study coordinator will request a specimen kit containing the required collection tubes and written instructions to be mailed to the participant by the RADIANT Central Lab. This request is submitted via the RADIANT Members Website (see Section 13.3.6.3). The participant should follow the instructions on the paperwork in the kit in order to schedule a visit at Quest for their sample collection and prepare for the visit.

Please note that the kit will contain a cold pack. The participant will need to freeze this cold pack prior to their Quest visit, and they will need to bring the frozen cold pack with them to Quest on the day of their visit.

The blood samples will be obtained at a local Quest Diagnostics lab and shipped back to the RADIANT Central Lab.

The specimen collection kit will include specimen collection and shipping instructions for Quest Diagnostics. The kit will also contain a participant letter explaining the Stage 2 remote collection procedures (can be found on Members Website).

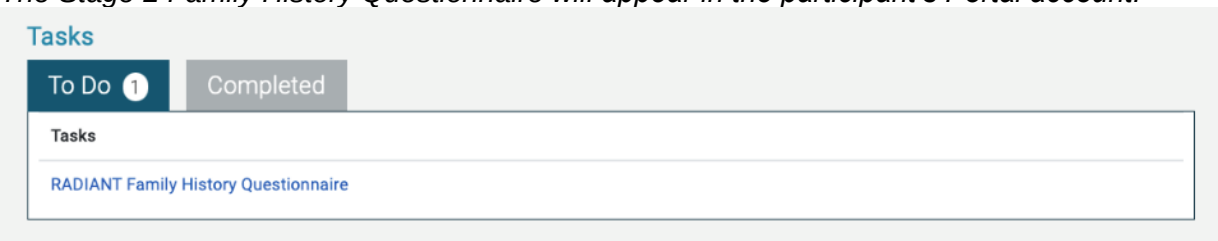
Please see section 4.2.7 for tips on scheduling at Quest.

5.2.4.3 Stage 2 Family History Questionnaire

After the Stage 2 consent information form is submitted, a Stage 2 Family History Questionnaire will appear in the Participant Portal 'to-do list'. The participant should complete this questionnaire prior to advancing to Stage 3. Site staff should follow up with the participant if the questionnaire remains incomplete and work with the participant to complete the questionnaire before (preferably), during, or immediately after the Stage 3 Standard Visit.

This questionnaire asks detailed questions about family history. Data from this questionnaire will be used to generate a pedigree which is reviewed by the Discovery Team after the Stage 3 Standard Visit.

The Stage 2 Family History Questionnaire will appear in the participant's Portal account:



5.2.5 STAGE 2 RETURN OF RESULTS

5.2.5.1 Return of Stage 2 Laboratory Results

There are no laboratory results that will be returned in Stage 2.

5.2.5.2 Returning Stage 2 Whole Genome Sequencing Results to the Participant#

CLIA-certified whole genome sequencing (WGS) will be completed at the Broad Institute. The Partners Laboratory for Molecular Medicine will perform the sequencing and issue the CLIA WGS report. This report will not contain any PHI – it will contain the participant study ID.

This report will be transferred to the DCC and shared with the RADIANT Genetic Counselor at the University of Maryland via the RADIANT Genetic Counseling Dashboard in the RADIANT Members Website.

Participants that agreed to receive the genetic results in the Stage 2 consent form will be invited to have a Genetic Counseling session with the RADIANT Genetic Counselor to discuss their results. The RADIANT Genetic Counselor will review the CLIA WGS report and then request that the participant's assigned clinical center schedules an appointment for the participant to virtually meet with the Genetic Counselor. The below automated email will be sent to the clinical center:

RADIANT
Rare and Atypical Diabetes Network

The following RADIANT participant is now ready to have an appointment scheduled with the genetics counselor:

Participant ID: 131572
Local ID: RAD-0127

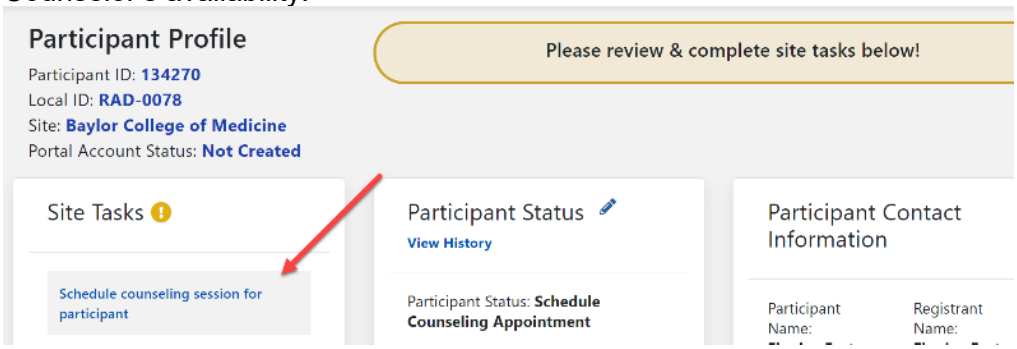
Next Steps:

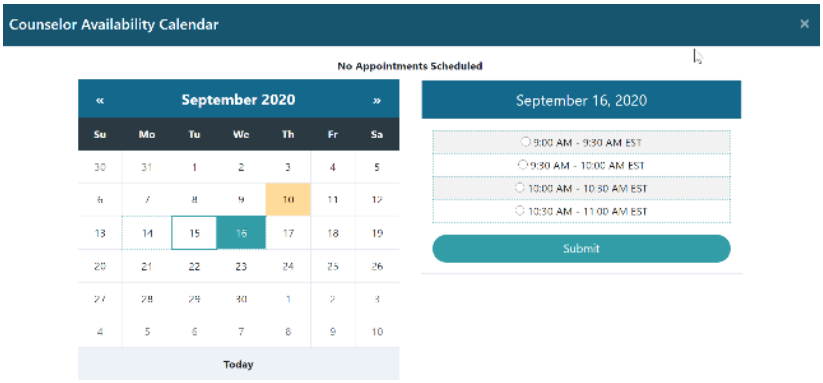
1. Login to the RADIANT Members Website to view the Participant Profile.
2. Contact participant to schedule a genetics counseling session at a date and time convenient for the participant. Available appointment times can be viewed by clicking on the "Schedule Genetics Counselor Appointment" link under the "Site Tasks" section of the participant profile.

If you have any questions, please contact RADIANT for assistance at Contact@AtypicalDiabetesNetwork.org.

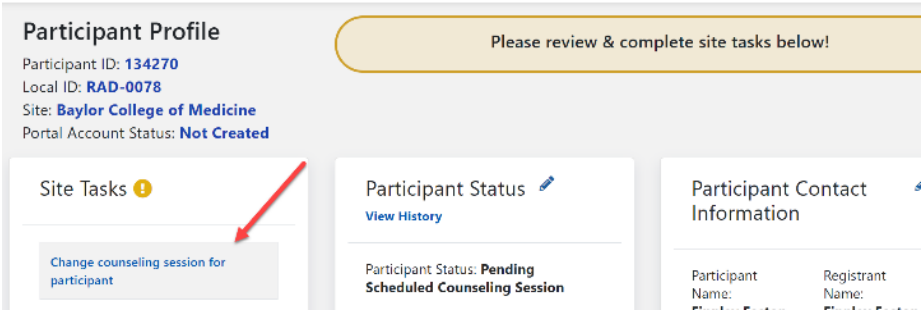
The Clinical Center team must then follow the procedure below to schedule the genetics counseling session:

1. Login to the RADIANT Members Website
2. Navigate to the Participant Profile (Section 13.3.6)
3. Click on the site task "Schedule counseling session for participant" to view the Genetic Counselor's availability.





4. Contact the participant to determine a date and time that both the Genetic Counselor and the participant are available. Inform the participant that the Genetic Counselor will call them on the phone at the scheduled time. If the participant prefers a Zoom call, please contact the RADIANT Genetic Counselor to determine feasibility.
5. Select the time in the “Counselor Availability Calendar” (see screenshot in step 3 above) and click Submit. The Genetic Counselor will be notified of the schedule session.
    a. If you need to change the session time, return to the Participant Profile and click the Site Task “Change counseling session for participant” to view the Genetic Counselor’s availability and schedule a different time.



Once the Clinical Center schedules the Genetic Counseling session, the Genetic Counselor will be notified. The Genetic Counselor will call the participant via phone (or Zoom, if requested by the participant and approved by the Genetic Counselor) at the scheduled time.

After the Genetic Counseling session, the Genetic Counselor will document in the RADIANT Members Website that the Genetic Counseling session was completed and will upload a results letter for the participant. The participant will be able to view the results letter in the RADIANT Participant Portal. The Clinical Center team will be able to view the results letter in the Study Details section of the Participant Profile in the RADIANT Members Website.

If the Genetic Counseling session cannot be completed (ex. the participant is a no-show at the scheduled time), the Genetic Counselor will submit a request to the Clinical Center to reschedule the Genetic Counseling session. The Clinical Center will receive the following email notification and must repeat the scheduling steps outlined above:

RADIANT
Rare and Atypical Diabetes Network

The following RADIANT participant's counseling session will need to be rescheduled:

Participant ID: 131604
Local ID: RAD-0159

Next Steps:

1. Login to the RADIANT Members Website to view the Participant Profile.
2. Contact participant to re-schedule their genetics counseling session at a date and time convenient for the participant. Available appointment times can be viewed by clicking on the "Schedule counseling session for participant" link under the "Site Tasks" section of the participant profile.

If you have any questions, please contact RADIANT for assistance at Contact@AtypicalDiabetesNetwork.org.

Genetic testing results will be reviewed by the Discovery Team – Genetics group on a regular basis.

- The study will only return variants related to atypical diabetes and (if the participant chooses) ACMG "secondary findings" genes. Variants in other genes will not be reported.
- Even though the researchers will be looking at all of a participant's DNA, it is possible that they will not find a genetic variant that is the cause of the participant's atypical diabetes.
- A negative result does not rule out a genetic cause or contribution to their diabetes.
- A positive result may not cause a change in diabetes treatment.
- A positive result may give unexpected information. A genetic variant that explains diabetes may also predict that someone is at risk for problems in a different body system.
- Sometimes the meaning of a positive result will be uncertain with regard to a participant's future health. We are still learning a lot about these genes.
- A positive result may mean that certain family members are at risk to develop diabetes (or other medical conditions related to the gene/disease at hand)
- We will not return variants of uncertain clinical significance (VUS) because we don't know what they mean

Secondary findings:

- Participants have the option to learn about gene variants that are not related to diabetes but may be important in managing or preventing other diseases. These are called "secondary findings".
- Learning of an increased risk for cancer or heart disease may be surprising or upsetting to some people. Knowing this information may provide opportunities to take action to reduce risk of disease (e.g., early mammograms for people at risk for breast cancer from *BRCA1* or *BRCA2* variants).
- Emphasize to parents that we will not give them information about their child's risk for adult-onset conditions. If the child turns 18 during the course of RADIANT, he or she can request this information.

Genetic Information Nondiscrimination Act (GINA) is a federal law passed in 2008 that aims to prevent health insurance or employment discrimination based on genetic information. Under GINA

- Health insurance companies and group plans may not request genetic information from this research

5.2.5.3 Returning Stage 2 Whole Genome Sequencing Results to the Healthcare Provider#

- **For Stage 2 consent versions 19Aug2022 and later:** If the participant consented to have WGS results (including both diabetes-related and secondary genetic results) returned to their healthcare provider in their Stage 2 consent form, the site that the participant is assigned to is responsible for faxing these results to the healthcare provider listed in the consent as outlined below:
  - If there is a reportable genetic finding, the RADIANT study team should share both the CAP/CLIA report AND the Genetic Counselor Letter with the provider.
  - If there are no reportable genetic findings, the RADIANT study team should share the Genetic Counselor Letter with the provider. (A CAP/CLIA report will not be issued if there are no reportable genetic findings.)

- **For Stage 2 consent versions prior to 19Aug2022:** Follow the instructions in the table below for the applicable scenario and email the project manager team with any questions: radiantteam@atypicaldiabetesnetwork.org

Scenario	Action Item
If there is a pathogenic/likely pathogenic genetic finding in RADIANT Stage 2 and a CAP/CLIA report is issued, AND the participant agrees for RADIANT to share their diabetes-related **and** secondary results with their provider:	The RADIANT study team should share both the CAP/CLIA report AND the Genetic Counselor Letter with the provider.
If there are no reportable genetic findings in RADIANT Stage 2 AND the participant agrees for RADIANT to share their diabetes-related **and** secondary results with their provider:	The RADIANT study team should share the Genetic Counselor Letter with the provider.
If the participant does not agree to share both their diabetes related **and** secondary results with their provider (regardless of whether or not there are reportable findings):	The RADIANT study team should not share any genetic findings with the provider. The participant may choose to share their report/letter with their provider on their own if desired.

6 FAMILY MEMBER PROCEDURES – SANGER OR WGS-TRIO

6.1 FAMILY MEMBER RECRUITMENT

If the RADIANT Discovery Team recommends that a proband's family members are enrolled in RADIANT, this decision will be recorded in the RADIANT Members Website and a new site task indicating that family member enrollment has been recommended will appear in Participant Profile for the proband in the RADIANT Members Website. A table detailing which family members have been recommended for enrollment and the type of enrollment (full participation beginning in Stage 1, Sanger Sequencing, or WGS-Trio) will also be included in the profile.

The RADIANT site must inform the proband of the recommendation and provide information for the proband to share with the recommended family members.

1. Use the IRB-approved family member recruitment letter templates to write a letter to the recommended family member. Note: The enrollment code referenced in the template is located in the family member enrollment table on the proband's Participant Profile in the Members Website.
2. Use the IRB-approved proband cover letter for family member recruitment to write a letter to the proband describing the recommendation and next steps.
3. Give the proband cover letter and family member recruitment letter(s) to the proband.
    a. ***Importantly, the site should <u>not</u> disclose any specific variant(s) arising from the Discovery Team review to the proband or family members at this time or during the consent process, as the clinical relevance of the variant and/or gene are not known at this time, and the variant has not undergone confirmation in a clinical laboratory. If the proband or family member asks, these points should be reiterated along with the fact that the variant may be disclosed in the future if the study reveals clinical relevance.***
4. The proband will share the family member recruitment letters(s) with the recommended family members.
5. The family members may contact the local study team with any questions.
    a. Family members recommended for full participation in RADIANT (beginning in Stage 1), may go to the RADIANT public website and complete the online consent form to proceed in the study (in the same manner as probands). When they complete the Stage 1 questionnaire, they will be

asked if they have an enrollment code (this question is in Section 1, the screening form). They must enter the enrollment code included in the family member recruitment letter.

b. Family members recommended for Sanger Sequencing or WGS-Trio will contact the local site to further discuss the study and consent. Upon consent, they will be prompted to set-up a portal account, complete the Family Member Questionnaire in the Portal, and have blood drawn for testing. (Additional details below.)

Site staff **should not** share information about the family members with the proband. For example, if a family member tells site staff that they do not want to participate in RADIANT, the proband should not be informed of this to maintain family member privacy.

6.2 FAMILY MEMBER ASSIGNMENT TO SITE FOR SANGER/WGS-TRIO AND AFFECTED/UNAFFECTED STATUS DETERMINATION

If a family member recommended for Sanger Sequencing or WGS Trio is interested in participating after receiving the RADIANT family member recruitment letter from the proband, they will reach out to the site to discuss the study and proceed with the consent process. The site should discuss the study with the participant, consent the participant using the appropriate family member consent form (and assent form as applicable), and determine if they are affected or unaffected (see definition below). This determination is required because the family member specimen collection kits are different for affected and unaffected family members.

Importantly, the site should not disclose any specific variant(s) arising from the Discovery Team review to the participant or family members at this time or during the consent process, as the clinical relevance of the variant and/or gene are not known at this time, and the variant has not undergone confirmation in a clinical laboratory. If the participant asks, these points should be reiterated along with the fact that the variant may be disclosed in the future if the study reveals clinical relevance.

(1) Site should ask family member *participants if they have ever (past or current) had a diagnosis of prediabetes, diabetes, or gestational diabetes*.

Stage 2 family member definitions of affected and unaffected:

- **UNAFFECTED family member:** someone who *does not* self-report a diagnosis (past or current) of prediabetes, diabetes, or gestational diabetes
  - Ex: A family member who had a random high blood sugar once, but no formal diagnosis of prediabetes/diabetes/gestational diabetes, would fall into the unaffected category.
  - These participants will complete blood collection for fasting glucose, HbA1c, and DNA.
- **AFFECTED family member:** someone who self-reports a diagnosis (past or current) of prediabetes, diabetes, or gestational diabetes
  - These participants will complete blood collection for DNA only.

(2) Sites should also assess whether the family member participant would prefer an in-person or a remote visit.

This conversation and the resulting affected/unaffected determination as well as in-person/remote preference should be documented in the Contact Log. Sites should then proceed with the steps noted below for Sanger or WGS-Trio, as appropriate.

6.3 FAMILY MEMBER PROCEDURES – SANGER SEQUENCING OVERVIEW

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 by the Discovery Team in Stage 3.

Consent for these family members will support blood sampling for DNA extraction for Sanger sequencing and, for unaffected participants only, a fasting blood glucose measurement and HbA1c to confirm the individual's reported "unaffected" status. If the family member is unable to provide a blood sample for DNA extraction, collection of saliva would be considered.

6.3.1 FAMILY MEMBER SANGER INFORMED CONSENT AND ASSENT PROCESS (IN-PERSON OR REMOTE VISIT)#

Consent will be obtained <u>remotely</u> for either an in-person or remote Family member Sanger visit. This is because the sample collection kit needs to be assigned to a family member participant prior to being requested by the site and shipped out by the Central Lab.**

- Sites are required to follow local institutional guidelines. For example, if your local site requires an in-person consent process prior to in-person procedures, the site will need to remotely consent the family member participant first (so that the kit can be appropriately assigned by the Central Lab), and then consent the family member participant again upon their arrival to the clinic for their in-person Family member Sanger visit. The second consent form information can be entered into the Stage 2 Family Member Sanger Consent Information form in the Participant Profile. Email radiantteam@atypicaldiabetesnetwork.org if you have questions about this process.

The consenting Clinical Center will mail a blank consent/assent form to the family member participant and schedule a time to discuss the consent either by telephone or if necessary, web-based video or audio call (such as Skype, Webex, FaceTime, etc) to discuss the Stage 2 Family Member Sanger consent. The family member participant will be asked to sign the consent and mail it back to the consenting Clinical Center. The family member participant must provide informed consent and assent (if applicable) for the Stage 2 Family Member Sanger Procedures <u>before</u> any Stage 2 Family Member Sanger Procedures occur.

A resource with helpful tips on performing remote consent can be found on the Members Website – Study Documents > Manual of Procedures > Stage 1 and Stage 2 MOP and Resources > Consenting Resources > 02. Telephone Consent Process to Obtain a Signed Consent Form

- Forms needed:
  - Forms are based on family member participant age and RADIANT stage – see Appendix 1
- Instructions:
  1. Discuss with family member participant if they would like you to mail them hard copies of the consent form ahead of time, or if they have access to a printer and can print them off.
     i. If mail requested – mail consent/assent forms and schedule consent phone call for after the forms arrive
     ii. If print requested – email consent/assent forms and schedule consent phone call
  2. Call family member participant (and parent/caregivers if needed). If the participant is a child (age 7-17 years old), ask to be put on speakerphone so that you can speak to the child and parent/caregiver at the same time.
  3. Explain what you are asking them to do for this stage of RADIANT and what is contained in the consent form. Encourage them to ask you any questions they may have as you go through the form. When you finish explaining the form, ask them "what questions do you have for me?" After all questions have been answered, ask "do you want to proceed with participating in this study?"
     iv. If no → Thank them for coming, check if they need parking validation and update the Participant Status to "Withdrawn" with the reason for withdrawal (ex. did not agree to participate in Stage 2 Family Member Sanger) in the RADIANT Members Website (see

section 12.2 – Withdrawals and section 12.3.6 – How To Edit Participant Status). Record this interaction in the Contact Log.

v. If yes → Proceed

vi. Reminder: Do not disclose any specific variant(s) arising from the Discovery Team review to the participant/family members at this time, as the clinical relevance of the variant and/or gene are not known at this time, and the variant has not undergone confirmation in a clinical laboratory. If the participant/family member asks, these points should be reiterated along with the fact that the variant may be disclosed in the future if the study reveals clinical relevance.

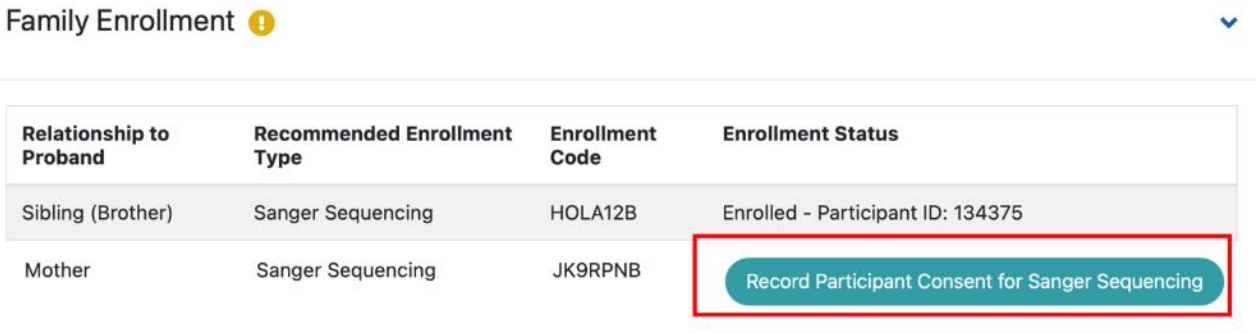
4. Direct the family member participant to areas where they need to initial and/or sign
5. Document consent process locally
6. Provide prepaid FedEx label* for family member participant to mail consent form back to you
7. Once consent is received, consenter signs and dates on the last page. If your local site requires PI signature, ensure PI has signed as well.
8. Make a copy of the signed consent/assent forms and return the copy to the family member participant
9. Enter consent information in RADIANT Members Website per directions below
10. Proceed with either remote or in-person specimen collection procedures. If family member participant chooses remote visit, family member participant is responsible for scheduling Quest visit.

*RADIANT FedEx account should only be used for approved RADIANT participant shipments:
Username: radiantstudy
Password: 2*YGaj.Cjedf42

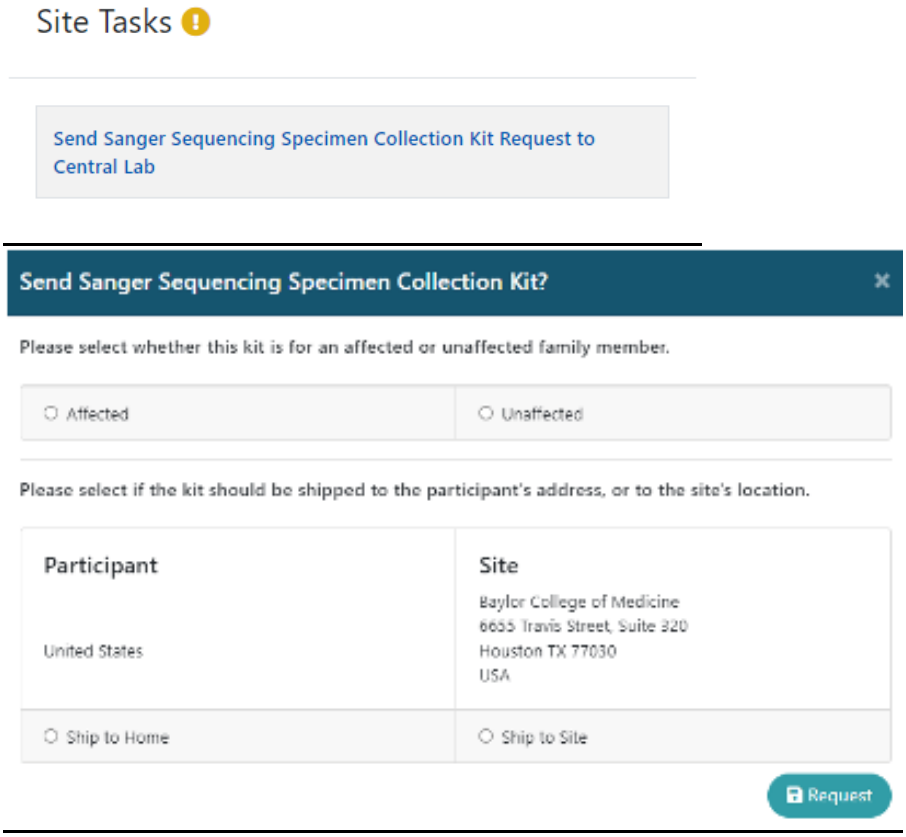
It would be possible to obtain in-person consent instead of remote consent, if desired, **however, the participant would then need to schedule another in-person or Quest visit at least 7 days later. This is to allow time for the site to enter the consent information and request the collection kit to be sent.

Documenting consent information and Participant Portal creation for family member participants

1. Family member participant consent information will be entered by navigating to the **proband's** Participant Profile, scrolling down to the Family Member Enrollment table, and selecting "Record participant consent for Sanger Sequencing"



2. Complete the RADIANT Stage 2 Family Member Sanger Consent & Contact Information form
3. After submission of the form, you will be taken to the family member participant's newly created Participant Profile page. You may request the appropriate kit by following the prompts in the Site Tasks list.



4. Follow the procedures for in-person or remote Family member Sanger visit in the sections below.

6.3.2 FAMILY MEMBER SANGER IN-PERSON VISIT PROCEDURE#

For family member participants that prefer an in-person visit, RADIANT site staff should consent the participant **remotely** (see section 6.3.1) and then work with the family member to schedule an in-person visit. Family member Sanger visits may be scheduled Monday-Thursday and must be shipped on the day of collection.

- UNAFFECTED FAMILY MEMBER PARTICIPANTS WILL NEED TO FAST FOR THIS VISIT. Fasting = not drink or eat anything other than water for the 10 hours prior to the visit. For this reason, we recommend scheduling unaffected family member Sanger visits for as early in the morning as possible to limit participant discomfort from fasting.

Be mindful of scheduling around holidays. See the Family Member Specimen MOPs for full information on scheduling near holidays.

When scheduling the Family member Sanger in-person visit with the participant, study coordinators must go over the following illness instructions:

- If you feel sick during the 7 days prior to your family member Sanger in-person visit, please call me to reschedule this visit. Feeling sick includes cold, flu, fever, vomiting, diarrhea, or any physical stress. This also includes chills, cough, shortness of breath, difficulty breathing, fatigue, muscle or body aches, headache, recent loss of taste or smell, sore throat, congestion, or nausea.
- Sites must also follow any local institutional guidelines for screening participants for COVID-19 symptoms prior to an in-person visit. Sites should also follow any other local COVID-19 procedures such as mandatory masking, temperature checks, etc.

It will take the Central Lab approximately 2 days for a kit to be prepared, sent, and received by the site. Local study coordinators need to give at least 7 days between requesting kit and having a visit for Family member Sanger collection.

*Study coordinators must send the family member participant the Stage 2 Sanger-WGS Trio Family Member Clinic Visit site instruction letter (can be found on Members Website) when they schedule a Family Member Sanger in-person visit.

6.3.2.1 Family Member Sanger Specimen Collection at Clinical Center

After the Family Member Sanger in-person visit has been scheduled, the site staff must request a specimen collection kit to be sent from the Central Lab to the site (see Section 6.3.1). It will take the Central Lab approximately 2 days for a kit to be prepared, sent, and received by the local study site. Local study coordinators need to give at least 7 days between requesting kit and having a visit for Family Member Sanger sample collection.

- Sites must select whether they need an affected kit or unaffected kit – see section 6.1 for more information.
  - UNAFFECTED FAMILY MEMBER PARTICIPANTS WILL NEED TO FAST FOR THIS VISIT. Fasting = not drink or eat anything other than water for the 10 hours prior to the visit.
    - Unaffected family member participant sample collection = sample for DNA extraction for Sanger sequencing, fasting glucose, and HbA1c
  - Affected family members do not need to fast for this visit.
    - Affected family member participant sample collection = sample for DNA extraction for Sanger sequencing

*Study coordinators must send the family member participant the Sanger-WGS Trio Family Member Clinic Visit site instruction letter (can be found on Members Website) when they schedule a Family Member Sanger in-person visit.

Blood will be collected for Family Member Sanger tests per protocol and shipped per protocol to the central RADIANT lab. Samples will be processed at the central RADIANT lab.

See Family Member Affected Specimen Collection & Processing MOP or Family Member Unaffected Specimen Collection & Processing MOP for details on sample collection and shipment.

6.3.2.2 Family Member Sanger Compensation#

Family member participants who come for an in-person visit will either 1) be given pre-paid parking validation passes or 2) be reimbursed for the cost of their parking. Providing participants with a pre-paid parking validation pass is preferred.

Pre-paid passes should be purchased by the local site. The local site should then send this receipt to their respective Administrative Core for reimbursement (see Section 2.3.1 for Administrative Cores). The same reimbursement process should be employed for participants who are reimbursed for the cost of their parking.

6.3.3 FAMILY MEMBER SANGER REMOTE VISIT PROCEDURE#

If a family member participant cannot come to a RADIANT Clinical Center for an in-person Family Member Sanger visit, consent and specimen collection can be obtained remotely per the procedures below (see Section 6.3.1 for information on consenting process).

6.3.3.1 Family Member Sanger Remote Specimen Collection#

Once the signed consent/assent form has been received by the Clinical Center, the local study coordinator will request a specimen kit containing the required collection tubes and written instructions to be mailed to the family member participant by the RADIANT Central Lab (see Section 6.3.1). The participant should follow the instructions on the paperwork in the kit in order to schedule a visit at Quest for their sample collection and prepare for the visit.

- Sites must select whether they need an affected kit or unaffected kit – see section 6.1 for more information.
  - UNAFFECTED FAMILY MEMBER PARTICIPANTS WILL NEED TO FAST FOR THIS VISIT. Fasting = not drink or eat anything other than water for the 10 hours prior to the visit.
    - Unaffected family member participant sample collection = sample for DNA extraction for Sanger sequencing, fasting glucose, and HbA1c
  - Affected family members do not need to fast for this visit.
    - Affected family member participant sample collection = sample for DNA extraction for Sanger sequencing

The family member participant's kit will contain instructions for how to schedule a Quest visit and whether they need to fast (unaffected) or not (affected) for this Quest visit. *Please note that the kit will contain a cold pack. The participant will need to freeze this cold pack prior to their Quest visit, and they will need to bring the frozen cold pack with them to Quest on the day of their visit.*

The blood samples will be obtained at a local Quest Diagnostics lab and shipped back to the RADIANT Central Lab.

Please see section 4.2.7 for tips on scheduling at Quest.

6.3.3.2 Family Member Questionnaire

After the Stage 2 consent information form is submitted, the family member participant will be prompted to set-up a Participant Portal account and the Family Member Questionnaire will appear in the Participant Portal 'to-do list'. The family member participant should complete this form prior to advancing to Stage 3. Site staff should follow up with the participant if the questionnaire remains incomplete.

This form asks detailed questions about things such as family member participant's demographics and medical history.

6.4 FAMILY MEMBER PROCEDURES – WGS-TRIO OVERVIEW

Full, iterative analysis of WGS, RNA, metabolomic, and deep phenotyping data may yield no clear candidate gene variants in the index case. In this scenario, the Discovery Team may in highly selected cases recommend trio-Whole Genome Sequencing (WGS) (proband + both parents) as an additional analytic step to narrow down the variants of interest. This recommendation will be made for approximately 5 participants per year depending on throughput and budget. Parents would consent, and blood samples would be collected for DNA extraction.

Consent for these family members will support blood sampling for DNA extraction for WGS and, for unaffected participants only, a fasting blood glucose measurement and HbA1c to confirm the individual's reported "unaffected" status. If the family member is unable to provide a blood sample for DNA extraction, collection of saliva would be considered.

6.4.1 FAMILY MEMBER WGS-TRIO INFORMED CONSENT AND ASSENT PROCESS (IN-PERSON OR REMOTE VISIT)#

Consent will be obtained remotely for either an in-person or remote Family member WGS-Trio visit. This is because the sample collection kit needs to be assigned to a family member participant prior to being requested by the site and shipped out by the Central Lab.**

- Sites are required to follow local institutional guidelines. For example, if your local site requires an in-person consent process prior to in-person procedures, the site will need to remotely consent the family member participant first (so that the kit can be appropriately assigned by the Central Lab), and then consent the family member participant again upon their arrival to the clinic for their in-person Family member WGS-Trio visit. The second consent form information can be entered into the Stage 2 Family Member WGS-Trio Consent Information form in the Participant Profile. Email radiantteam@atypicaldiabetesnetwork.org if you have questions about this process.

The consenting Clinical Center will mail a blank consent/assent form to the family member participant and schedule a time to discuss the consent either by telephone or if necessary, web-based video or audio call (such as Skype, Webex, FaceTime, etc) to discuss the Stage 2 Family Member WGS-Trio consent. The family member participant will be asked to sign the consent and mail it back to the consenting Clinical Center. The family member participant must provide informed consent and assent (if applicable) for Family Member WGS-Trio before any Stage 2 Family Member WGS-Trio procedures occur.

A resource with helpful tips on performing remote consent can be found on the Members Website – Study Documents > Manual of Procedures > Stage 1 and Stage 2 MOP and Resources > Consenting Resources > 02. Telephone Consent Process to Obtain a Signed Consent Form

- Forms needed:
  - Forms are based on family member participant age and RADIANT stage – see Appendix 1
- Instructions:
  1. Discuss with family member participant if they would like you to mail them hard copies of the consent form ahead of time, or if they have access to a printer and can print them off.
     i. If mail requested – mail consent forms and schedule consent phone call for after the forms arrive
     ii. If print requested – email consent forms and schedule consent phone call
  2. Call family member participant (and parent/caregivers if needed). If the participant is a child (age 7-17 years old), ask to be put on speakerphone so that you can speak to the child and parent/caregiver at the same time.
  3. Explain what you are asking them to do for this stage of RADIANT and what is contained in the consent form. Encourage them to ask you any questions they may have as you go through the form. When you finish explaining the form, ask them “what questions do you have for me?” After all questions have been answered, ask “do you want to proceed with participating in this study?”
     i. If no → Thank them for coming, check if they need parking validation and update the Participant Status to “Withdrawn” with the reason for withdrawal (ex. did not agree to participate in Stage 2 Family Member Sanger) in the RADIANT Members Website (see section 12.2 – Withdrawals and section 12.3.6 – How To Edit Participant Status). Record this interaction in the Contact Log.
     ii. If yes → Proceed
  4. Direct the family member participant to areas where they need to initial and/or sign
  5. Document consent process locally
  6. Provide prepaid FedEx label* for family member participant to mail consent form back to you
  7. Once consent is received, consenter signs and dates on the last page. If your local site requires PI signature, ensure PI has signed as well.
  8. Make a copy of the signed consent/assent forms and return the copy to the family member participant
  9. Enter consent information in RADIANT Members Website per directions below

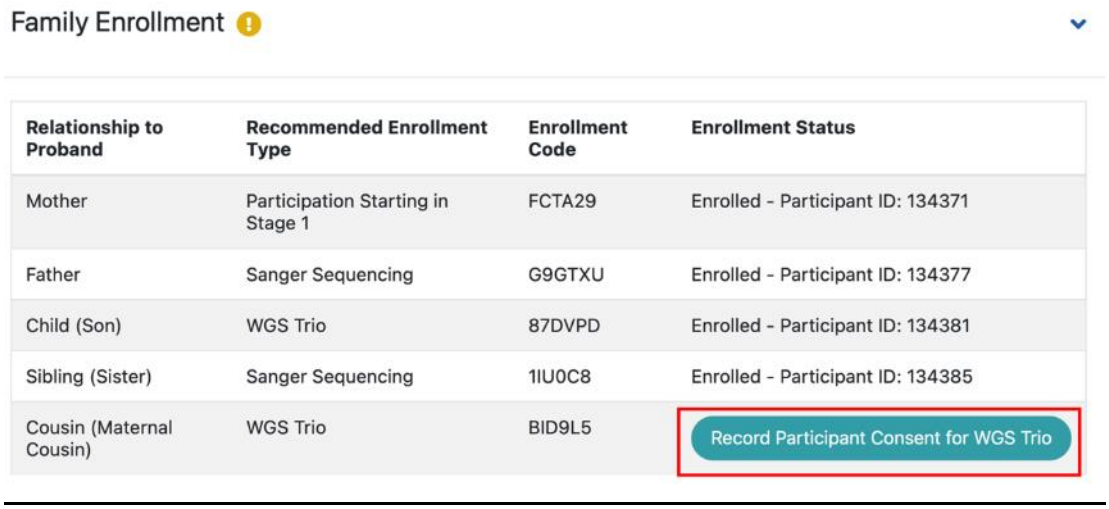
10. Proceed with either remote or in-person specimen collection procedures. If family member participant chooses remote visit, family member participant is responsible for scheduling Quest visit.

*RADIANT FedEx account should only be used for approved RADIANT participant shipments:
Username: radiantstudy
Password: 2*YGaj.Cjedf42

It would be possible to obtain in-person consent instead of remote consent, if desired, **however, the participant would then need to schedule another in-person or Quest visit at least 7 days later. This is to allow time for the site to enter the consent information and request the collection kit to be sent.

Documenting consent information and Participant Portal creation for family member participants

1. Family member participant consent information will be entered by navigating to the **proband's** Participant Profile, scrolling down to the Family Member Enrollment table, and selecting "Record participant consent for WGS Trio"



2. Complete the RADIANT Stage 2 Family Member WGS Trio Consent & Contact Information form
3. After submission of the form, you will be taken to the family member participant's newly created Participant Profile page. You may request the appropriate kit by following the prompts in the Site Tasks list.
4. Follow the procedures for in-person or remote Family member WGS-Trio visit in the sections below.

6.4.2 FAMILY MEMBER WGS-TRIO IN-PERSON VISIT PROCEDURE#

For family member participants that prefer an in-person visit, RADIANT site staff should consent the participant **remotely** (see section 6.4.1) and then work with the family member to schedule an in-person visit. Family member WGS-Trio visits may be scheduled Monday-Thursday and must be shipped on the day of collection.

- UNAFFECTED FAMILY MEMBER PARTICIPANTS WILL NEED TO FAST FOR THIS VISIT. Fasting = not drink or eat anything other than water for the 10 hours prior to the visit. For this reason, we recommend scheduling unaffected family member WGS-Trio visits for as early in the morning as possible to limit participant discomfort from fasting.

Be mindful of scheduling around holidays. See the Family Member Specimen MOPs for full information on scheduling near holidays.

When scheduling the Family member WGS-Trio in-person visit with the participant, study coordinators must go over the following illness instructions:

- If you feel sick during the 7 days prior to your Family member WGS-Trio in-person visit, please call me to reschedule this visit. Feeling sick includes cold, flu, fever, vomiting, diarrhea, or any physical stress. This also includes chills, cough, shortness of breath, difficulty breathing, fatigue, muscle or body aches, headache, recent loss of taste or smell, sore throat, congestion, or nausea.
- Sites must also follow any local institutional guidelines for screening participants for COVID-19 symptoms prior to an in-person visit. Sites should also follow any other local COVID-19 procedures such as mandatory masking, temperature checks, etc.

It will take the Central Lab approximately 2 days for a kit to be prepared, sent, and received by the site. Local study coordinators need to give at least 7 days between requesting kit and having a visit for Stage 2 family member WGS-Trio collection.

*Study coordinators must send the family member participant the Sanger-WGS Trio Family Member Clinic Visit site instruction letter (can be found on Members Website) when they schedule a Family Member WGS-Trio in-person visit.

6.4.2.1 Family Member WGS-Trio Specimen Collection at Clinical Center

After the Family Member WGS-Trio in-person visit has been scheduled, the site staff must request a specimen collection kit to be sent from the Central Lab to the site (see Section 6.4.1). It will take the Central Lab approximately 2 days for a kit to be prepared, sent, and received by the local study site. Local study coordinators need to give at least 7 days between requesting kit and having a visit for Family Member WGS-Trio sample collection.

- Sites must select whether they need an affected kit or unaffected kit – see section 6.1 for more information.
  - UNAFFECTED FAMILY MEMBER PARTICIPANTS WILL NEED TO FAST FOR THIS VISIT. Fasting = not drink or eat anything other than water for the 10 hours prior to the visit.
    - Unaffected family member participant sample collection = sample for DNA extraction for WGS-Trio sequencing, fasting glucose, and HbA1c
  - Affected family members do not need to fast for this visit.
    - Affected family member participant sample collection = sample for DNA extraction for WGS-Trio sequencing

*Study coordinators must send the family member participant the Sanger-WGS Trio Family Member Clinic Visit site instruction letter (can be found on Members Website) when they schedule a Family Member WGS-Trio in-person visit.

Blood will be collected for Family Member WGS-Trio tests per protocol and shipped per protocol to the central RADIANT lab. Samples will be processed at the central RADIANT lab.

See Family Member Affected Specimen Collection & Processing MOP or Family Member Unaffected Specimen Collection & Processing MOP for details on sample collection and shipment.

6.4.2.2 Family Member WGS-Trio Compensation#

Family member participants who come for an in-person visit will either 1) be given pre-paid parking validation passes or 2) be reimbursed for the cost of their parking. Providing participants with a pre-paid parking validation pass is preferred.

Pre-paid passes should be purchased by the local site. The local site should then send this receipt to their respective Administrative Core for reimbursement (see Section 2.3.1 for Administrative Cores). The same reimbursement process should be employed for participants who are reimbursed for the cost of their parking.

6.4.3 FAMILY MEMBER WGS-TRIO REMOTE VISIT PROCEDURE#

If a family member participant cannot come to a RADIANT Clinical Center for an in-person Family Member WGS-Trio visit, consent and specimen collection can be obtained remotely per the procedures below (see Section 6.4.1 for information on consenting process).

6.4.3.1 Family Member WGS-Trio Remote Specimen Collection#

Once the signed consent/assent form has been received by the Clinical Center, the local study coordinator will request a specimen kit containing the required collection tubes and written instructions to be mailed to the family member participant by the RADIANT Central Lab – see Section 6.4.1. The participant should follow the instructions on the paperwork in the kit in order to schedule a visit at Quest for their sample collection and prepare for the visit.

- Sites must select whether they need an affected kit or unaffected kit – see section 6.1 for more information.
  - UNAFFECTED FAMILY MEMBER PARTICIPANTS WILL NEED TO FAST FOR THIS VISIT. Fasting = not drink or eat anything other than water for the 10 hours prior to the visit.
    - Unaffected family member participant sample collection = sample for DNA extraction for WGS-Trio sequencing, fasting glucose, and HbA1c
  - Affected family members do not need to fast for this visit.
    - Affected family member participant sample collection = sample for DNA extraction for WGS-Trio sequencing

The family member participant's kit will contain instructions for how to schedule a Quest visit and whether they need to fast (unaffected) or not (affected) for this Quest visit. *Please note that the kit will contain a cold pack. The participant will need to freeze this cold pack prior to their Quest visit, and they will need to bring the frozen cold pack with them to Quest on the day of their visit.*

The blood samples will be obtained at a local Quest Diagnostics lab and shipped back to the RADIANT Central Lab.

Please see section 4.2.7 for tips on scheduling at Quest.

6.5 FAMILY MEMBER SANGER OR WGS-TRIO RETURN OF RESULTS

For Family Member Sanger, testing will be performed on a research-basis at Baylor College of Medicine. In rare circumstances, a CLIA-confirmation of a research finding may be requested. If that CLIA result was likely pathogenic or pathogenic, and the participant opted to receive results in their consent form, the CLIA report would be returned to the RADIANT participant in the same way that probands receive results – see section 5.2.5.2.

For Family Member WGS-Trio, participants may receive diabetes findings (less likely as WGS-Trio is only done in situations where the proband's WGS was unrevealing) or secondary findings if they are likely pathogenic or pathogenic and they opted to receive results in their consent form. These results would be returned to the RADIANT participant in the same way that probands receive results – see section 5.2.5.2.

7 RECONSENTING PEDIATRIC PARTICIPANTS#

When RADIANT pediatric participants turn 18 years old, they will need to be reconsented to continue participation as an adult.

It is the responsibility of whichever site the participant is assigned to at the time of their 18th birthday to perform the reconsent. They should be reconsented for whatever Stage they are currently in.

Reminders from the Data Coordinating Center: An email reminder will be sent from the DCC to each site to indicate when a participant will be turning 18 the following month:

RADIANT
Rare and Atypical Diabetes Network

The following RADIANT participants at your site will turn 18 years old in February:

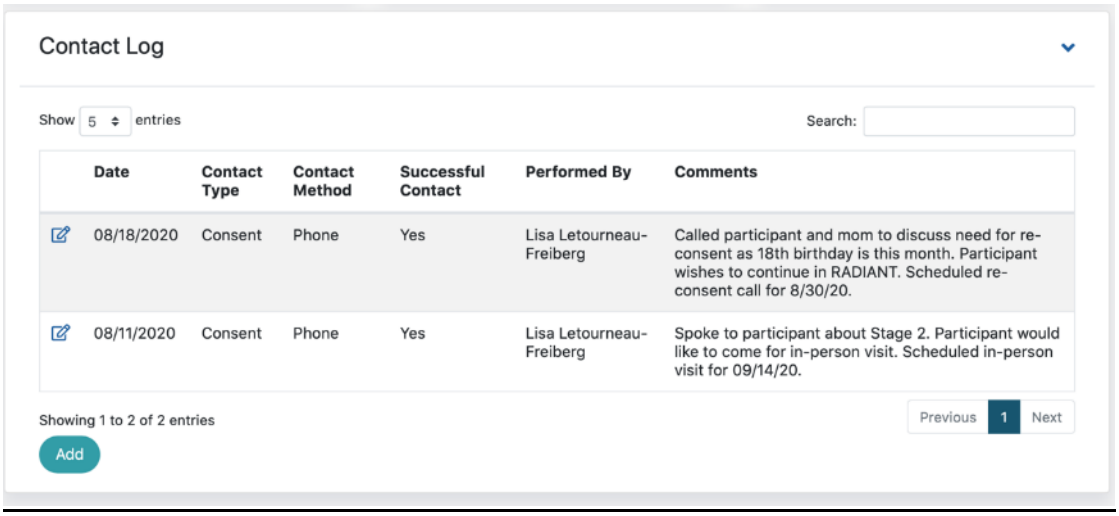
134253

Please remember to reconsent these participants after they turn 18 years old and enter the consent information on the Participant Profile in the RADIANT Members Website accordingly.

Please email the RADIANT DCC team at Contact@AtypicalDiabetesNetwork.org if you have any questions.

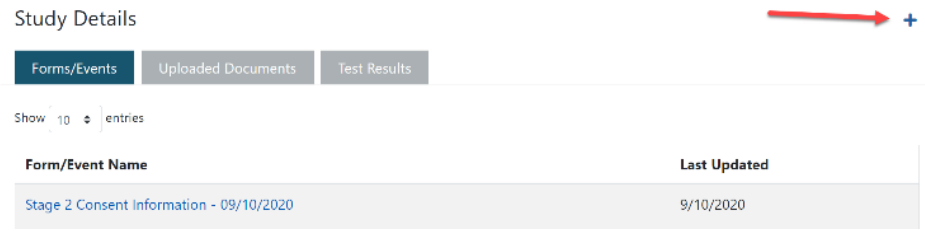
Study coordinators should reach out to those participants who are about to turn 18 and make a plan for reconsent.

1. Review email from DCC of participant that is turning 18 at your site
2. Connect with the participant and their parents when they are still 17 to explain that, after their 18th birthday, they will need to reconsent as an adult if they wish to continue participating in RADIANT. Document this interaction in the Contact Log in the Participant Profile.

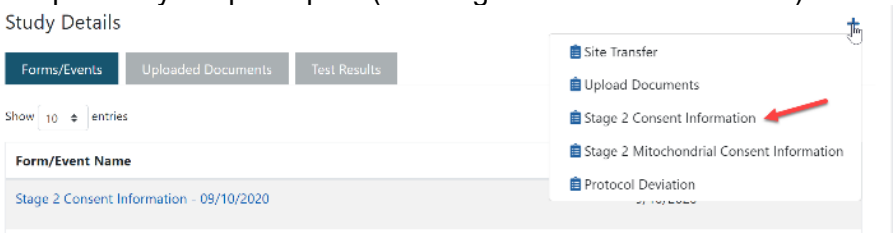


3. If the participant wishes to continue, schedule a reconsent appointment (see details on remote consenting for Stage 2 for additional information) on or after their 18th birthday. Document this interaction in the Contact Log in the Participant Profile.
4. When the newly signed consent form is received back from the participant, record the Consent Information in the Participant Profile.
    a. Scroll down to the Study Details section of the page.

b. Click the plus sign on the right side of the section, to open the dropdown menu of PRN forms.



c. Click the consent information form that corresponds to the type of consent completed by the participant (ex. Stage 2 consent information).



d. Complete and submit the consent information form.

8 PROCESS FOR PARTICIPANTS WHO REQUIRE LEGALLY AUTHORIZED REPRESENTATIVE

Participants who are 18 years old or older who are unable to consent for themselves may participate in RADIANT with the support of a legally authorized representative (LAR).

Stage 1 – The Stage 1 consent form has a space for the signature of a LAR. If the LAR completes an online version of the Stage 1 consent form, the participant record will be noted as a 'screen pause' until it can be reviewed and confirmed by a Project Manager at a lead site. The Project Manager will notify the DCC if the participant's status should be update to screen pass.

Stage 2 – The site consenting the participant for Stage 2 would require a local consent form with a LAR signature line prior to enrolling anyone that requires an LAR. If your consent needs to be modified to include an LAR signature block, please email radiantteam@atypicaldiabetesnetwork.org.

An LAR will be used in the event one of the following occurs:

1. It has been documented in the participant's medical record that the individual lacks the capacity to make the decision to participate in the proposed study. This documentation could be by either the participant's current or previous treating physician or by an investigator of the research site where the participant is enrolled.
2. The individual has been ruled incompetent by a court of law and has assigned medical decision-making capacity to someone other than the participant.

An assessment (either in-person or remotely by teleconference) of the participant is required in order to properly assess cognitive status to determine if an LAR signature is required. The site investigator is responsible for assessing the appropriate consenting procedures on an individual basis. For those that require an LAR there may be an additional opportunity for the participant to either sign an assent document or alternatively a verbal assent. The site investigator or other consenting site personnel will discuss the study with both the LAR and the participant and depending on the capacity of the participant will document the consent accordingly.

A participant's decisional capacity should be reassessed during each stage of the study to ascertain whether the LAR requirements are still being met. Those with a fluctuating decisional making capacity should be consented with procedures that are appropriate at the time of the assessment. This may mean that a different

combination of consent/assent/verbal assent is used at varying points throughout the study for an individual participant. A summary of the assessment and subsequent consent process should be documented in the participant's research record.

9 PROTOCOL DEVIATION REPORTING#

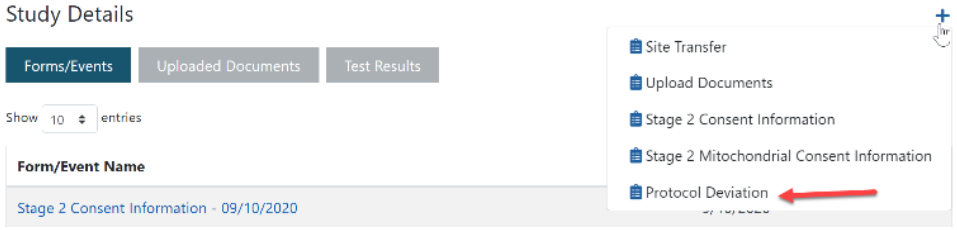
A protocol deviation occurs when the activities in a study diverge from the IRB-approved protocol.

Any protocol deviations will be documented in the Members Website. If a protocol deviation was also an adverse event, both forms should be completed.

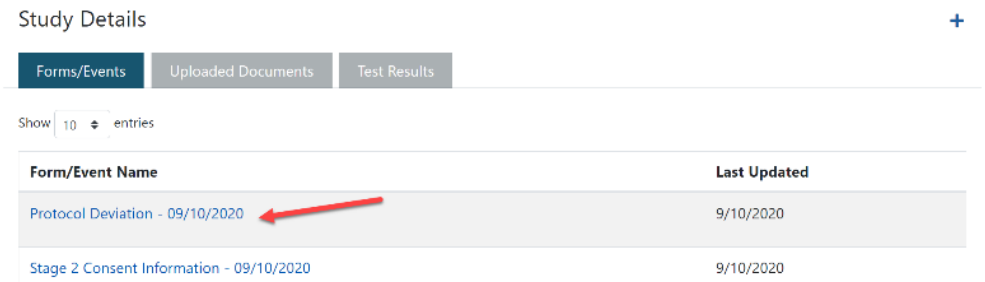
Sites must also adhere to their local IRB reporting requirements for protocol deviations, if needed.

Procedure:

1. Study staff complete paper source.
2. Study staff complete and submit online protocol deviation form in RADIANT Members Website.
   a. Login to the RADIANT Members Website
   b. Navigate to the Participant Profile (section 13.3.6)
   c. Scroll down to the Study Details section.
   d. Click the plus sign in the upper right part of Study Details Section.
   e. Click "Protocol Deviation" to open the protocol deviation form.



   f. Complete the protocol deviation form and click "Submit" at the bottom of the form.
   g. The completed form will be listed in the Study Details section, Forms/Events tab. Click the name of the form to open and view/edit the form if needed.



3. The RADIANT Protocol Oversight Committee will review and adjudicate these deviations on a monthly basis.

10 ADVERSE EVENT REPORTING#

Protocol-related adverse events (AE), events that are associated with study procedures, will be documented and reported.

Examples of reportable AEs that are associated with study procedures include:

- Dizziness after study blood draw
- Anxiety attack during MRI

- Seizure when fasting for Insulin Tolerance Test
- Allergic reaction to lidocaine injection during skin biopsy
- Substantial distress related to results disclosed to a subject, such as those leading to absenteeism or major depression episode
- Hyperglycemic coma, DKA, or requiring insulin for IVGTT, hyperglycemic clamp, graded glucose infusion, MMT long
- Hypoglycemia for hyperinsulinemic-euglycemic clamp, 2-step hyperinsulinemic-euglycemic clamp, MMT long
- Claustrophobia for brain or liver MRI
- Bleeding, infection, pain, or scarring for biopsies

AEs related to diabetes or progression of diabetes will not be solicited or reported. Examples of these non-reportable AEs include:

- Hyperglycemia and/or hypoglycemia in a participant with diabetes that occurs when a study procedure is not being performed

All AEs related to study procedures will be recorded on local source documents regardless of severity. Only AEs that meet the following CTCAE grading criteria AND are related to study procedures will be reported on a standardized electronic case report form via the RADIANT Members Website:

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

Reported AEs will be reviewed by an independent safety monitor (ISM).

Grading: Grading will be consistent with the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf).

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disability; limiting self care ADL**.
Grade 4: Life-threatening consequences; urgent intervention indicated.
Grade 5: Death related to AE.

*Information on ADL can be found in the CTCAE link above.

CTCAE Grading for Hypoglycemia:

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of glucose in the blood.					

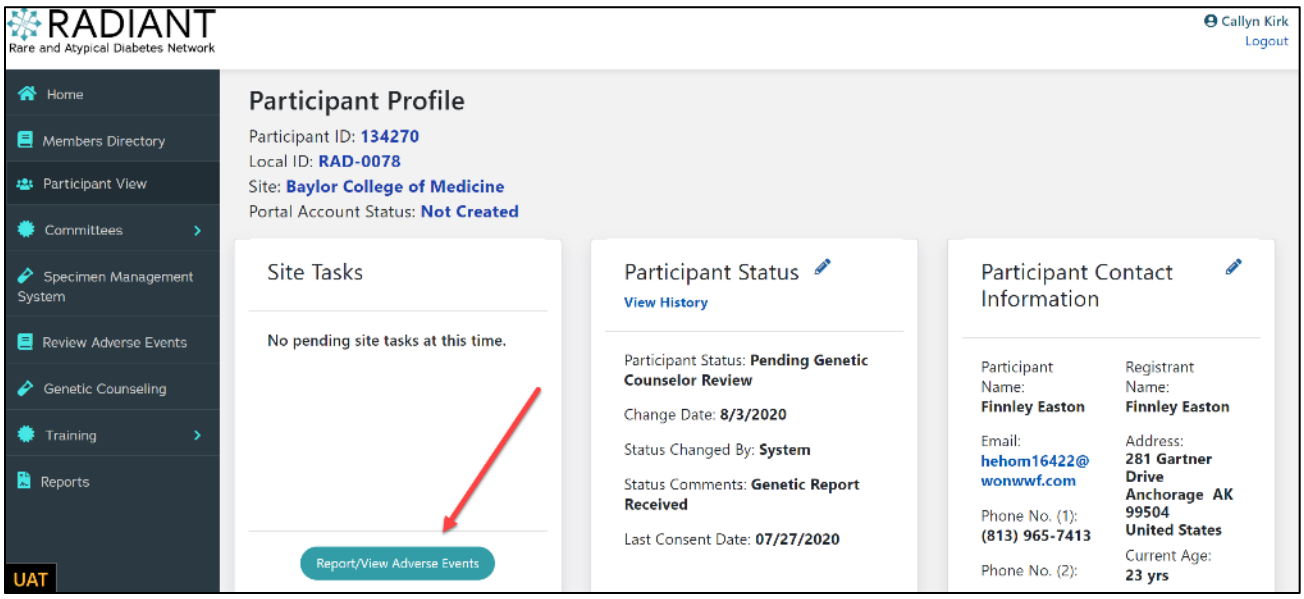
CTCAE Grading for Hyperglycemia:

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hyperglycemia	Abnormal glucose above baseline with no medical intervention	Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes	Insulin therapy initiated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of blood sugar. It is usually an indication of diabetes mellitus or glucose intolerance.					

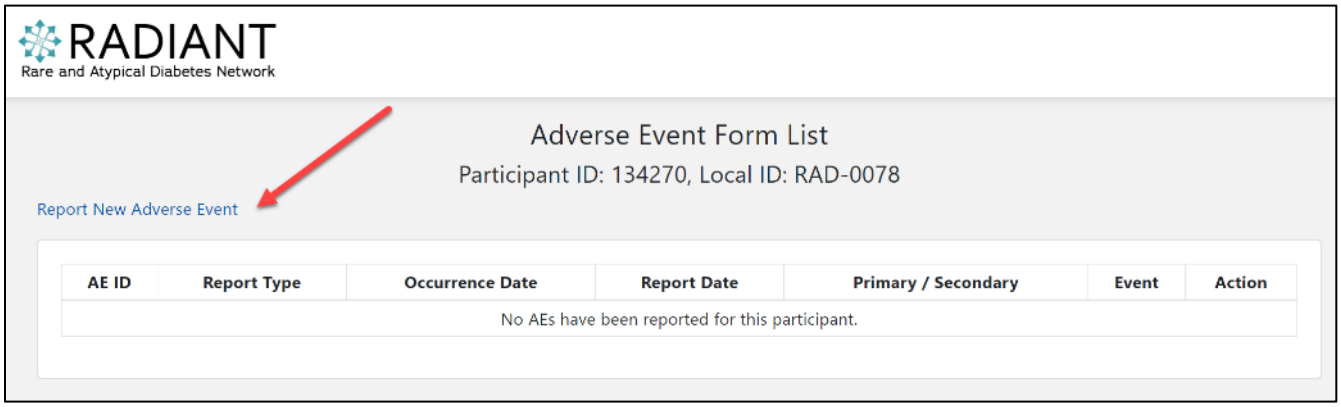
Reporting timeline: Sites should follow local IRB requirements for reporting adverse events (ex: within 24 hours, if applicable)

10.1 REPORTING AN ADVERSE EVENT IN THE MEMBERS WEBSITE#

1. Login to the RADIANT Members Website.
2. Navigate to the Participant Profile (see section 13.3.6).
3. In the Site Tasks section of the Participant Profile, click “Report/View Adverse Events”



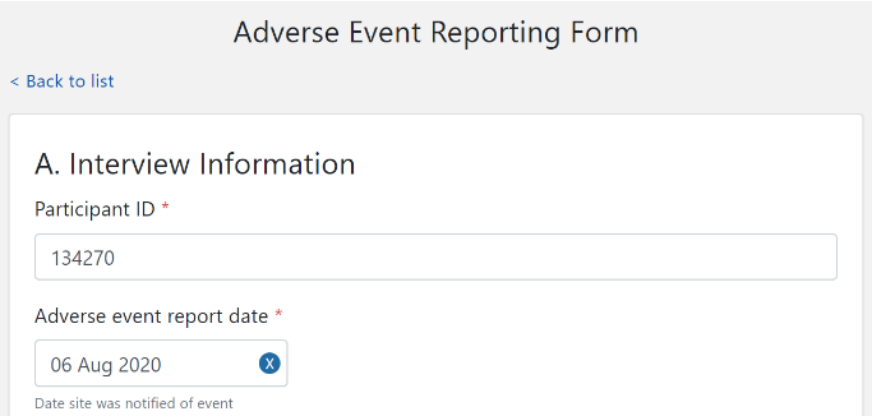
4. The Adverse Event Form List for the participant will open. Click “Report New Adverse Event”.



5. Complete the Adverse Event Reporting Form.

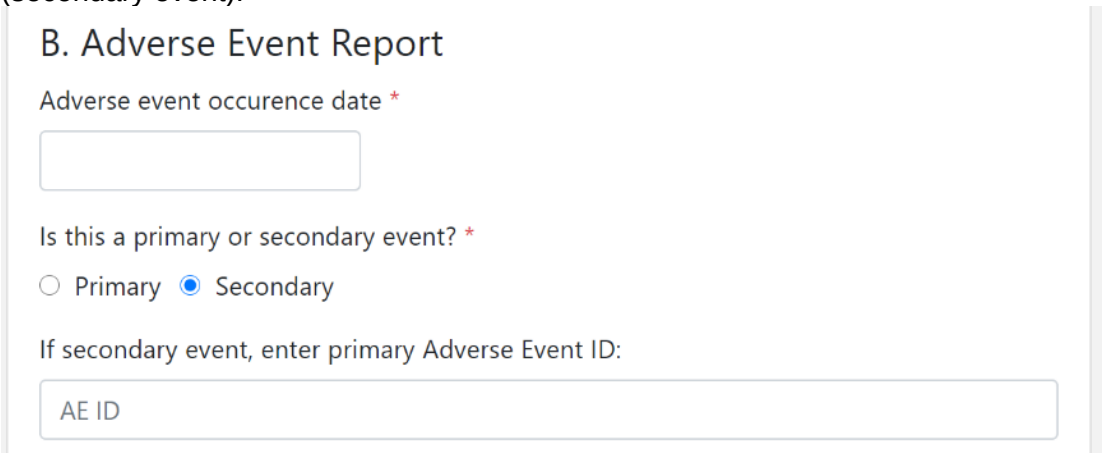
Section A. Interview Information:

- *Participant ID:* Automatically entered in the form by the system.
- *Adverse event report date*: This refers to the date the event was first learned. Note: This is not the date the AE Reporting Form is completed.



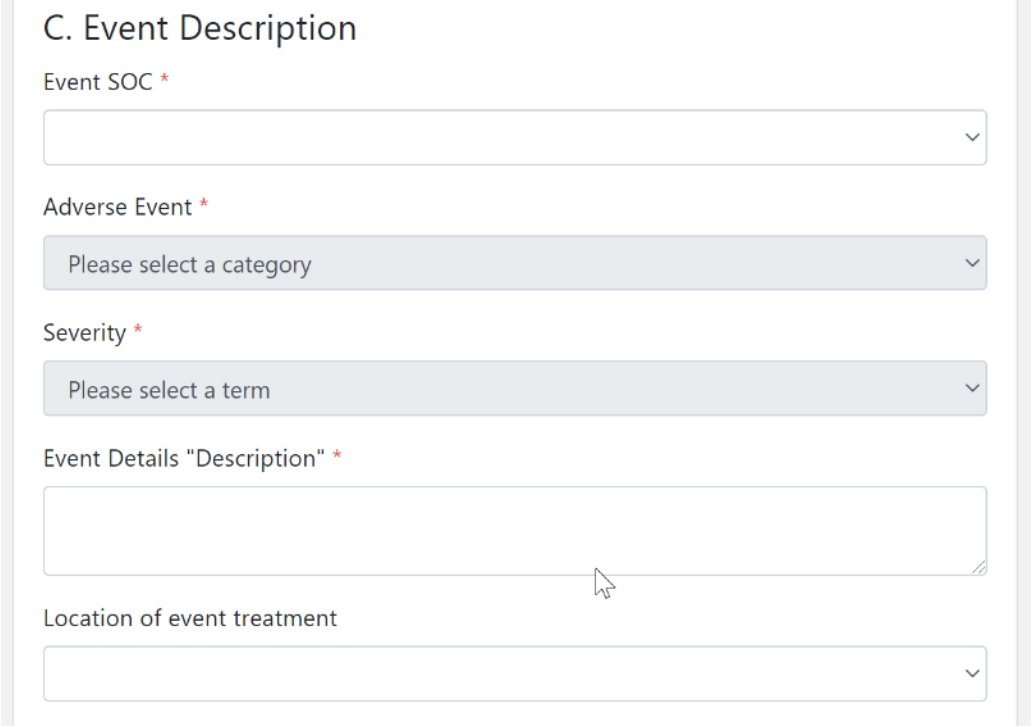
Section B. Adverse Event Report:

- *Adverse Event Occurrence date*: This refers to the date on which the adverse event began. Note: Date **cannot** be prior to patient registration date.
- *Is this a primary or secondary event?*
    - A **primary** AE is the main event.
    - A **secondary** AE is not a worsening or change in severity of the primary event, but it is an AE caused by or related to the primary event. If reporting a secondary event, enter the AE ID of the related primary AE.
    - For example: Participant suffers a hypoglycemia (primary event) which caused severe dizziness (secondary event).



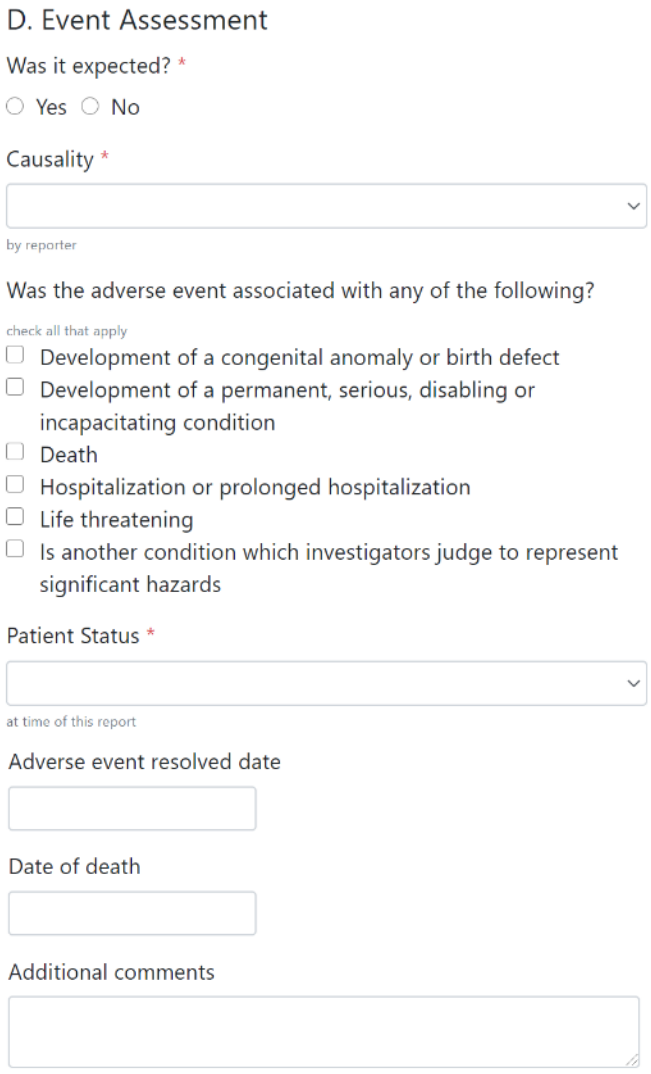
Section C: Event Description:

- *Event SOC*: This refers to the body system that the AE falls under. There is a drop-down list of options defined according to the CTCAE.
- *Adverse Event:* This refers to more specific description of the type of AE. There is a pre-populated drop-down list of the options. The drop-down list of options depends the SOC selected, and are defined according to CTACE.
- *Severity*: There is a pre-populated drop-down list of options specific to the type of AE.
- *Event Details "Description"*: This section should be completed for each event. Enter a brief narrative regarding the event. Should include: Dates, Times, Places, Details, Course of Event, Interventions, and resolutions as applicable.
    - *Note: Do not include participant name or gender in the notes, for example:*
        - **Not Acceptable**: *"He developed a rash."*
        - **Acceptable:** *"The **subject** developed a rash."*
- *Location of Event Treatment*: Select from drop-down list: Outpatient, inpatient, ER, none, unknown, other. If other, a new write-in field will appear for you to specify the location of treatment.



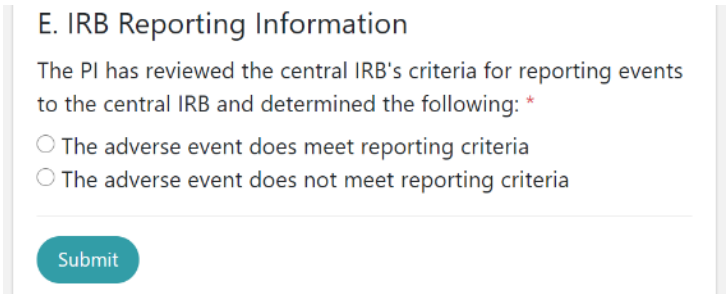
Section D: Event Assessment:

- *Expected*: Select “Yes” or “No”. Factors that determine if AE is expected:
  - If it is listed in the ICF; or
  - If it is expected due to the type of disease under investigation.
- *Causality (by reporter)*: This refers to the relatedness of the event to the study.
- *Was the adverse event associated with any of the following?*: Select all responses that apply. If any of these options are selected, the AE will be considered a Serious Adverse Event.
- *Patient Status (at time of report)*: Select options from pre-populated drop down list.
- *Adverse Event Resolved Date*: Completed only if AE is resolved at time of report.
- *Date of Death*: Completed only if AE results in death.
- *Additional Comments*: Add any additional pertinent information that is not captured elsewhere on the form.



Section E: IRB Reporting Information

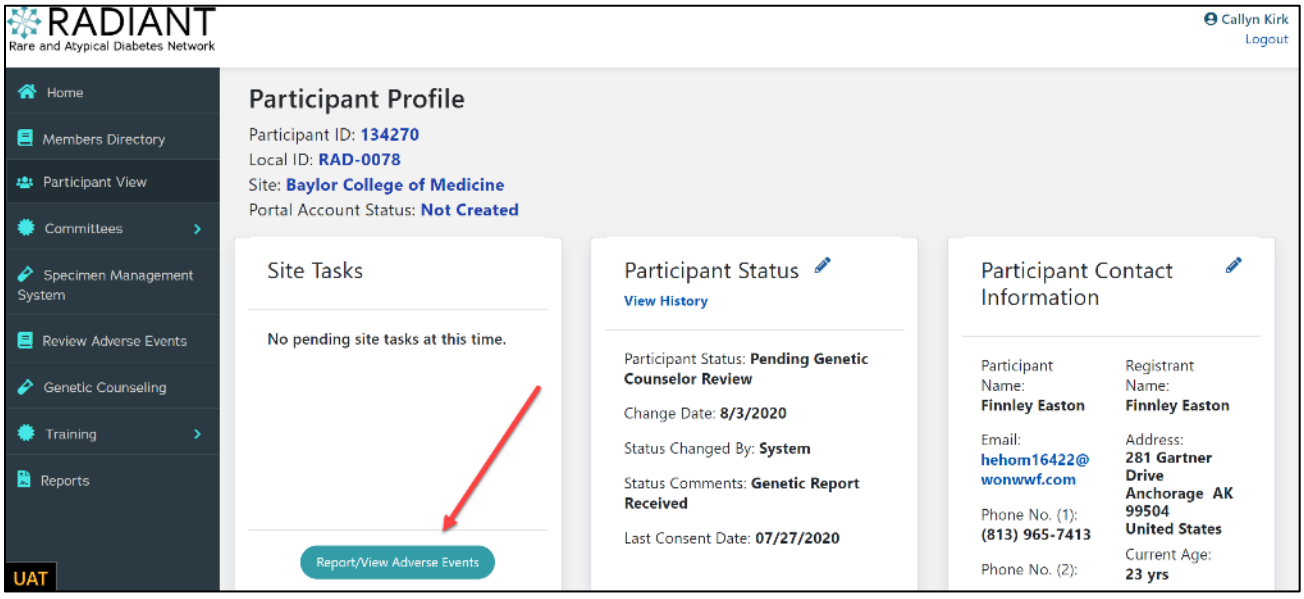
- Indicate the PI's assessment of whether the AE meets the central IRB's criteria for reporting AEs to the central IRB. Please see this document from University of Utah Central IRB to determine if the AE meets criteria for reporting it to the central IRB: https://irb.utah.edu/_resources/documents/pdf/IGS%20-%20Adverse%20Events-Unanticipated%20Problems%20Assessment%20070219.pdf



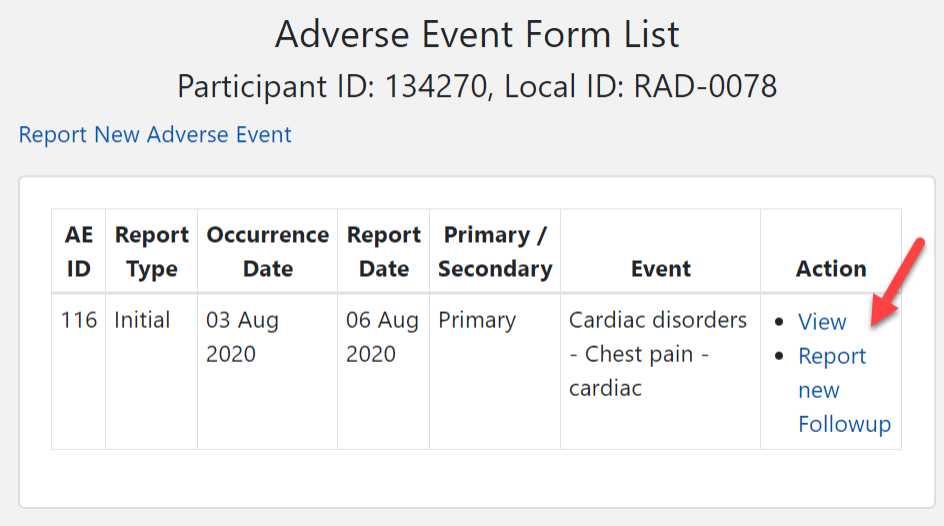
6. Click "Submit" at the bottom of the form.
7. You will receive a confirmation message that the AE has been submitted with the AE #.

10.2 VIEWING AND EDITING PREVIOUSLY REPORTED ADVERSE EVENTS

1. Login to the RADIANT Members Website.
2. Navigate to the Participant Profile (see section 13.3.6).
3. In the Site Tasks section of the Participant Profile, click “Report/View Adverse Events”



4. The Adverse Event Form List for the participant will open. This list includes previously reported AEs for this participant. In the Action column:
    a. Click “View” to view the adverse event.
    b. Click “Report new Follow-up” to submit a follow-up report for the AE. (Any modifications or updates that need to be made to a previously submitted AE should be submitted by entering a follow-up report.)



11 LABORATORY PROCESSING

11.1 LABORATORY PROCESSING AT RADIANT CENTRAL LAB

Please refer to the RADIANT specimen collection, processing, and shipping MOPs for more information.

11.2 LABORATORY PROCESSING AT BROAD INSTITUTE – WHOLE GENOME SEQUENCING

Sample requirements for whole genome sequencing: Minimum concentration of 30 ng/uL in 100-150 uL.

- This provides 1 ug for whole genome sequencing and 1 ug for Sanger sequencing with some extra sample.
- The whole genome sequencing lab will automatically process any sample with >250 ng of material. If less than that if available, study group will need to decide if they'd like to proceed with that sample (although it may fail) or if that sample should not undergo sequencing.

DNA samples from the Central Lab will be received at regular intervals, Monday-Friday to the Laboratory for Molecular Medicine (LMM). Samples arriving at LMM will be received, accessioned, quantified, and then arrayed into Broad Clinical Research Sequencing (CRSP) tubes. Samples will be stored at 4°C and shipped to the CRSP lab by courier once or twice a week. DNA remaining at LMM will be inventoried and stored at 4°C until it is known if confirmation sequencing is required. Once the clinical assessment is completed the sample will be stored at -80°C.

Upon arrival at the CRSP lab, samples will be put on the top of the queue for sample receipt and accession. Samples will then have an aliquot taken for initial QC checks, which include PicoGreen and fingerprinting. Samples confirmed to have enough DNA will immediately proceed into the next plate for clinical whole genome sequencing. After samples are plated, they will undergo PCR-free whole genome library construction then sequenced on a NovaSeq to a deliverable of 95% of the genome covered to at least 20x. The sequencing data will be compared to the fingerprinting results to ensure that no plate swaps occurred. A technical report will be generated by the CRSP lab and shared with the project.

Most samples arriving at CRSP will be processed immediately upon receipt, but in cases where that is not possible (ie. samples are received Friday afternoon) samples will be received, accessioned, then stored at the appropriate temperature alongside other clinical whole genome sequencing samples. Samples will then continue in the whole genome sequence process at the next business day.

11.2.1 SHIPPING, ANALYSIS, AND RESULTS INFORMATION – WHOLE GENOME SEQUENCING

Sample(s) to be sent from RADIANT Central Lab (UF) to LMM/Broad:

- 1 DNA aliquot for WGS/Sanger – concentration 100 ng/uL in 45 uL, 4500 ng DNA total
    - The sample is sent from the RADIANT Central Lab at University of Florida (UF) to LMM. LMM keeps a portion of the aliquot for Sanger, then pass the rest to CRSP at the Broad. CRSP performs the WGS.

Tube labeling & identifiers used:

- Using matrix tubes, pre-etched barcode
- Labeling is standard Central Lab DNA/RNA label –
  Ultra-cold polyester aliquot label wrapped around matrix tube (covers etched barcode on the side)
  Line 1: Linear barcode matching the 2D code on the bottom of the tube
  Line 2: Text of the number represented in the barcode
  Line 3: PID & date of receipt (date sample rec'd in Central Lab) 12 digit

  CLIA requirement to have 2 identifiers on tube that match the Requsition Form.
  2 identifiers on tube are: PID + text of number represented in barcode
  PID + text of number represented in barcode will be included on Requisition Form as 'Specimen ID 1' and 'Specimen ID 2' fields.

Paperwork to be sent:

1. UF does not need to include any sample manifest paperwork in the box with the samples for LMM.
2. The Requisition forms (one form per sample) will be automatically generated by the DCC and emailed to LMM.

Notification Emails and Uploads After Shipment:

1. UF uploads shipment information to the DCC.
2. The DCC automatically generates requisition forms for the samples in the shipment and emails them to LMM.
3. The DCC sends an automated shipment notification email with a .csv event log file to Broad Project Manager.

Frequency of shipment:

- Monthly batches – shipped on 2nd Tuesday of the month. Will arrive 2nd Wed of the month.

Shipping address:

ATTN: Clinical Laboratory
Laboratory for Molecular Medicine
65 Landsdowne Street
Cambridge, MA 02139
Phone: 617-768-8500

Sample receipt plan:

- Broad Project Manager will enter date received and any sample comments in .csv file, then sFTP that file back to the DCC when samples are received.
    - Comments entered in the event log .csv file would include any pertinent details about the state of the sample which could later inform us on sample status. For instance, if informing us that a sample was damaged in transit or was received thawed when expected to be frozen.

Sample run plan:

- LMM will run any samples that we send to them monthly (no batch minimum)
- Sample timeline:

    - WGS: Max 30 days (avg 21 days)
    - Clinical analysis, assessment, any needed Sanger seq, and reporting: Additional 4-6 weeks
- LMM CAP/CLIA reports only including likely pathogenic or pathogenic variants (VUS not reported, benign/likely benign not reported)
- ACMG secondary findings reported if participant consented for ACMG secondary findings
- Pediatric-only variants reported for pediatric participants

Sample results plan:

- Full raw data is delivered into Terra by CRSP. Broad team processes data from Terra.
    - The DCC will download the raw (BAM/CRAM) and processed (VCF) files and subsetted files from the Terra repositories as they become available. The DCC will catalog and store those files against future analysis needs.
        - Terra workspace #1 – All raw CRAMs directly from the seq lab
        - Terra workspace #2 – All processed data (CRAMs and VCF) owned by Jason's team
    - Broad will send the following WGS files to Baylor (via Terra):
        - VCF files
            - Full file: For adults who opted into primary and secondary/ACMG findings
            - Subsetted file: For participants <18 years old (only genes related to diabetes or child-onset diseases included) and/or who opt out of secondary findings (only diabetes-related genes included)
        - CRAM files
            - Full file: For adults who opted into primary and secondary/ACMG findings
            - Subsetted file: For participants <18 years old (only genes related to diabetes or child-onset diseases included) and/or who opt out of secondary findings (only diabetes-related genes included)
    - Broad will send the following WGS files to the DCC (via Terra):
        1. BAM – for all participants
        2. CRAM – for all participants
        3. VCF – for all participants
        4. Subsetted VCF – for participants <18 years old and/or who opt out of secondary findings (same file version sent to Baylor)*
        5. Subsetted CRAM - for participants <18 years old and/or who opt out of secondary findings (same version sent to Baylor)*
        6. * For cases with a subsetted file, DCC would receive both the full file AND the subsetted file from Broad for storage.
- BCM will obtain the data from Broad/LMM via Terra, then BCM will upload the data into Codified.
- CAP/CLIA reports – LMM will sFTP file back to DCC
    - LMM will name reports as: [LMM Report ID e.g. PM21-01234]-[RADIANT Participant ID].pdf
- Broad Project Manager will:
    - Upload a .csv file containing RADIANT IDs of participants with negative findings to the same FTP folder LMM is using for CAP/CLIA reports
        - New .csv files will be added to that folder as Broad Project Manager receives updates from LMM on participants with negative results
        - Filename format: RADIANT negative participants [date, formatted as M.DD.YY].csv

Other shipping instructions:

- All specimens should be packed in materials that prevent its container from being damaged during shipment. All blood, DNA, prenatal, and other specimens should be shipped to us using an overnight delivery service.
- LMM website: https://personalizedmedicine.partners.org/laboratory-for-molecular-medicine/faq/default.aspx#spray_h2

11.3 LABORATORY PROCESSING AT BAYLOR COLLEGE OF MEDICINE – RNA SEQUENCING

Sample requirements for RNA sequencing: Minimum 1ug of Total RNA (With the exception to accept a pre-approved subset of samples at 250 ng) and a RIN (RNA Integrity Number) of 6 or greater (minimum 5).

DNA samples from the Central Lab will be received at regular intervals, Monday-Friday in the Intake Laboratory at the Human Genome Sequencing Center at BCM. Samples arriving will be received, accessioned, and assayed for DNA quality and quantity (see passing metrics below). Samples will be stored in a -80C freezer until they are processed as pools of 35 samples.

Total RNAseq Library Preparation, Sequencing, and Analysis

Whole transcriptome sequencing (total RNAseq) data will be generated for RADIANT project samples using the Illumina TruSeq Stranded Total RNA with Ribo-Zero Globin kit (20020612, Illumina Inc.). Standard HGSC intake requirements for this pipeline are 1 ug total RNA to generate hight quality data (With the exception to accept a pre-approved subset of samples at 250 ng) and a RIN (RNA Integrity Number) of 6 or greater (minimum 5) to be shipped to HGSC on dry ice in 2D barcoded tubes and dissolved in nuclease free 1X TE or water in a preferred volume of 10-20 ul (~100 ng/ul concentration). To monitor sample and process consistency, synthetic RNA designed by External RNA Controls Consortium (ERCC) (4456740, ThermoFisher) will be added to the total RNA at the beginning of cDNA preparation. Universal Human Reference RNA (UHR) (740000, Agilent Inc.), will be prepared in parallel through cDNA and library steps as a process control. In addition, HGSC has an RNA lab on a separate floor from the DNA lab and is exclusively used for handling RNA material. Paired-end libraries will be prepared on Beckman BioMek FXp liquid handlers. TruSeq UD Indexes (Cat # 20022370) are used to barcode the samples during library preparation. In order to generate a minimum of 50M read-pairs (100 M total reads) per sample, libraries will be pooled n equimolar ratios as pools of 35 samples and sequenced on the NovaSeq 6000 instrument using the S4 reagent kit (300 cycles) to generate 2x150bp paired-end reads.

The HGSC RNA-Seq analysis pipeline is a combination of open-source software and internally developed protocols that cleans and processes raw RNA sequence profile data (FASTQs), providing robust QC metrics and has the flexibility to map the reads to either GRCh37 reference or GRCh38 (after excluding the alternate contigs).

Table. RNA-Seq pipeline components

Software	Version	Application
STAR	2.5.3a	Alignment, junctions
Sambamba	0.6.7	Bam sort
Picard	2.18.4	Post-processing
RNA-SeQC	1.1.7	Gene quantification and QC
Cufflinks	2.2.1	Gene and isoform quantification
SAMtools	1.9	Alignment tool
GRCh38	38 (no_alt)	Reference genome
GENCODE	26	Gene annotation file
ERCCQC	1.0	Monitor RNA-Seq consistency https://github.com/BCM-HGSC/ERCCQC

Latest versions of software for sequence alignment (STAR v.2.5.3a), for marking of duplicate reads (Picard v.2.18.4) and for conversion of BAM files to FastQ files (Samtools v.1.9) are part of this pipeline. In addition to these components, the pipeline uses Cufflinks (v.2.2.1) for measuring differential expression of transcripts, RNA-SeQC (v.1.1.7) and ERCCQC (v.1.0) to generate Quality control metrics on the RNA-Seq data. The ERCCQC software currently running in our RNASeq pipeline was developed in house and is available in Github at the listed address in the table. HGSC will deliver fastq and cufflink files for each sample.

11.3.1 SHIPPING, ANALYSIS, AND RESULTS INFORMATION – RNA SEQUENCING

Sample(s) to be sent from RADIANT Central Lab (UF) to BCM Lab:

- RNA aliquot for RNA seq – concentration 100 ng/uL, target 1000 ng total
    - Can go as low as 250 ng total on the occasional sample but need prior approval from Baylor RNA sequencing team

Tube labeling & identifiers used:

- Using matrix tubes, pre-etched barcode
- Labeling is standard Central Lab DNA/RNA label –
  Ultra-cold polyster aliquot label wrapped around matrix tube (covers etched barcode on the side)
  Line 1: Linear barcode matching the 2D code on the bottom of the tube
  Line 2: Text of the number represented in the barcode
  Line 3: PID & date of receipt (date sample rec'd in Central Lab) 12 digit

Paperwork to be sent:

1. PDF Sample Intake Form
    a. Version as of 1/17/2023: BCM HGSC sampleintake_v4.2_RADIANT Study_filled
2. Excel sheet –
    a. Version as of 1/17/2023: BCM HGSC SampleIntakeTemplateV1.01_HGSC_gender
    b. The fields in red are required for sample submission.
    c. Do not need to fill in the last 4 columns in red (only for internal use)
    d. Individual ID is the Participant ID . Sample ID is the etched barcode number.
3. Central Lab will generate the above and email this PDF and Excel sheet to sampleintake@hgsc.bcm.tmc.edu and Shalini (project manager) jhangian@bcm.edu AHEAD OF THE SHIPMENT (send paperwork on Friday, Baylor to give feedback by Monday, ship samples on Tuesday)
4. Central Lab will include a copy of the PDF and Excel sheet as hard copies in the box with the samples as well.

DCC:

1. DCC will provide Central Lab with gender so they can complete forms.
2. DCC will send automated emails to BCM RNA-Seq lab team indicating whether RNA seq should proceed or not for each sample (only samples that do not have a pathogenic or likely pathogenic variant in a known monogenic diabetes gene will get RNA seq).
    a. Baylor will store samples before/after regardless of whether they are run or not.
3. Central Lab will sFTP a .csv event log file to the DCC which includes the samples, shipment date, and tracking information for the samples shipped to the Baylor lab. This will trigger a shipment notification email from the DCC to the Baylor lab which will include a partially completed event log file for them to use in receipting the samples. This email notification will be sent to sampleintake@hgsc.bcm.tmc.edu, sabo@bcm.edu and jhangiani@bcm.edu.

Frequency of shipment:

- Monthly batches – shipped on 2nd Tuesday of the month. Will arrive 2nd Wed of the month.

Shipping address (see 'Other shipping instructions' for more shipping details):

ATTN: Sample Intake Team - Research
Human Genome Sequencing Center
Baylor College of Medicine
1 Baylor Plaza, N-1505 Alkek Bldg., MS 226
Houston, TX. 77030
Phone: 713-798-4096

Sample receipt plan:

- Baylor will enter date received and any sample comments in .csv file event log file (see more info in DCC section, item #3 above), then sFTP that file back to the DCC when samples are received

Sample run plan:

- DCC will send automated emails to BCM RNA-Seq lab team indicating whether RNA seq should proceed or not for each sample (only samples that do not have a pathogenic or likely pathogenic variant in a known monogenic diabetes gene will get RNA seq).
- Baylor has a 35 sample batch minimum for RNA-Seq.

Sample results plan:

- Raw data (fastq or BAM files) and processed gene expression raw count and Transcripts Per Million (TPM) data in a tabulated text file format will be transferred to DCC using Expedat (Baylor)
- Discovery Team (DT) members at Baylor will be reviewing the RNA seq data and entering results in the DT RNA seq reviewer form, which will then be included in the DT case review slides for the DT review call.
- *(BCM will not be generating CAP/CLIA reports for RNA seq results based on the current plan.)*

Other shipping instructions for Central Lab:
(Please see 'Guidelines for RNA Shipping In Aq. Solution_rev' for full details)

RNA Samples in DNAase and RNAase free1X TE or in DEPC-water in Matrix with 2D-barcoded tubes with Sepra Seals and in Racks*
*Matrix 0.75 ml V-bottom tubes/latch racks, Cat. #3732 for tubes and #4464 for the Sepra seals.

1. RNA samples should be shipped on dry ice for priority overnight delivery, such as with FEDEX.
2. The tubes should be capped tightly to prevent accidental spillage or cross contamination and the tubes placed inside a rack with a lid (secondary containment) or alternatively inside a 50 ml conical tube with the cap screwed tightly.
3. Wrap the secondary containers in plastic bags that can be sealed (zip-lock) and cushion them with some type of padding.
4. Place the samples in a Styrofoam box and cover them with dry ice. Do not tape the Styrofoam lid to allow for gas venting.
5. Place the Styrofoam box inside a sturdy cardboard box and tape the box securely.
6. Label the outside of the box appropriately for DRY ICE---refer to requirements specified by the DOT and IATA for dry ice shipments.
    a. Air bill: The air bill must include the statement "Dry Ice, Class 9, UN1845, number of packages X net weight in kilograms."
    b. Labeling. The outermost container must be labeled with a hazard class 9 label, UN 1845, and total weight of dry ice in kilograms.
7. For Standard service or Express Service, DNA samples can be sent by any type of overnight delivery as long as the delivery method has traceability (tracking).
8. When a tracking number is obtained, please send it by email to: sampleintake@hgsc.bcm.tmc.edu
9. BCM will notify the sender by email when the package is received and upload .csv file with sample receipt date to DCC.

11.4 LABORATORY PROCESSING AT BAYLOR COLLEGE OF MEDICINE – MITOCHONDRIAL SEQUENCING

Sample requirements for mitochondrial sequencing: 100 ng DNA

DNA samples from the Central Lab will be received as needed for mitochondrial sequencing, in the Posey Laboratory at Baylor College of Medicine. Samples arriving will be received, accessioned, and assayed for DNA quality and quantity. Samples will be stored in a -80 freezer until they are processed.

Mitochondrial sequencing and analysis
Amplification of the mitochondrial genome will be performed by long-range PCR (LR-PCR) using TakaRa LA Hot Start Taq enzyme applied to 100 ng of total genomic DNA. Indexed paired-end DNA libraries will be prepared using purified LR-PCR products that have been fragmented to 200 bp. Pooled libraries will consist of 12 indexed

DNA libraries per single flow cell on a HiSeq2000to achieve a mean depth of coverage of >10,000X with 100% of the mitochondrial genome covered at 40X or greater.

Illumina CASAVA software will be used to demultiplex reads belonging to the same index, and any reads having a median quality score < 25 filtered out using NextGENe software. Reads having 1 unknown assigned base call will also be filtered out. NextGENe Viewer will be used to visualize aligned reads, with variant calling performed using the Revised Cambridge Reference Sequence (RCRS) and two different heteroplasmy cutoffs: 1% and 20%. Deletion heteroplasmy will be calculated from the segmental mean read depth of deleted and undeleted mitochondrial genome regions.

11.5 LABORATORY PROCESSING AT BAYLOR COLLEGE OF MEDICINE – RESEARCH-BASED SANGER SEQUENCING

Sample requirements for Sanger sequencing: 300ng gDNA or 25ng purified DNA fragments

DNA samples from the Central Lab will be received as needed for family member research-based Sanger sequencing, in the Posey Laboratory at Baylor College of Medicine. Samples arriving will be received, accessioned, and assayed for DNA quality and quantity. Samples will be stored in a 4C freezer until they are processed.

Research-based Sanger sequencing and analysis
[IN Posey Lab] Sample DNA Template Preparation
Amplification of the gDNA sequence of interest will be performed by standard PCR using HotStart Taq+ enzyme (#203205, QIAGEN). The size of the amplified fragments and DNA amount will be confirmed with Agarose Gel Electrophoresis. Purify PCR products with ExoSAP-IT (#78-200-200UL, Fisher Scientific). Prepare 60ng/5ul DNA per tube for each sample to BCM CPEH DNA Sequencing Core.

IN BCM CPEH DNA Sequencing Core] Sanger sequencing and analysis
Sequencing Preparing
1) The template and primer volume are enough for reaction requested: 2ul per reaction for DNA template and 0.5ul per reaction for primer (10uM).
2) The DNA concentration: 5-10ng/ul for 500-1000bp each sample

Cycle Sequencing
Applied Biosystems Cycle Sequencing Kits: BigDye Terminator v3.1
3) Select the sequencing chemistry.
4) Prepare cycle sequencing reactions.
5) Run sequencing reactions in a thermal cycler.

Extension Product Purification
6) Purify the sequencing reaction products using Sephadex G50 purification method. Load 4% Sephadex solution onto clean Centri-Sep plate (ABI, # 4367819) with a reused assay plate under the Centri-Sep plate.

Capillary Electrophoresis
7) After purification, run samples on Electrophoresis Instrument. The Capillary Electrophoresis is performed with Applied Biosystems instrument, ABI 3730 Analyzer. The Capillary Electrophoresis Output is the *.ab1 file.

Data Analysis
AB1 files will be loaded into Sequencing Analysis Software6 (V6.0) in the Core. After analyzing, text files contained nucleotide sequencing will be generated and sent out. The AB1 files could be loaded into SnapGene Viewer, Mutation Surveyor and CodonCode Aligner software for further blasting analysis and variant calling if need.

*Reference: DNA Sequencing by Capillary Electrophoresis Applied Biosystems Chemistry Guide

11.5.1 SHIPPING, ANALYSIS, AND RESULTS INFORMATION – RESEARCH-BASED SANGER SEQUENCING

Sample(s) to be sent from RADIANT Central Lab (UF) to BCM Lab:

- For family members: 1 DNA aliquot for research-based sanger – concentration 100 ng/uL target 100 uL, 10,000 ng DNA total
- For proband: Same DNA aliquot that is allotted for mitochondrial sequencing. (There is enough DNA in that aliquot for both sanger sequencing & mitochondrial sequencing.)

Family members samples may be sent from the Central Lab in multiple batches, depending on when they are received at the Central Lab. The proband sample will be sent with the first family member sample the Central Lab receives. Proband participant ID is included in the kit request file generated by DCC for Central Lab, so the Central Lab knows which proband sample to include with family member sample(s). Baylor will hold the family member sample(s) and proband sample from the first batch until all expected family member samples are received. The DCC will provide Baylor with an automated report on the RADIANT Members Website that indicates probands and family members recommended for Sanger sequencing and the status of the sample.

Tube labeling & identifiers used:

- Using matrix tubes, pre-etched barcode
- Labeling is standard Central Lab DNA/RNA label –
  Ultra-cold polyester aliquot label wrapped around matrix tube (covers etched barcode on the side)
  Line 1: Linear barcode matching the 2D code on the bottom of the tube
  Line 2: Text of the number represented in the barcode
  Line 3: PID & date of receipt (date sample rec'd in Central Lab) 12 digit
  2 identifiers on tube are: PID + text of number represented in barcode

Paperwork to be sent:

1. Manifest listing RADIANT IDs, sample type (DNA), sample volume, sample concentration
   a. The Central Lab will create this manifest, include a hard copy in the shipment, and email a copy to Yidan.Li@bcm.edu, Jennifer.Posey@bcm.edu, and radiantteam@atypicaldiabetesnetwork.org ahead of the shipment.

Shipment Notifications:

- Central Lab will sFTP a .csv event log file to the DCC which includes the samples, shipment date, and tracking information for the samples shipped to the Baylor lab.
  - Sample Names for event log: DNA, HbA1c, Glu
  - This will trigger an automated shipment notification email from the DCC to the Baylor lab team which will include a partially completed event log file for them to use in receipting the samples.
    - Email subject line: "RADIANT Sample Transfer (BAYLOR)"
    - This email notification will be sent to all Baylor site members with role "Lab User – Read/Write" or "Lab User – Read Only" in the RADIANT Members Directory.

Frequency of shipment:

- Monthly batches – shipped on 2nd Tuesday of the month. Will arrive 2nd Wed of the month.
- Note:
  - The Baylor lab is able to receive shipments on Mondays through Fridays.
  - The Baylor lab cannot receive shipments on Saturdays, Sundays, or institutional holidays.

Shipping address:

Posey Lab, c/o Yidan Li
Baylor College of Medicine
One Baylor Plaza, Room T607
Houston, TX 77030

713-798-5733
Yidan.Li@bcm.edu
Jennifer.Posey@bcm.edu

Sample receipt plan:

- Samples arriving will be received, accessioned, and assayed for DNA quality and quantity. Samples will be stored in a 4C freezer until they are processed.
- Baylor will enter date received and any sample comments in .csv file event log file (see more info in "Shipment Notifications" section above), then sFTP that file back to the DCC when samples are received.

Sample run plan:

- Baylor lab will perform research-based Sanger of variant identified in proband

Sample results plan:

- Turn-around time for results is approximately 2 weeks once all expected family members samples are received.
- Baylor Lab will create xls document to include variants studied, primers used, PCR reaction protocol and setup, PCR conditions used, gel confirmation with lane label definitions (what sample is in what well), the Sanger results, and the Sanger tracings themselves as snapshots
- Sanger files will also be provided as AB1 files
    - AB1 files will be loaded by Baylor lab into Sequencing Analysis Software6 (V6.0) in the Core. After analyzing, text files contained nucleotide sequencing will be generated and sent out. The AB1 files could be loaded into SnapGene Viewer, Mutation Surveyor and CodonCode Aligner software for further blasting analysis and variant calling if need.
- No report for participants will be prepared because these are research-based tests (not performed in a CAP/CLIA lab)
- The Baylor lab manager or Jennifer Posey will upload Sanger Sequencing results via a "Family Sanger Sequencing Results Form" in the proband's page within the Discovery Team Dashboard. Form will include:
    - Variant studied
    - Summary of Sanger Results
    - Upload tool to upload the xls file described above
    - Upload tool to upload the AB1 file described above
    - Upload tool for pedigree created by Sanger lab

11.6 LABORATORY QUALITY CONTROL PROCEDURES AND MONITORING PLAN

11.6.1 QUALITY CONTROL PROCEDURES

11.6.1.1 Broad Institute – Whole Genome Sequencing

The following QCs will be performed by the CLIA lab at the Broad (CRSP):

1. Sample quantification for all incoming DNA
    a. Pico quantification will be performed for all incoming DNA before continuing on to clinical whole genome sequencing. The lab requests ~1ug of genomic DNA be provided but will automatically process any sample >250ng. Samples with <250ng of DNA will result in a stop of work and the CRSP project manager will notify the project and request for them to decide how that samples should move forward. If the sample does not move forward a failed clinical test report will be issued and a new DNA aliquot, in a new tube will be requested.
2. Library Construction QC during sample processing
    a. During clinical whole genome processing, samples will be tested for library quantity. If a sample fails to meet the lab's specifications, the lab will automatically reattempt the sample if there is

stock material available. If the sample fails a second attempt, the CRSP project manager will notify the project and a failed technical report will be generated for the sample. In most cases, a new DNA aliquot will be requested.

3. Sample concordance testing (aka fingerprinting)
    a. An independent aliquot of the sample will be taken for DNA fingerprinting QC, an orthogonal test using a Fluidigm genotyping assay. The genotype data generated is checked for concordance with the WGS data to determine if any sample plating errors occurred. If fingerprinting fails on the first attempt, then the lab will automatically rerun if there is stock material available. If the fingerprint fails the second attempt, the lab will do additional checks to ensure no plating swaps occurred. Laboratory technical supervisor(s) and/or the laboratory director will determine whether or not the WGS data should be released with a passing report. In most cases, if there is no other indications of sample plating error on the plate, the sample data will be released to the project. In some circumstances, the laboratory may issue a failed test report due to a failed fingerprinting assay and request a new DNA aliquot.
4. Data quality QC
    a. After whole genome sequencing is completed, a number of standard metrics are reviewed by the clinical team. The specifications for release of data and a passing clinical technical report include: >= 95% covered at 20x, mean coverage >= 30x, % PF (passing filter) high quality bases and contamination <2.5%, which are all shared on the clinical technical report. The lab team also evaluates a number of other sample quality metrics that are not available on the report including, total Gb produced, and % reads aligned. If any of these fail, the laboratory will attempt to bring the sample up to coverage when appropriate and if additional material is available When the sample reaches >=95% at 20x coverage, a pass technical report will be issued.

11.6.1.2 Baylor College of Medicine – RNA Sequencing

HGSC QCs:

The following QCs will be performed by HGSC

1. Sample quantification for all incoming RNA
    a. Caliper GX (for larger sets) or Agilent Bioanalyzer (for smaller sets) quantification will be performed for all incoming RNA before proceeding with Whole transcriptome sequencing. The lab requests ~1ug of Total RNA (With the exception to accept a pre-approved subset of samples at 250 ng) and a RIN of 6 or greater (minimum 5). Information about samples with <1ug of Total RNA and RIN < 6 will be conveyed to the project manager who will then inform the collaborators and request them to decide how that samples should move forward. If the sample does not move forward a new aliquot, in a new tube may be requested.

2. Library Construction QC during sample processing
    a. Library construction QC metrics for a passing sample are: average library size ≥ 350 bp without a visible dimer, and library yield enough to facilitate a 5 nM/20 ul solution for pooling and sequencing. If a sample fails to meet the lab's specifications, the lab will automatically reattempt the sample if there is stock material available. If the sample fails a second attempt, the project manager will notify the collaborators.

3. Data quality QC
    a. After RNA Sequencing is completed, a certain set of standard metrics are reviewed by the QA/QC team. The specifications for release of data include: >100 M reads per sample, > 70% mapping rate, <50% duplication rate, <10% RNA read fraction, >95% strand specificity (this metric will be lower if the RNA sample has DNA contamination), >10X mean per base coverage. The lab team also evaluates a number of other sample quality metrics internally.

	Plex	Total SE's	Reads(M)/Sample	Read Mapping Rate (%)	Duplication Rate (%)	rRNA Rate (%)	Strand Specificity (%)	MEAN PER BASE COV
Cancer Project 1	50	44	122.0	86.9	39.7	0.2	97.4	63.8
Complex Disease 2	35	326	176.1	86.7	33.4	2.4	96.2	73.8
Cancer Project 2	35	35	147.9	87.2	49.1	0.3	98.1	72.6
			148.7	**86.9**	**40.7**	**0.9**	**97.2**	**70.1**
		Passing Metrics	*>100*	*>70*	*<50*	*<10*	*>95*	*>10*

11.6.1.3 Baylor College of Medicine – Mitochondrial Sequencing

Baylor College of Medicine will generate a report of per-sample metrics for all samples studied by mitochondrial genome sequencing using the established long-range PCR (LR-PCR) method.

Reports will contain the following standard technical metrics: total reads, mean depth of coverage, mapping rate, analytic sensitivity, analytic specificity, deep-sequencing index (DSI), and instrumental sequencing error rate.

Description of Mitochondrial QCs:

1. Analytic sensitivity: the analytic sensitivity of a sequencing run is calculated as the percentage of bases of the reference sequence covered by sequencing reads.
2. Analytic specificity: The analytic specificity of a sequencing run is calculated as the percentage of reads mapped to an mtDNA reference sequence compared to the total reads generated for a given sample.
3. Deep sequencing index: The DSI will be calculated from a set of 6 parameters, utilizing an External QC (ExQC) approach to ensure accurate quantification of heteroplasmy for identified variants. ExQCs consist of 7 synthetic DNA fragments 150bp in length with known variants at specified positions. Dilutions of these fragments are pooled together to create an ExQC solution containing 0.1%, 0.5%, 2%, 5%, 20%, and 50% of wildtype and variant alleles 1, 2, 3, 4, 5, 6, respectively (**Table 1**), representing a range of heteroplasmy levels. This solution is spiked into each indexed sample so that the reliability of per-sample quantitative measurements can be evaluated.

TABLE 1	Variant position						
	1	2	3	4	5	6	
Reference allele	A	T	G	C	G	T	Parts in QC mix
ExQC_1	T	A	T	T	T	G	1
ExQC _2		A	T	T	T	G	4
ExQC _3			T	T	T	G	15
ExQC _4				T	T	G	30
ExQC _5					T	G	150
ExQC _6						G	300
ExQC _7	A	T	G	C	G	T	500
Total ExQC mix	A/T	A/T	G/T	C/T	G/T	T/G	1000
Ratio	1/999	5/995	2/98	5/95	20/80	50/50	
Mutant allele	0.1%	0.5%	2%	5%	20%	50%	

Reference allele	99.9 %	99.5 %	98%	95%	80%	50%

The DSE will then be calculated from 6 parameters: (a) the mean number of reads mapped to ExQC DNA, (b) the mean number of sample reads normalized to the mean number of reads mapped to ExQC DNA, (c) the correlation coefficient of the expected versus observed values of ExQC DNA heteroplasmy, (d) the ratio of the standard deviation of the mean number of reads to the mean number of reads mapped to sample DNA, (e) the analytic specificity, and (f) the analytic sensitivity of a run (**Figure 1**).

$$DSI = \frac{\omega_1 \frac{\text{Mean read}_{\text{ExQC}}}{10\,000} + \omega_2 \frac{\text{Mean read}_{\text{mtDNA}}}{\text{Mean read}_{\text{ExQC}}} + \omega_3 CC(\text{ExQC}_{\text{heteroplasmy}}) + \omega_4 \frac{\text{STDEV}_{\text{mtDNA}}}{\text{Mean read}_{\text{mtDNA}}} + \omega_5 \text{Specificity}_{\text{mtDNA}} + \omega_6 \text{Sensitivity}_{\text{mtDNA}}}{\frac{1}{N_{\text{previous runs}}} \sum_{i=1}^{N-1} DSI_i}$$

Figure 1. Formula used to calculate DSI.

As an additional control step, a 1.1% heteroplasmy m.3243 variant is spiked into every run. Heteroplasmy calculations for this variant must be 1.1% +/- 0.1% for the results of the batch run to be accepted.

4. Instrumental sequencing error rates: The control DNA sequences comprising the ExQCs are used to calculate instrumental sequencing error by comparing the number of incorrect nucleotides of the control DNA sequence to the total number of nucleotides mapped to the control DNA sequences.

References

1. Zhang W, Cui H, **Wong LJ**. Comprehensive one-step analyses of mitochondrial genome by massively parallel sequencing. Clin Chem 2012;58:1322-31 PMID:22777720
2. Cui H, Li FY, Chen D, Wang G, Truong CK, Enns G, Graham B, Milone M, Landsverk ML, Wang J, Zhang W, **Wong LJ**. Comprehensive next generation sequence analyses of the entire mitochondrial genome reveals new insights into the molecular diagnosis of mitochondrial DNA disorders. Genet Med 2013, 15:388-94, PMID:23288206

Parameter(s)	Criteria for Passing (Baylor RNAseq)	Criteria for Passing (Baylor MitoSeq)	Criteria for Passing (Broad CLIA WGS)
Total Reads	>50,000,000 read pairs***		
Mapping Rate	>70%	>95%	
rRNA Read fraction	<10%		
Strand Specificity*	>95%		
Mean per base coverage	>10X		
% Contamination			<2.5%
Estimated Library Size			7.0 x 10^9 unique molecules
% Bases @ 20X		100%	95%
PF HQ Aligned Bases			8.0x10^{10} bases
Mean Coverage		10,000X	30X
Control heteroplasmy detection		1.1% +/- 0.1%	
Analytic sensitivity		>99%	
Analytic specificity		>97%	
Deep sequencing index		> 85	
Sequencing error rate		< 1%	

Quality Control (QC) will be assessed by each lab internally and reported to the RADIANT study team on a regular basis.

QC Reporting Plan (V06/09/20)

The following reports will be generated and reviewed by the appropriate committee (Lab Committee or Quality Control/Monitoring Committee). QC reports will be reviewed monthly at the start of study. Review may be decreased to quarterly after several months, if desired.

QC reports from Central Lab:

1. Daily quality control report
    a. This report will be used to assess daily quality for each assay (including DNA/RNA extraction)
    b. Committee may recommend action if report shows assay shifting out of target range (+/- 2 SD from target)
2. Long term drift report
    a. This report will be used to monitor the stability of calibrators to ensure there is no analytical drift over time.
    b. Committee may recommend action if report shows a trend month-to-month to determine if there is a calibrator issue.
3. Site lab performance report
    a. This report will be used to monitor site performance regarding sample collection, processing, and shipment.
    b. This report should include information about Quest performance for remote visits (or could be in a separate report).
    c. Committee will review results and share results with individual sites/site staff. If trends are noted, committee may recommend action (additional training, etc).
    d. Committee recommends running these reports monthly for at least the first few months of study launch.
4. Reports from external proficiency programs (CAP, any other external program they participate in)

QC reports from Broad Institute for Whole Genome Sequencing:

1. Clinical technical report from CRSP (per sample)
    a. Contain % covered at 20x, mean coverage, and % contamination
2. Batch/aggregate report
    a. Contain % covered at 20x and turnaround times

QC reports from Baylor College of Medicine for RNA Sequencing:

1. Technical report from HGSC (per sample)
    a. Contain total reads, mapping rate, rRNA read fraction, strand specificity, and mean per base coverage
2. Batch/aggregate report
    a. Contain same metrics as above

Reports from Baylor College of Medicine for Mitochondrial Sequencing:

1. Technical report (per sample)
    a. Contain mean depth of coverage, mapping rate, control heteroplasmy detection, analytic sensitivity, analytic specificity, deep-sequencing index (DSI), and instrumental sequencing error rate.
2. Batch/aggregate report
    a. Contain same metrics as above

11.7 SPECIMENS SYSTEM LAB TRANSFER PROCESSES

Stage 2

This process will assume that the sample collection kit was shipped successfully to the participant/site and the samples were shipped back.

1. Samples are receipted by the RADIANT Central Lab using either:
    a. An event log csv file upload using the “RCVD” Event value
    b. A request to the RADIANT specimens API: https://api.atypicaldiabetesnetwork.org/api/specimens/receive
2. Samples are then aliquotted by the RADIANT Central Lab using either:
    a. An event log csv file upload using the “ALIQ” Event value
        i. The child aliquot vial barcode will need to be provided in the ALIQ column of the upload file
    b. A request to the RADIANT specimens API: https://api.atypicaldiabetesnetwork.org/api/specimens/aliquot
3. The child samples may then be shipped to the processing lab by the RADIANT Central Lab. This will be indicated in the RADIANT system by either:
    b. An event log csv file upload using the “SENT” Event value
        i. The LabID column should indicate to which sample processing lab the aliquot sample will be shipped: Baylor (127) or Broad (1200)
    b. A request to the RADIANT specimens API: https://api.atypicaldiabetesnetwork.org/api/specimens/transfer
4. The sample processing lab (Baylor or Broad) will need to indicate that the samples are received or any status updates by either:
    b. An event log csv file upload using a specific Event value: RCVD (Received), QNS (Quantity Not Sufficient), or LOST (Lost).
    c. A request to the RADIANT specimens API: https://api.atypicaldiabetesnetwork.org/api/specimens/receive https://api.atypicaldiabetesnetwork.org/api/specimens/quantitynotsufficient

        https://api.atypicaldiabetesnetwork.org/api/specimens/lost

12 RETENTION AND WITHDRAWALS

12.1 RETENTION

Retention may be a challenge in RADIANT, as it is in all long-term studies. In RADIANT, retention may be a greater challenge considering that participants will be asked to continue follow-up for several years while not having the opportunity to visit clinical sites on a regular basis. Every attempt will be made to obtain study measurements and record study outcomes in all enrolled participants. Participants will be followed up on a regular basis. The first goal is to ensure that participants have access to timely study procedures as determined by the Discovery Team. The expectation is that study staff will make attempts to keep participants engaged and knowledgeable about their participation in RADIANT. Part of this effort is to contact participants at least twice per year by phone or by sending letters or study updates (newsletter).

If participants do not adhere to the full protocol, no participant will be withdrawn from continued follow-up in the study unless the participant formally withdraws consent. Although this may happen rarely, most participants with poor adherence will still agree to be contacted from time to time (to encourage completion of recommended testing, re-engage, and potentially to obtain data by phone). The goal is that every participant will complete follow-up in the study to the extent possible up to the study close and completion of data collection as specified in the study protocol.

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. Study participant duration is expected to vary depending upon the nature of the additional testing necessary. Those who only undergo testing needed to identify known forms of diabetes participate in at most two study visits, while those accepted for additional data and sample collection will participate in two or more visits over the course of the project.

Retention strategies:

1. The Administrative Cores or Clinical sites will send newsletters and reminder cards (such as birthday and/or holiday postcards) to participants to keep them engaged during the course of the study.
2. Study Coordinators will reach out to participants quarterly to maintain engagement in the study.
3. The Recruitment and Retention Committee will closely monitor recruitment and retention data and adjust their strategies to address the specific needs or problem areas that are identified as the study progresses.

12.2 WITHDRAWALS

Participants may withdraw from RADIANT if they no longer wish to continue participating in the study. If a participant states that they no longer wish to continue in the study, the following steps should be taken:

1. Site staff should document the conversation with the participant in the Contact Log of the Participant Profile
2. Site staff should complete a local Note To File specifying the withdrawal and the reason (if known). This should be stored locally.
3. Site staff should update the participant's status to 'withdrawn' – see section 13.3.6 for information on how to change a participant's status. Be sure to document the reason for withdrawal (if known) in the status comment box when updating the status.
4. Once a participant withdraws, they should no longer be contacted by RADIANT study staff.

If a participant changes their mind and recontacts RADIANT in the future asking to rejoin the study, their participant status would be updated to active, and they would need to consent in order to move forward in the study (e.g. if they withdrew prior to the Stage 3 Standard Visit, they would begin consent with the Stage 3 Standard Visit/Stage 3 Tier 1 consent form).

- Email radiantteam@atypicaldiabetesnetwork.org if this occurs for assistance with the status change back to active participation

13 DATA MANAGEMENT#

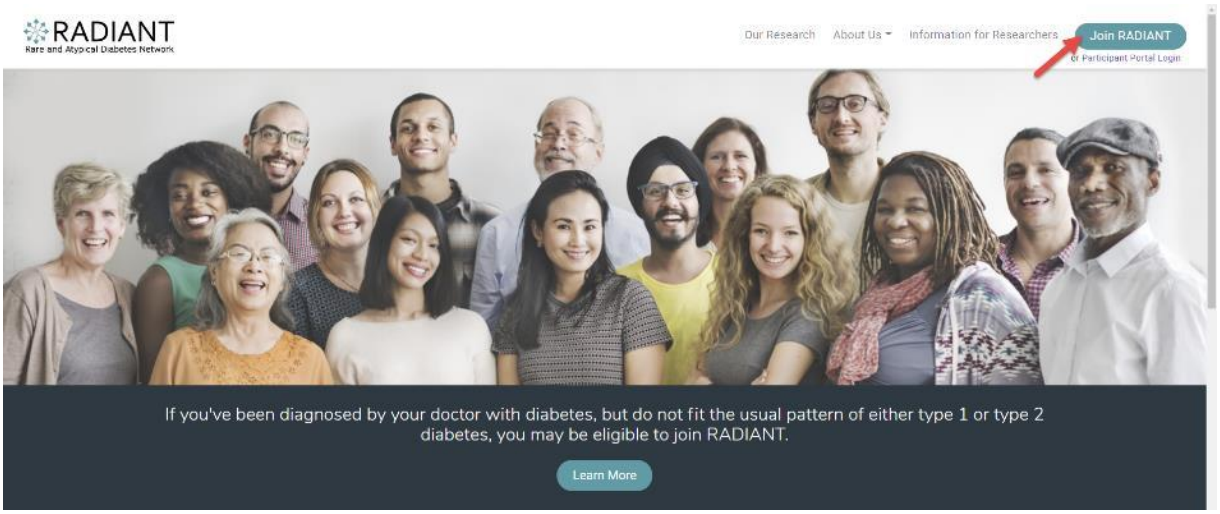
13.1 PUBLIC WEBSITE

The RADIANT Public Website (https://www.atypicaldiabetesnetwork.org) includes information about the RADIANT study, how to join the study, a list of the participating clinical centers, information for researchers, a link to the RADIANT Participant Portal login, a link to the RADIANT Members Website login and more.

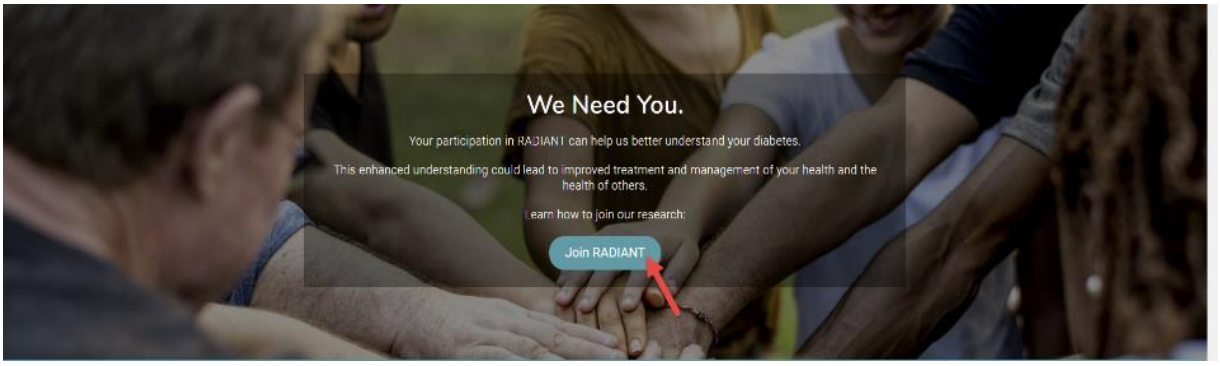
13.1.1 JOINING RADIANT VIA PUBLIC WEBSITE

Patients can join RADIANT via the Public Website as described below:

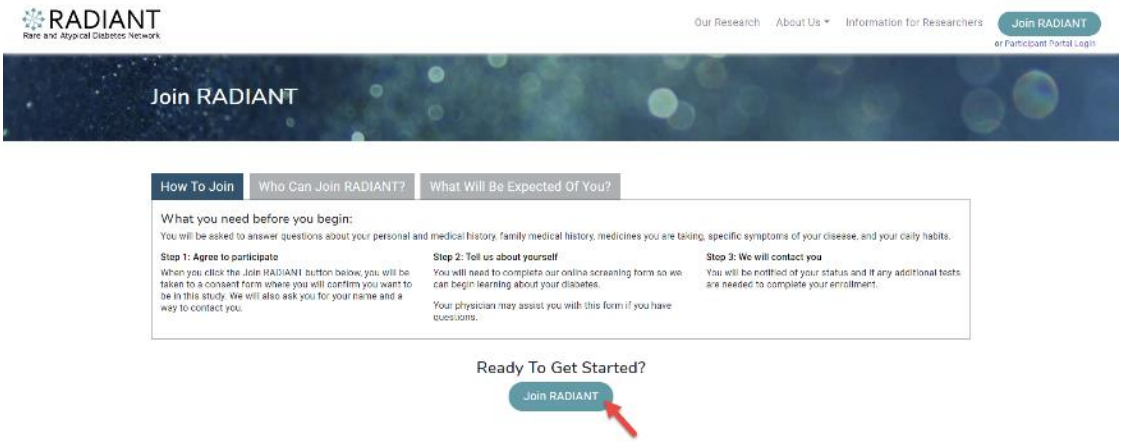
1. Go to the public website: https://www.atypicaldiabetesnetwork.org
2. Click the “Join RADIANT” button. This button is located in two places on the homepage:
    a. Upper right hand corner of the public website homepage



    b. In the “We Need You” section on the homepage (scroll about halfway down the homepage)



3. The “Join RADIANT” webpage will open. This page includes information on how to join, who can join, and what will be expected. Click “Join RADIANT” at the bottom of the page.

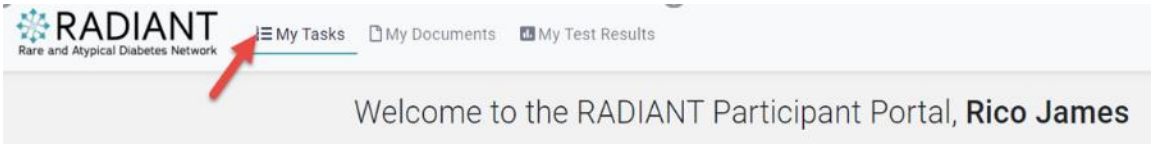


4. The online RADIANT Stage 1 Informed Consent Form will open. Read the consent form, answer the questions, and click “Submit”.
5. If the participant agreed to participate in the study, a copy of the consent form will be automatically emailed to the participant.

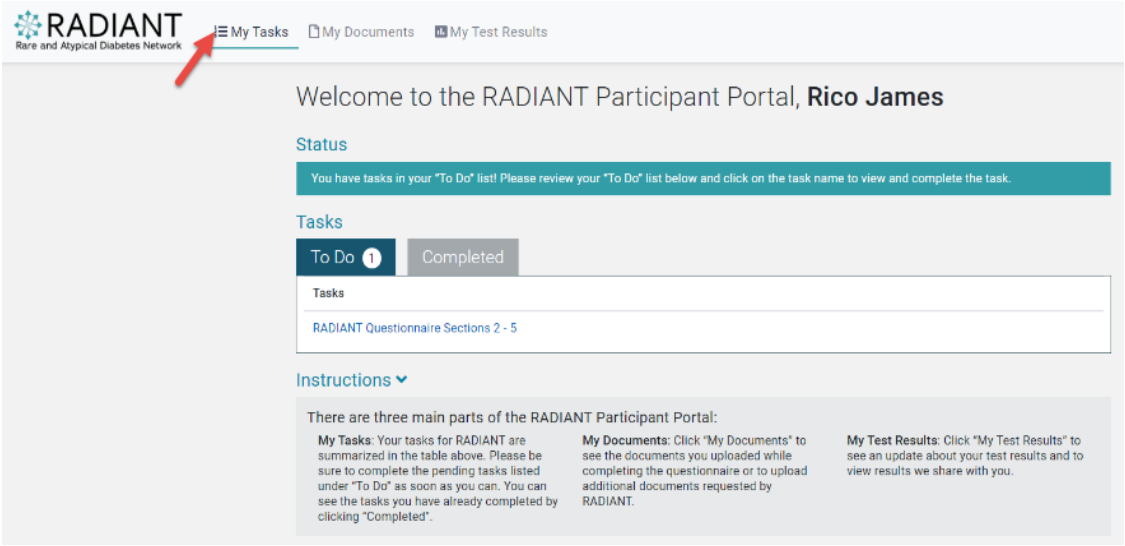
13.2 PARTICIPANT PORTAL

The RADIANT Participant Portal is an online portal for study participants to complete study tasks such as the stage 1 questionnaire sections 2-5, upload documents, and view study results. Screen Pass participants will be prompted to set-up an account for the Participant Portal (section 13.2.1). After setting up their account, participants must login in with their email address and password to access the Participant Portal (section 13.2.2).

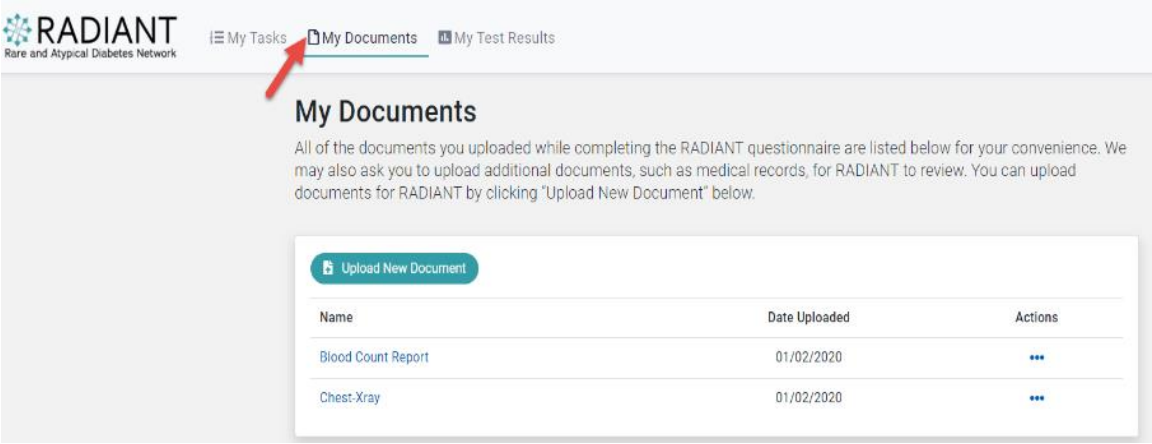
The Participant Portal consists of three main sections: My Tasks, My Documents, and My Test Results. The participant can navigate to each section by clicking the section name at the top of the Participant Portal webpage as shown below:



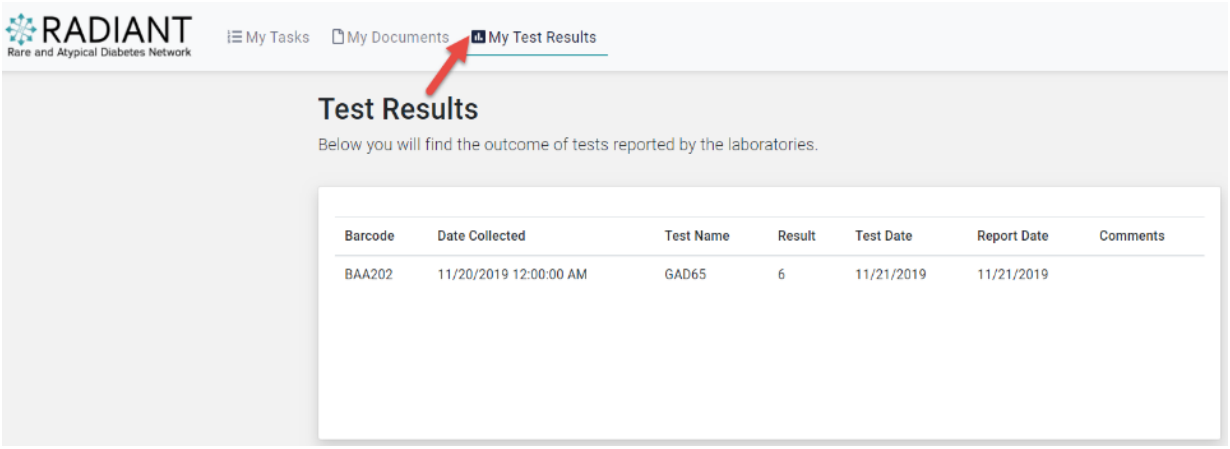
1. My Tasks: The My Tasks section is displayed by default when the participant logs in to the Participant Portal. Pending tasks are listed under “To Do”. The participant can click the “Completed” tab to view tasks they have already completed. This section also includes a status update for the participant in green and an instructions summary at the bottom.



2. My Documents: The “My Documents” section displays all of the documents the participant uploaded while completing the Stage 1 questionnaire. The participant may choose to upload additional documents by clicking “Upload New Document”.



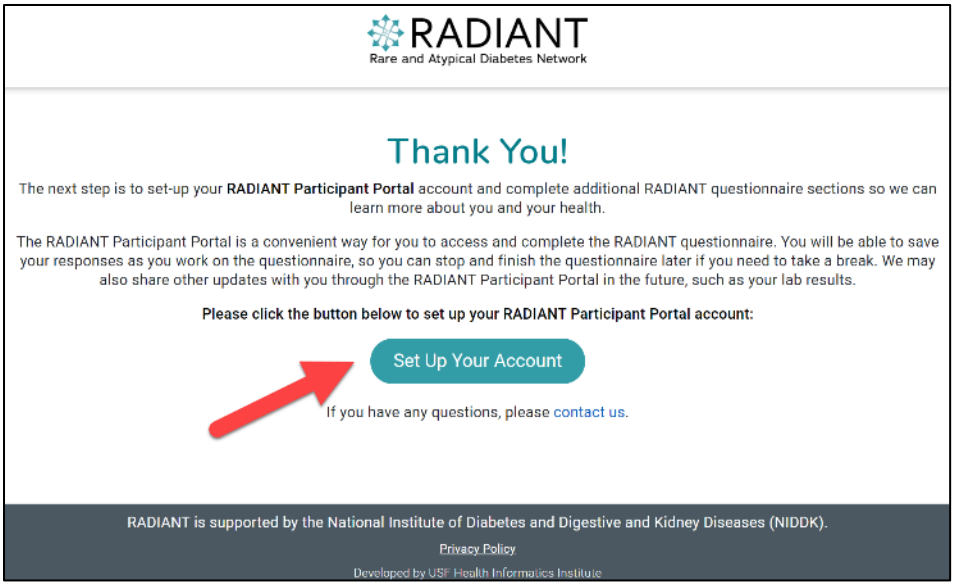
3. My Test Results: The “My Test Results” section includes the participant’s test results reported by the lab, if the participant agreed to receive test results in the consent form.



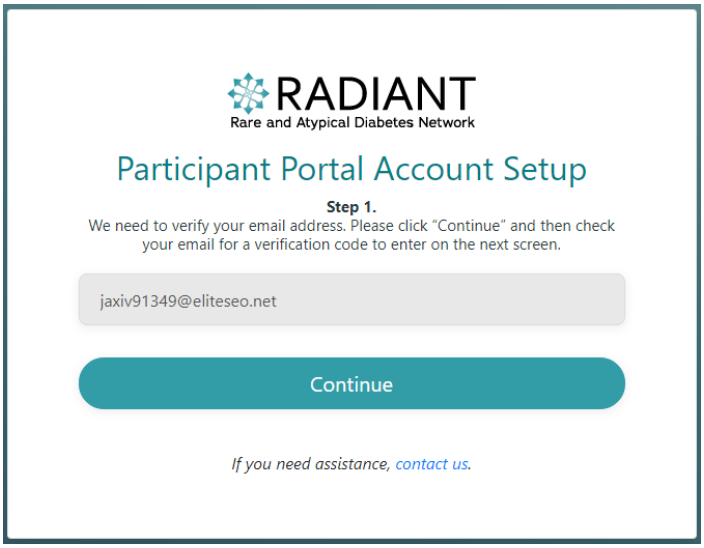
13.2.1 PARTICIPANT PORTAL ACCOUNT SET-UP

Screen Pass participants will follow the steps below to set up their RADIANT Participant Portal account:

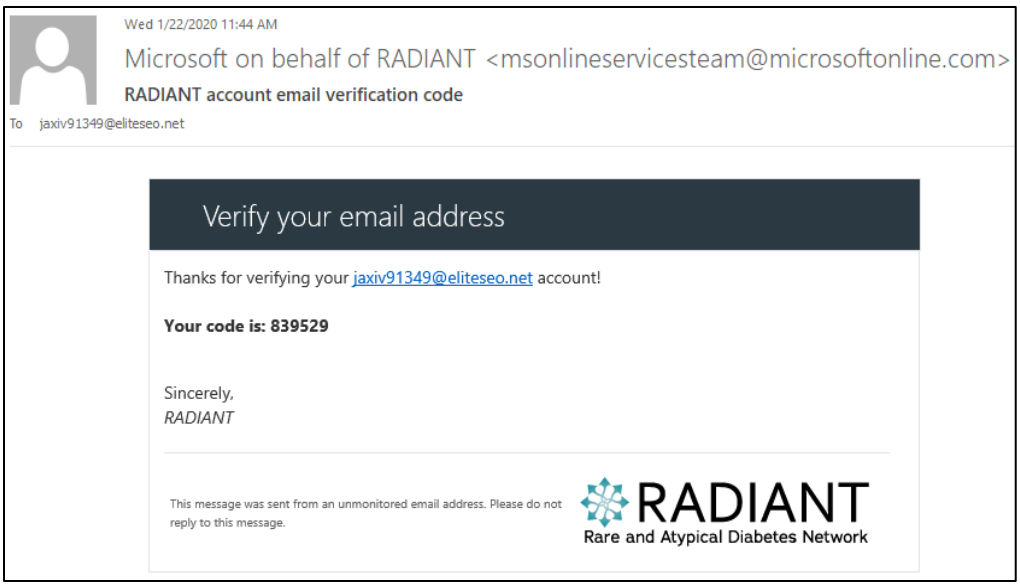
1. After completing Section 1 of the Stage questionnaire, participants with a status of “Screen Pass” will see the message below. The participant will click on “Set Up Your Account” to proceed.



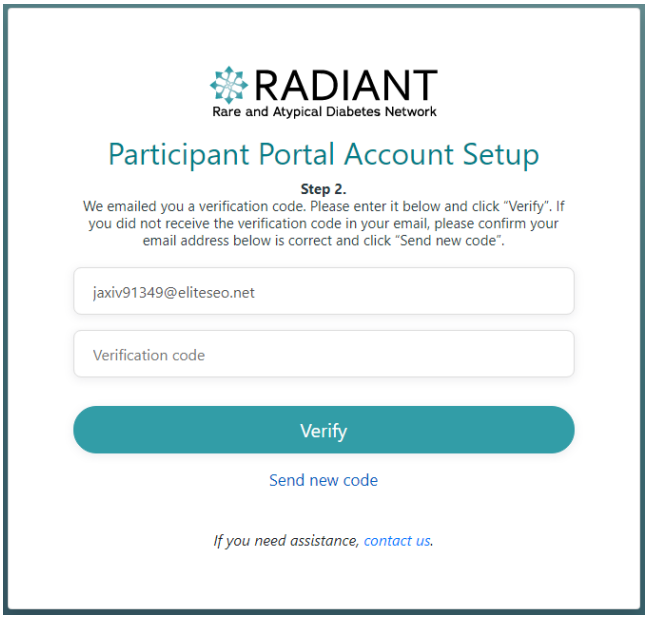
2. The Participant Portal Account Set-up module will open. The participant will click “Continue” to begin the email verification process.



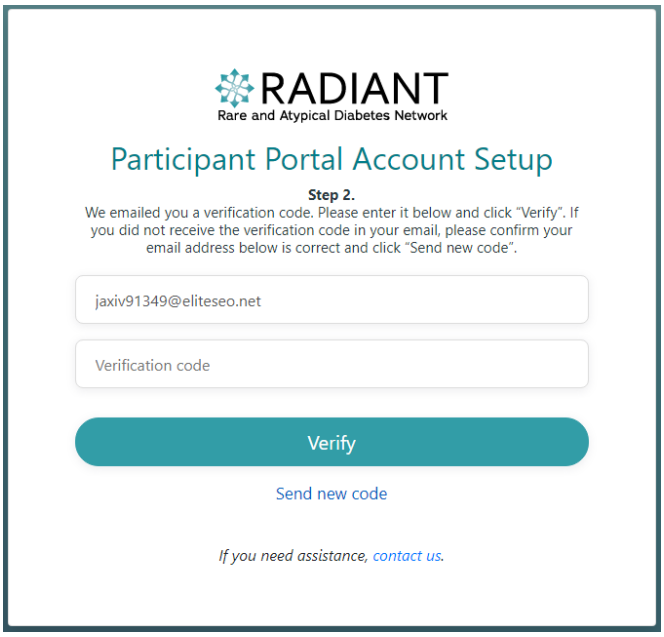
3. An email will be sent to the participant with a verification code. Example shown below:



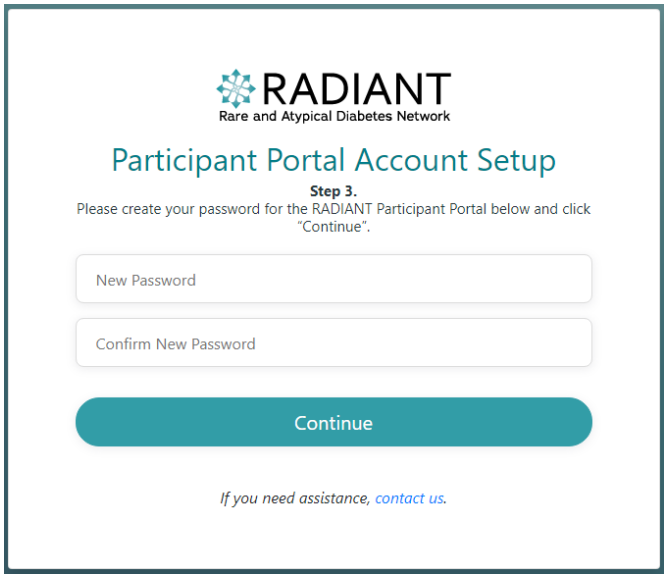
4. Participant will enter the verification code in the Participant Portal account set-up module and click “Verify”.



5. If the participant did not receive the verification code email, the participant can click “Send new code” to receive another verification code email.



6. After the verification code is entered, the participant will create their password and click “Continue”.

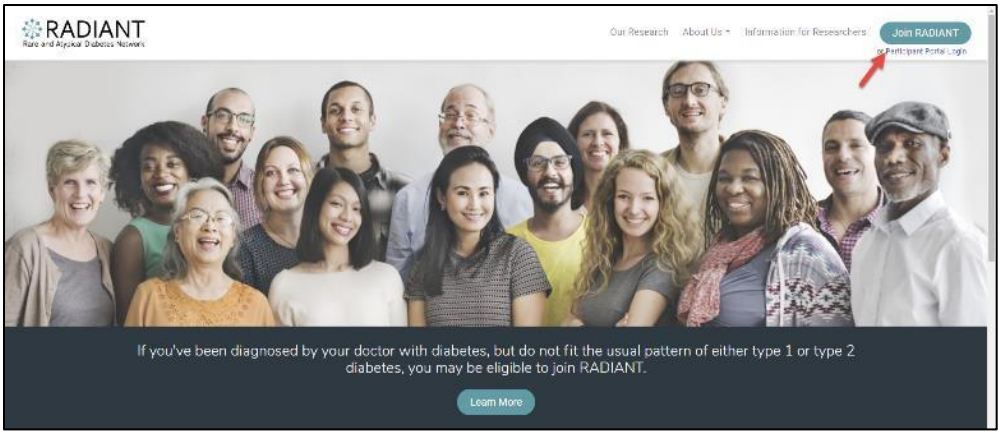


7. Participant Portal account set-up is complete. The participant can login to the Participant Portal with their email address and password.

13.2.2 PARTICIPANT PORTAL LOGIN

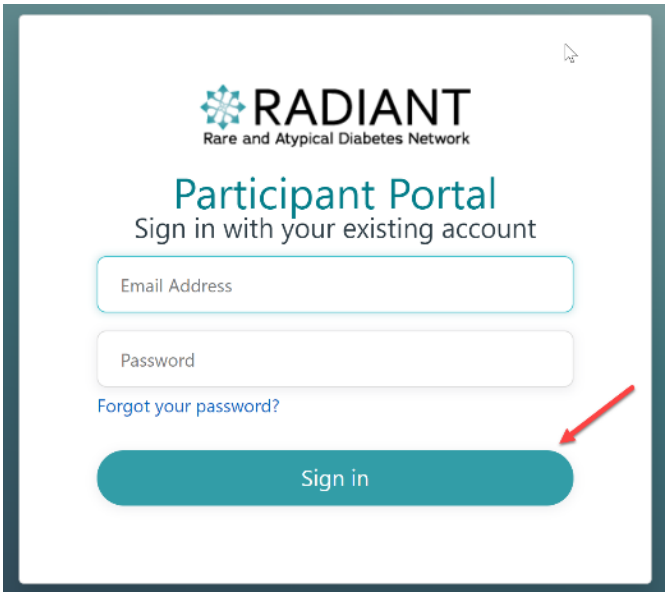
After a participant sets up their Participant Portal account (section 13.2.1), they can then login to the Participant Portal at any time following the steps below.

1. Navigate to the Participant Portal Login Page. Participants can navigate to this page three different ways:
    a. Go to: https://portal.atypicaldiabetesnetwork.org. This is the direct link to the Participant Portal login page.
    b. Go to the RADIANT Public Website: https://www.atypicaldiabetesnetwork.org
        i. Click on “Participant Portal Login” at the top right corner of the homepage

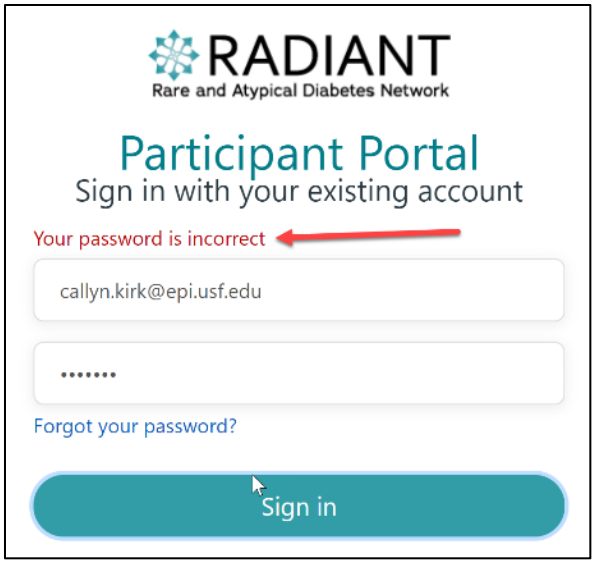


ii. OR, scroll to the bottom of the homepage and click “RADIANT Participant Portal Login”

2. The “Participant Portal Login” page will open. The participant will enter their email address and the password they created during the account set-up process (section 13.2.1), and click “Sign in”.



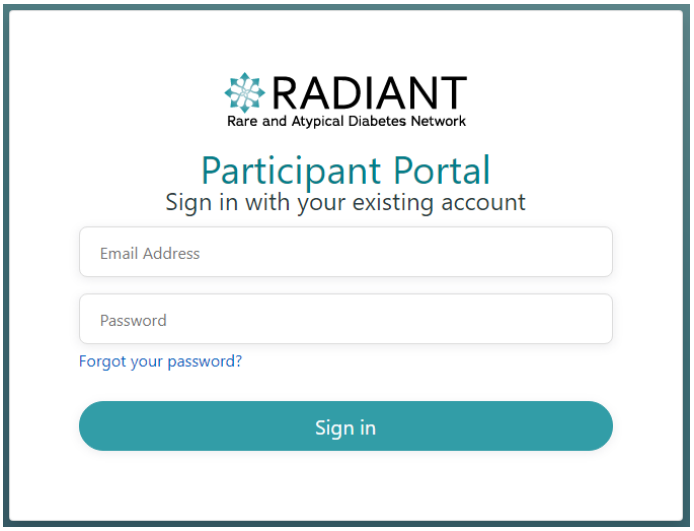
3. The email address and password will be verified by the system and, if accurate, the participant will be logged into the Participant Portal. If the password is incorrect, the participant will receive an error message (see screenshot below). The participant can either try re-entering their password or can reset their password (section 13.2.3).



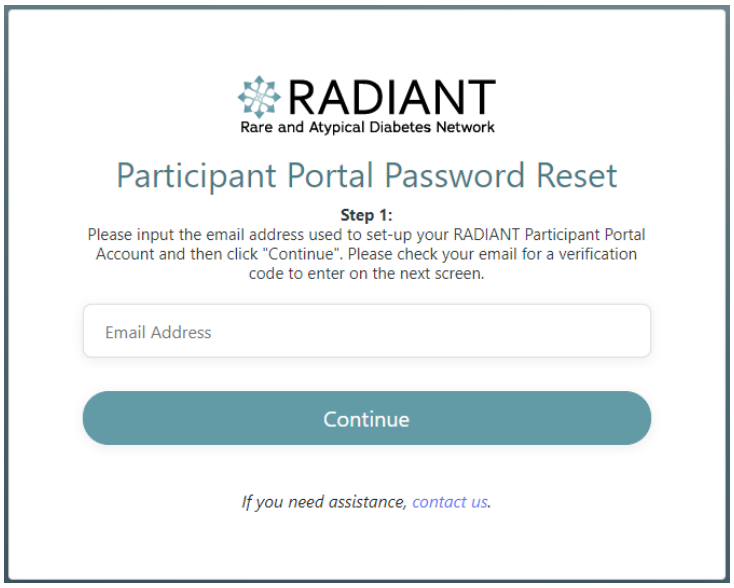
13.2.3 PARTICIPANT PORTAL PASSWORD RESET

Participants can reset their Participant Portal password by following the steps below:

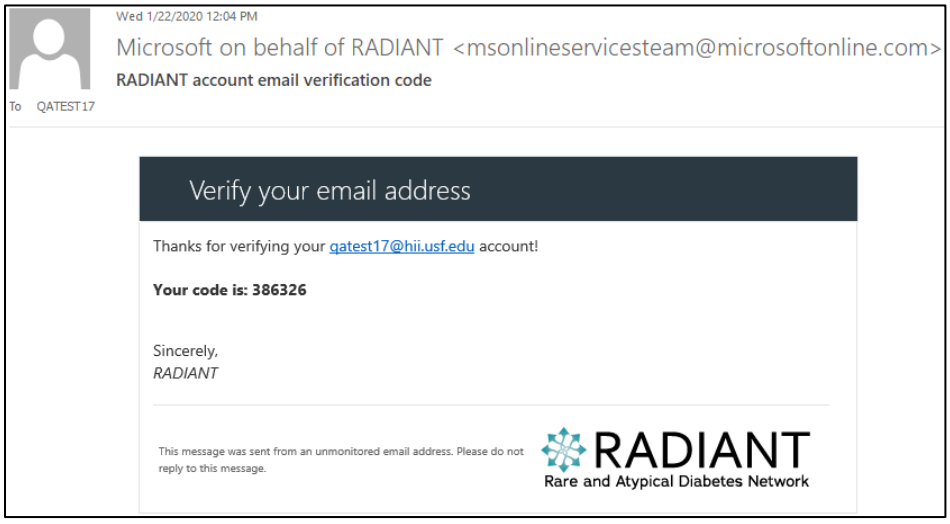
1. On the Participant Portal login page, click “Forgot your password?”



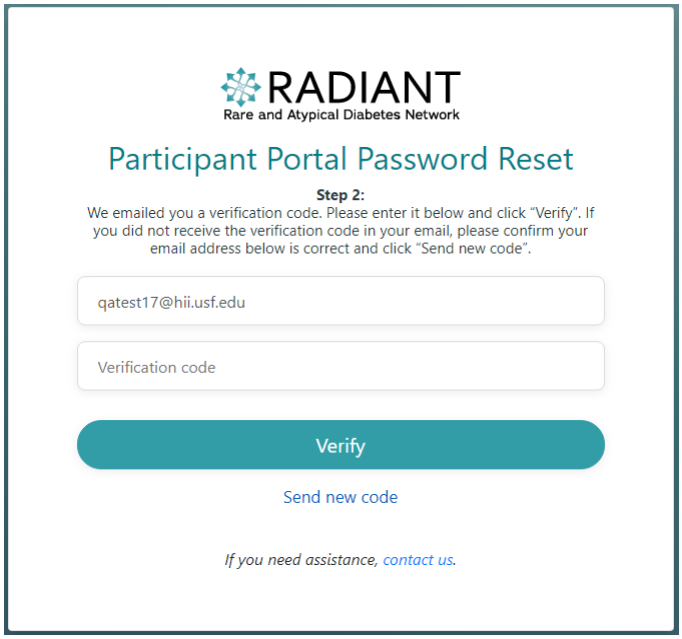
2. The Participant Portal Password Reset module will open. The participant will enter the email address used to sign up for RADIANT Participant Portal and click “Continue”.



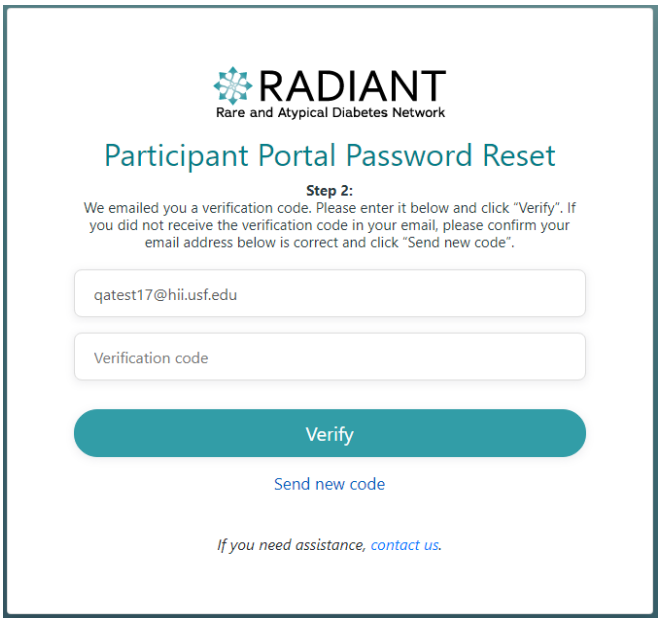
3. A verification code will be emailed to the participant.



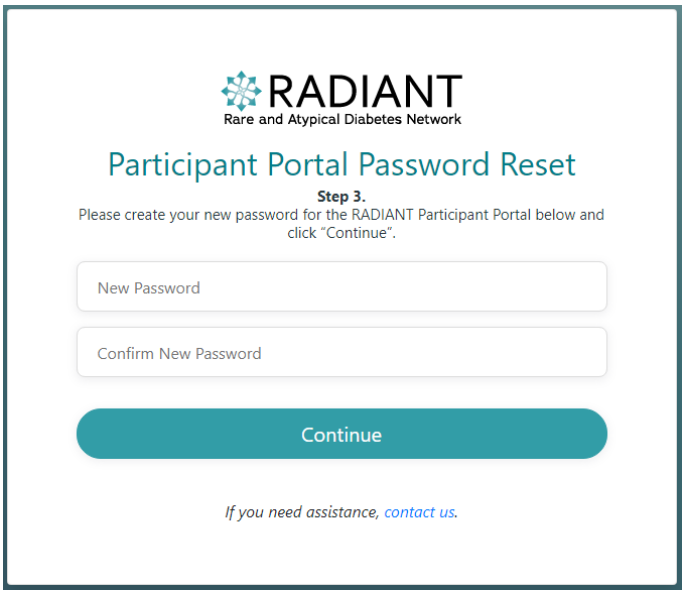
4. The participant will type the verification code in the “Verification code” box and click “Verify”.



5. If the participant did not receive the verification code, the participant can click on “Send new code” to receive another verification code email.



6. After the code is verified, the participant will be prompted to create a new password. The participant will type the new password twice and click “Continue” to proceed.



7. Password reset is now complete. The participant can login to the Participant Portal with their email address and new password.

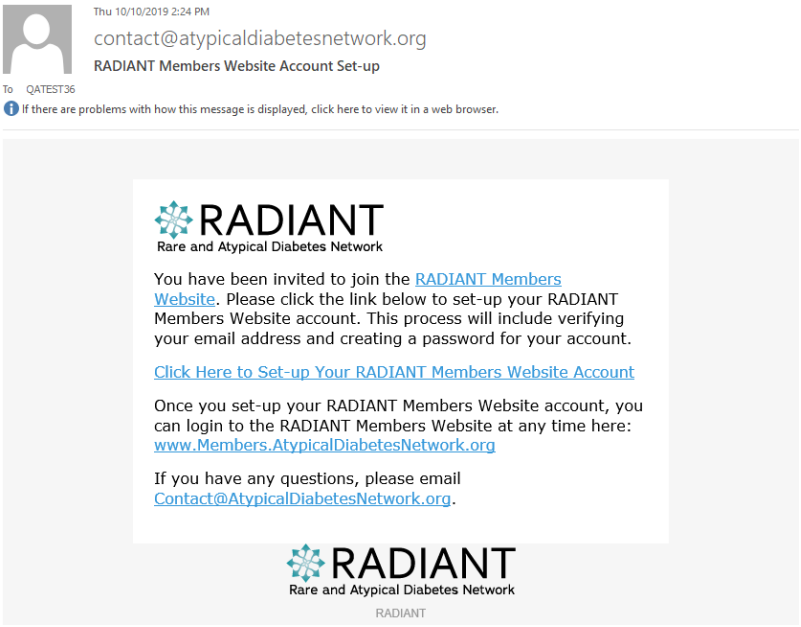
13.3 MEMBERS WEBSITE#

The RADIANT Members Website (http://members.atypicaldiabetesnetwork.orghttp://www.members.atypicaldiabetesnetwork.org/) is a RADIANT investigator and staff website that includes study materials, training modules, a member directory, and online data capture systems for RADIANT. Details on accessing and using the Members Website are included this section.

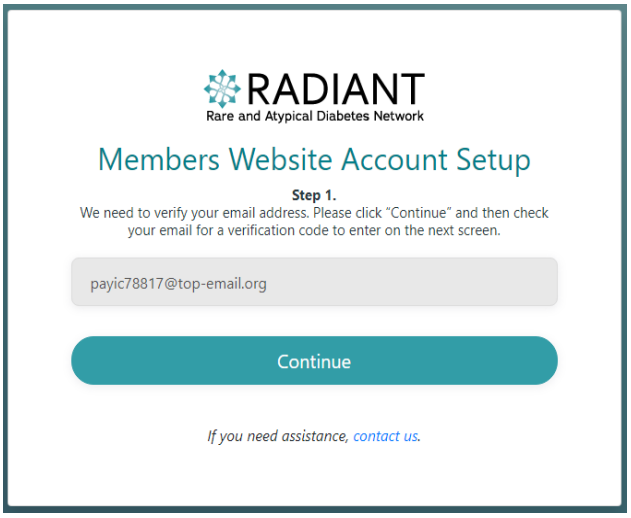
13.3.1 ACCOUNT SET-UP#

All RADIANT study team members must have a RADIANT Members Website account in order to login and access the RADIANT Members Website. The process for setting up a Members Website account is described below:

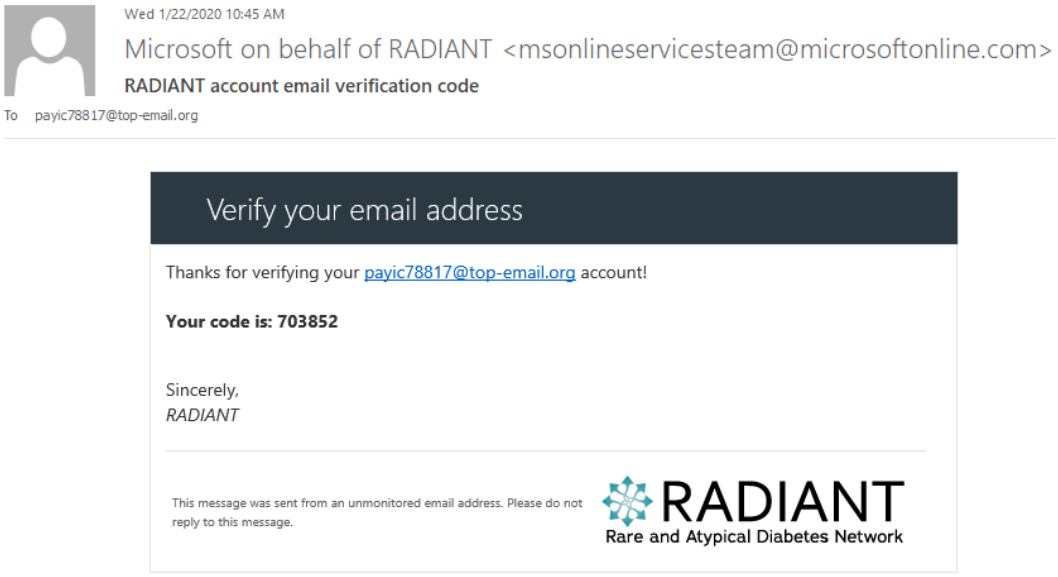
1. The new member must be added to the Member Directory in the RADIANT Members Website by the DCC, Administrative Core Project Managers, or other local study team members who already have a Members Website account. (See section 13.3.4 for more information about the Members Directory and how to add a new member to the Member Directory.)
2. After the member is added to the Member Directory, the member will receive an email with a link to set-up their Members Website account. The following steps are actions the new member must take to complete their account-setup.
3. Upon receiving the RADIANT Members Website Account Set-up email, click 'Click Here to Set-up Your RADIANT Members Website Account' in the email.



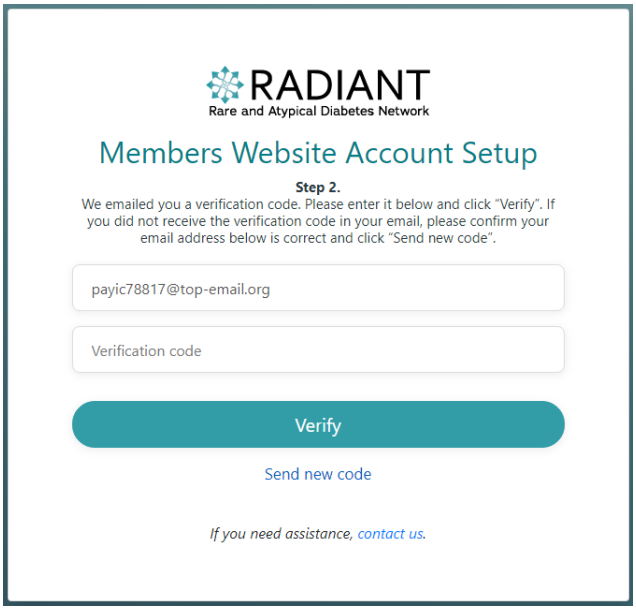
4. The Members Website Account Setup module will open. Click “Continue”.



5. You will receive an email with a verification code.

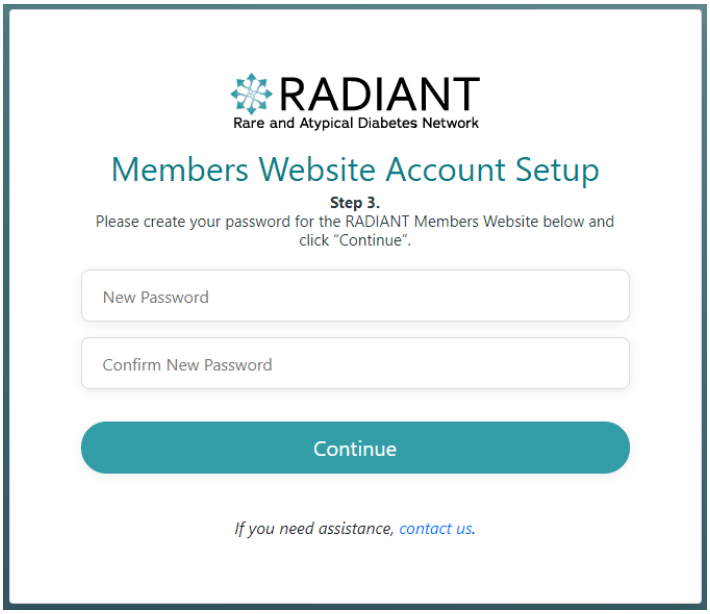


6. Enter the verification code in the “Verification code” box and click “Verify”.

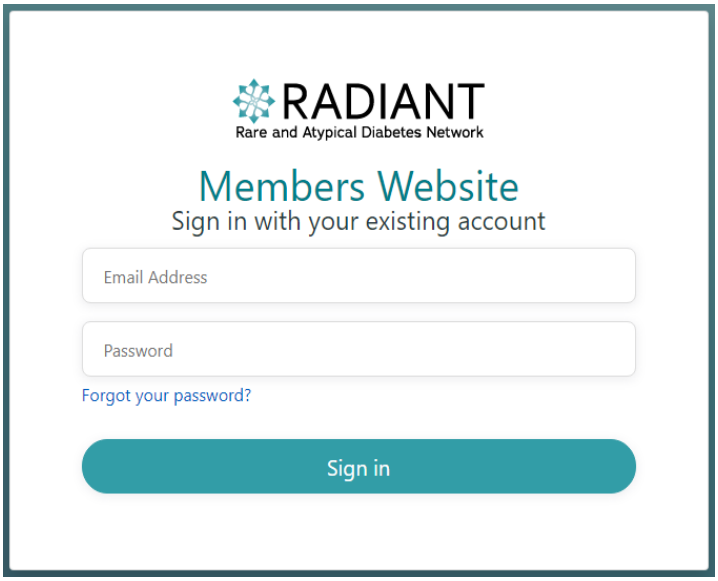


7. If you did not receive the verification code, you can click on “Send new code” to receive another verification code email.

8. Once you have successfully entered the verification code, you will be prompted to create your password for the Members Website. Type your password in the “New Password” and “Confirm New Password” fields and click “Continue” to proceed.



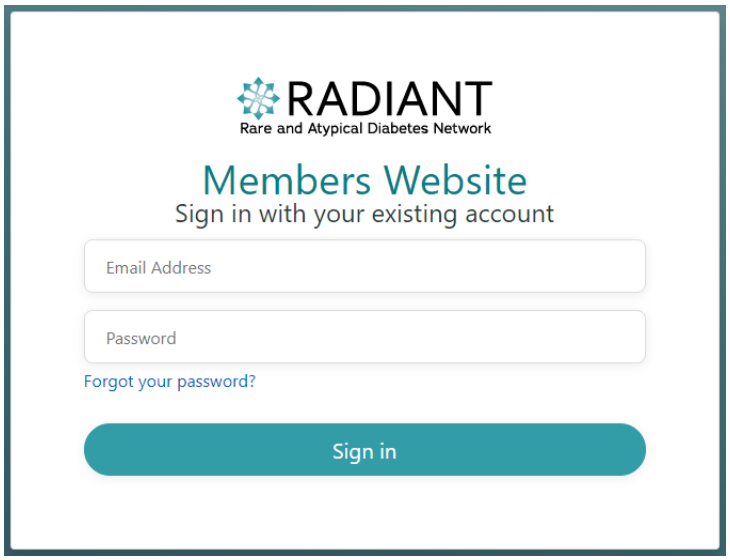
9. You have completed the Members Website Account Setup process. The login page will appear. You may now login to the Members Website with your email address and password.



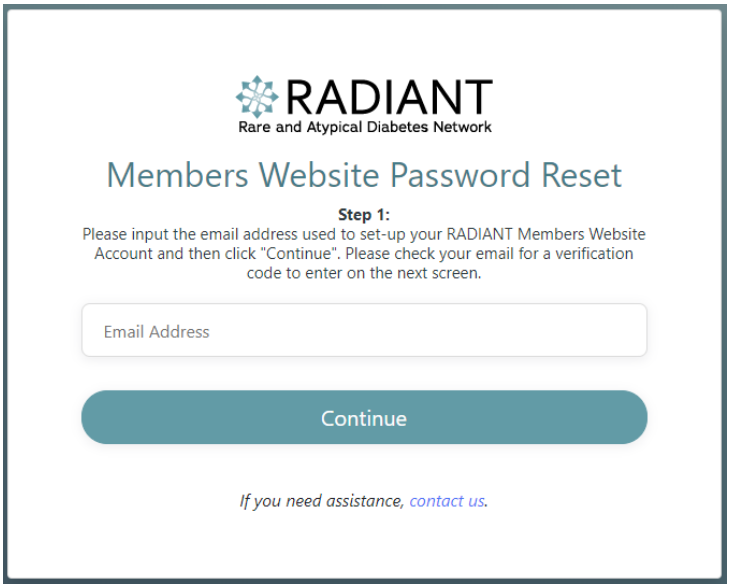
13.3.2 PASSWORD RESET#

Members can reset their Members Website Account password by following the steps below:

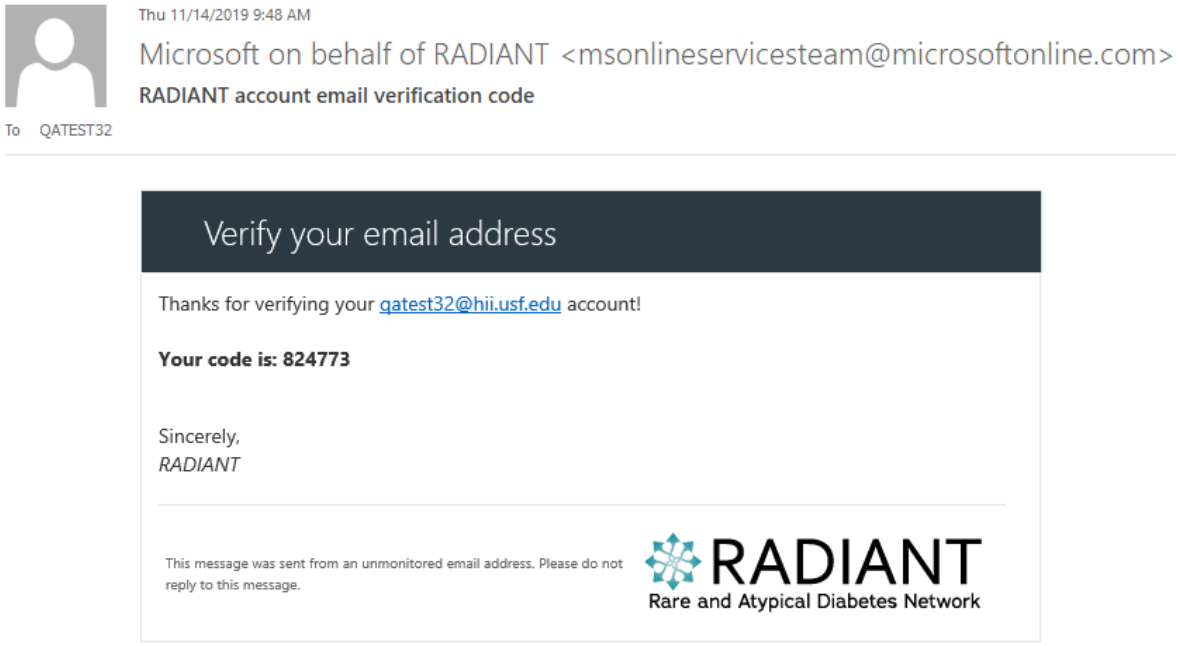
1. On the Members Website login page, click "Forgot your password?"



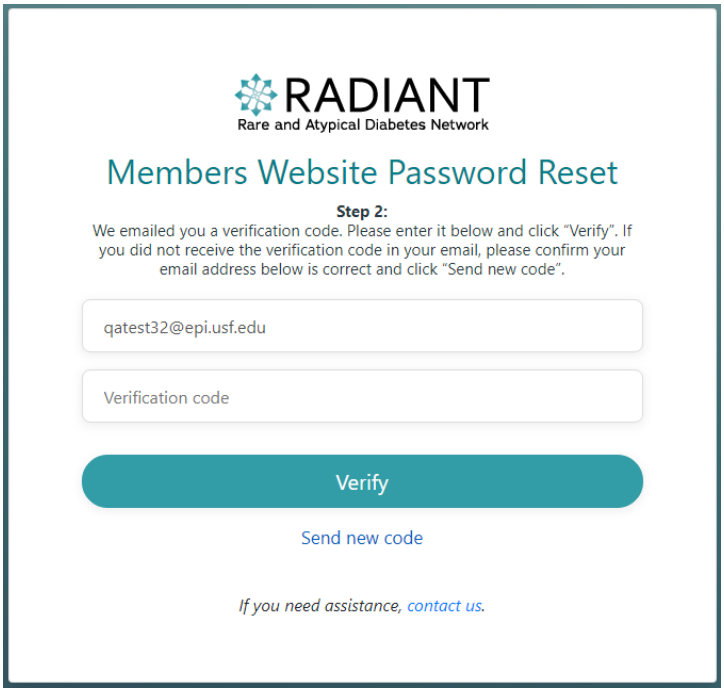
2. The Members Website Password Reset module will open. Type in the email address affiliated with your RADIANT Members Website account and click “Continue”.



3. You will receive an email with a verification code.

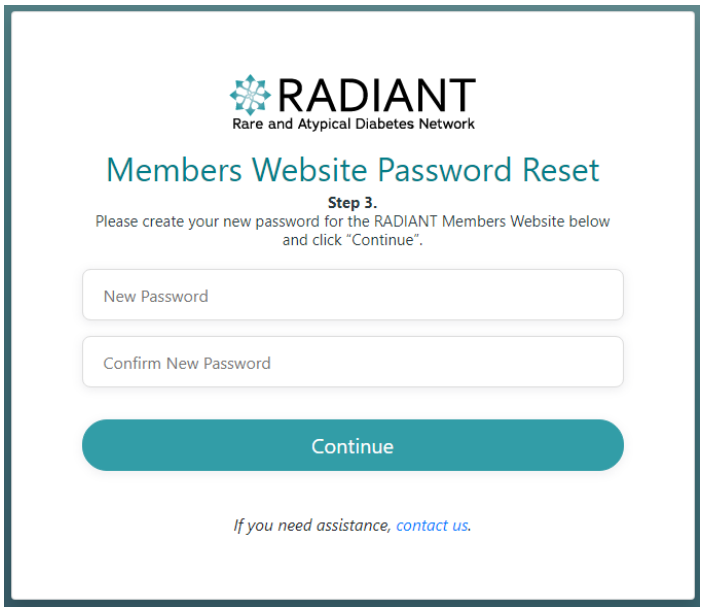


4. Enter the verification code in the “Verification code” box and click “Verify”.

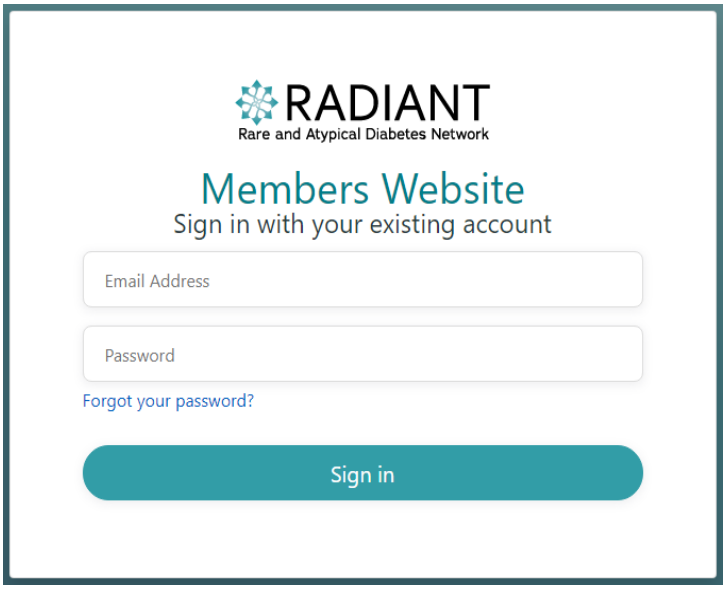


5. If you did not receive the verification code, click “Send new code” to receive another verification code email.

6. Once you have successfully entered the verification code, you will be prompted to create your new password for the Members Website. Type your password in the “New Password” and “Confirm New Password” fields and click “Continue” to proceed.

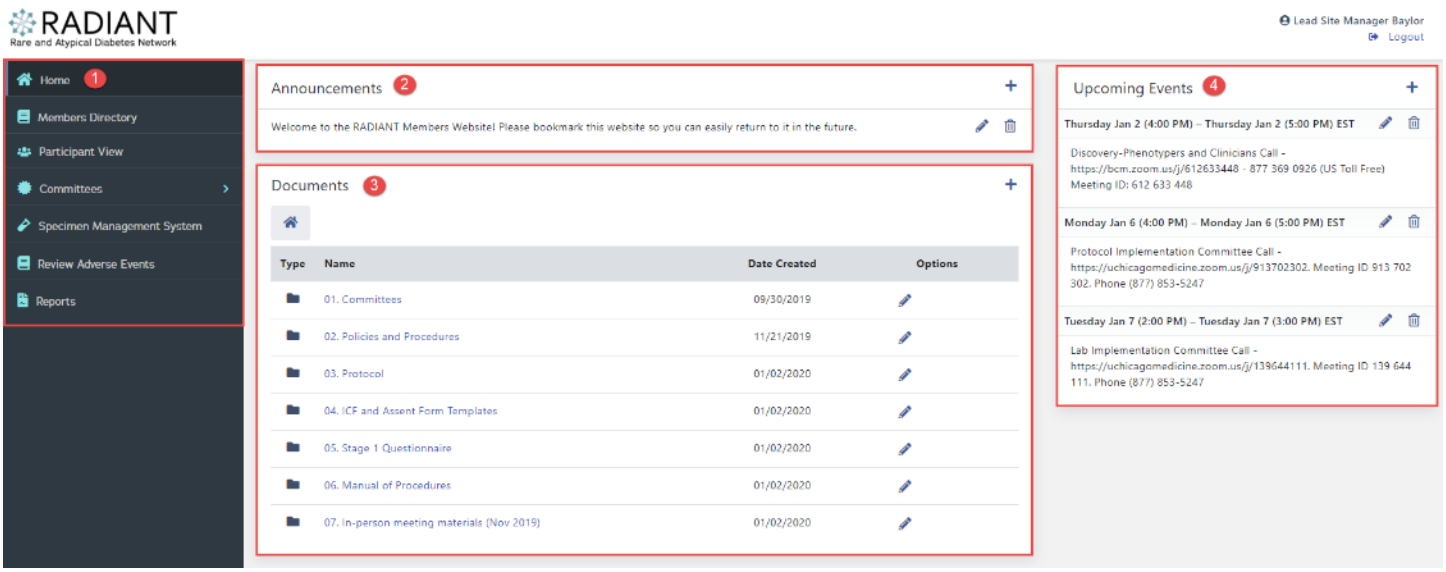


7. You have completed the Members Website Password Reset process. The login page will appear. Login to the Members Website with your email address and new password.



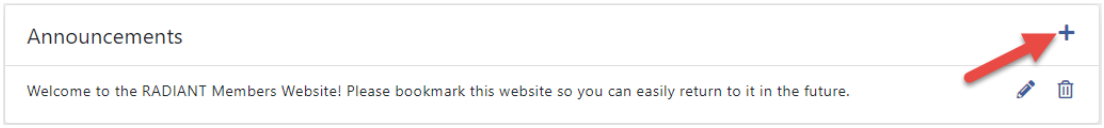
13.3.3 MEMBERS WEBSITE HOMEPAGE OVERVIEW#

The Members Website homepage consists of four main sections:

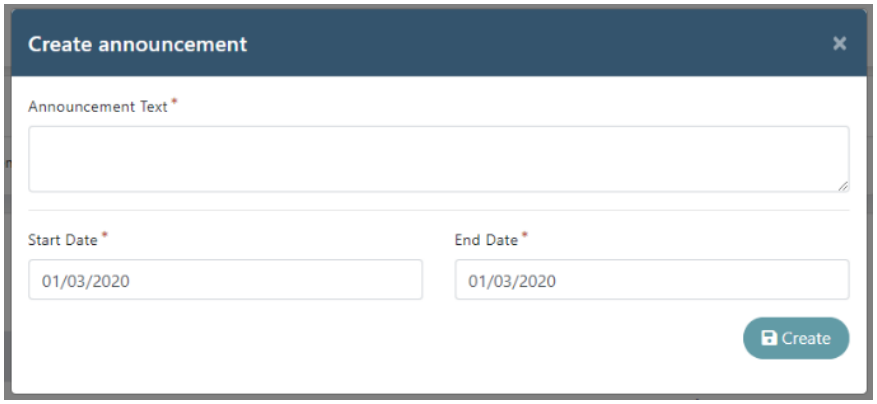


- **Left-hand Navigation Pane:** This section includes links to different parts of the Members Website (ex. Members Directory, Participant View, Committees, Specimen Management System, Reports). The particular links that appear in your left-hand navigation pane depend on your role in the study, as some parts of the Members Website require special permissions.

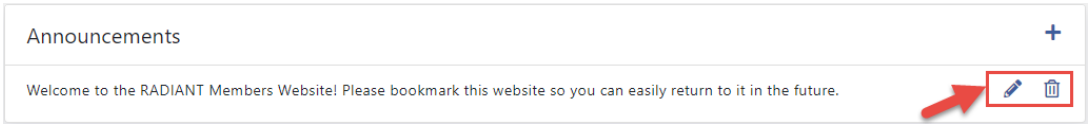
- **Announcements:** This section includes announcements intended for all members. The DCC and Administrative Core Project Managers may add announcements.
  - *How to Add New Announcements:*
    - Click on the + icon in the Announcements section of the Home page.



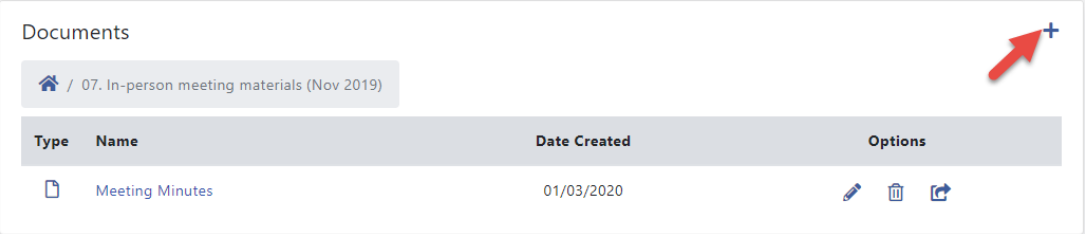
    - A pop-up window will appear like the picture below. Enter the Announcement Text, Start Date and End Date. Click 'Create' when you are done.



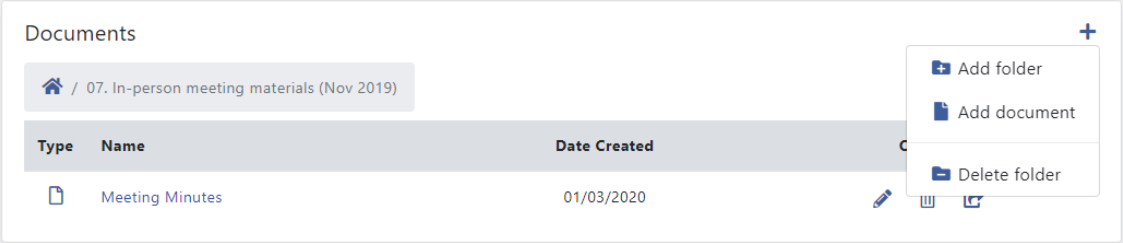
  - *How to Edit/Delete Existing Announcements:* Click on the pencil icon to edit the announcement or click on the trash icon to delete the announcement. If you choose to delete an announcement, you will need to Confirm deletion.



- **Documents:** This section consists of folders with specific documentation relating to RADIANT, such as the Protocol, ICF and Assent Form Templates, Policies and Procedures, Manual of Procedures, Recruitment Materials, and Committee Materials. Click on the folder name to view the documents within the folder.
    - *How to Add/Delete Documents and Document Folders:*
        - Click on the + icon in the Documents section.

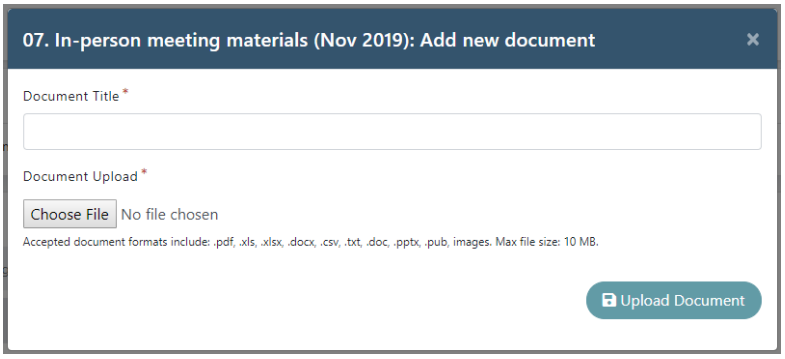


        - A pop-up window will appear like the picture below. Click “Add folder”, “Add document”, or “Delete folder”.

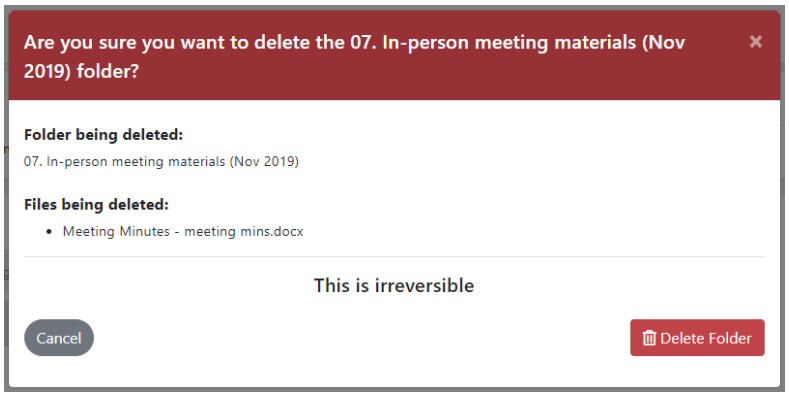


            - Add folder: a pop-up window will appear like the picture below. Enter Folder Name and click ‘Add folder’ when you are done.

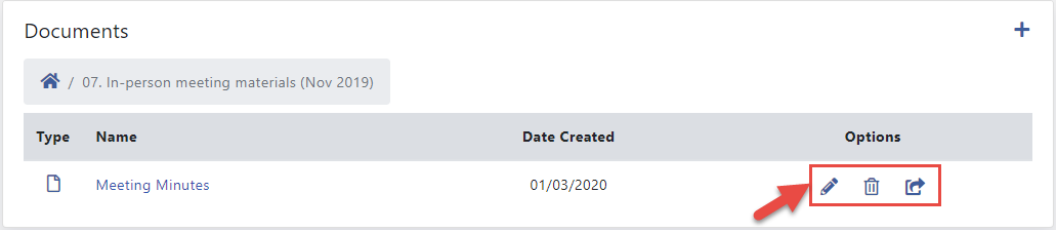
            - Add document: a pop-up window will appear like the picture below. Enter Document Title and choose a file to upload under Document Upload. Click ‘Upload Document’ when you are done.



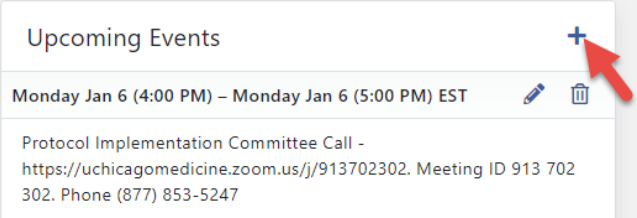
            - Delete Folder: a pop-up window will appear like the picture below. Confirm deletion. Please note that the action to delete is irreversible.



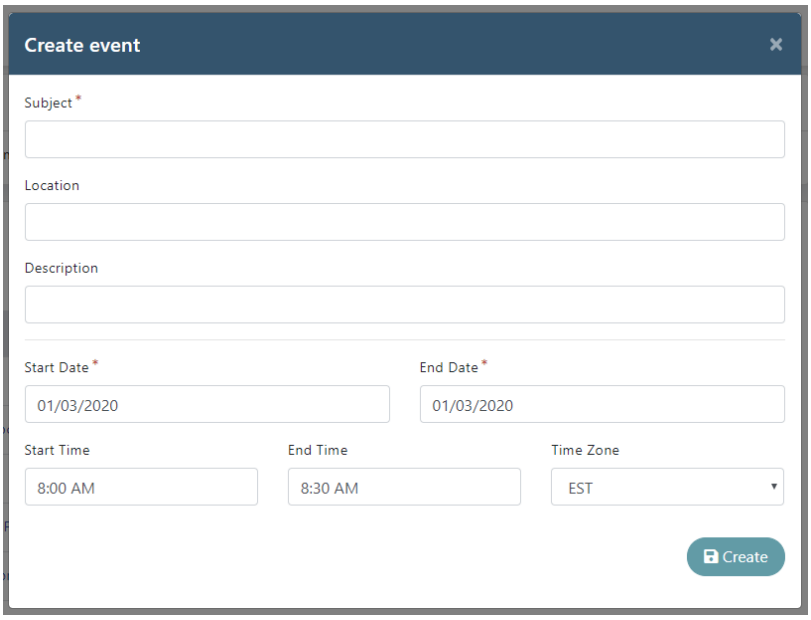
- Options for previously uploaded documents: Navigate to the document and review the "options" to the right of the filename (see screenshot below).
  - Click on the icon to rename the document.
  - Click on the icon to delete a document.
  - Click on the icon to copy the document link to conveniently share it with other study members.



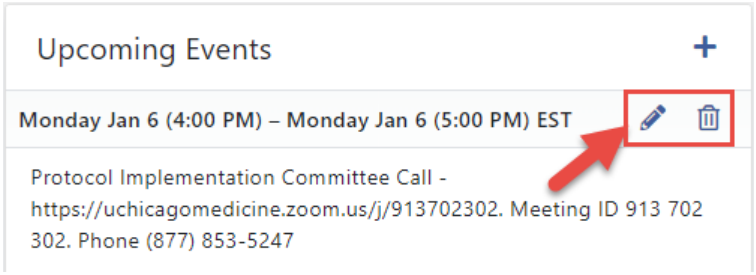
- **Upcoming Events:** This section lists upcoming events, such as the next in-person study group meeting.
  - *How to Add New Upcoming Events:*
    - Click on the + icon in the Upcoming Events section of the Home page.



    - A pop-up window will appear like the picture below. Enter the Subject, Start Date and End Date. Click 'Create' when you are done.

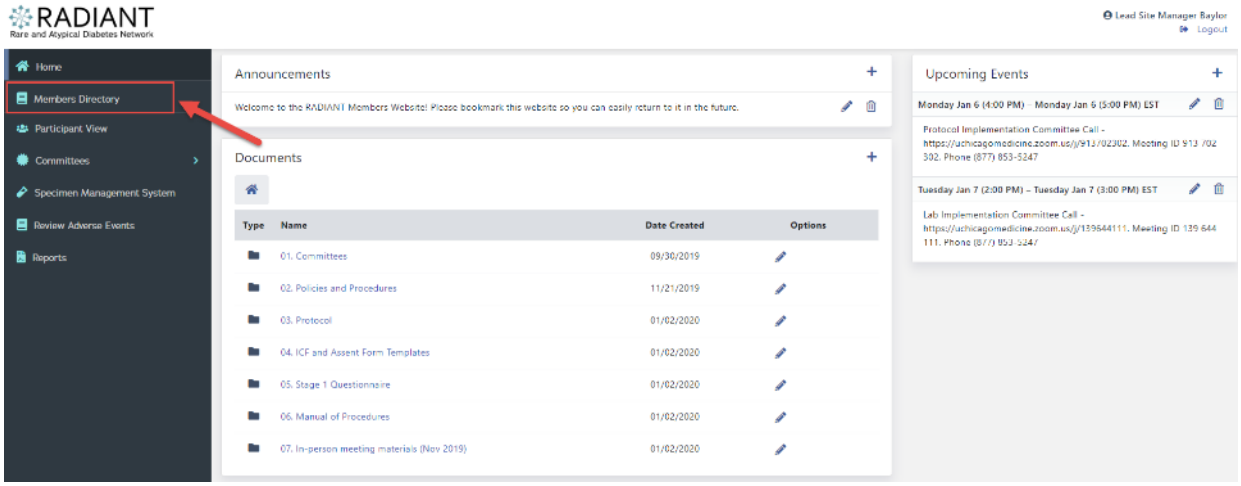


- *How to Edit Existing Upcoming Events:* Click on the icon next to the event date to edit the event or click on the icon to delete the event. If you choose to delete an event, you will need to Confirm deletion.

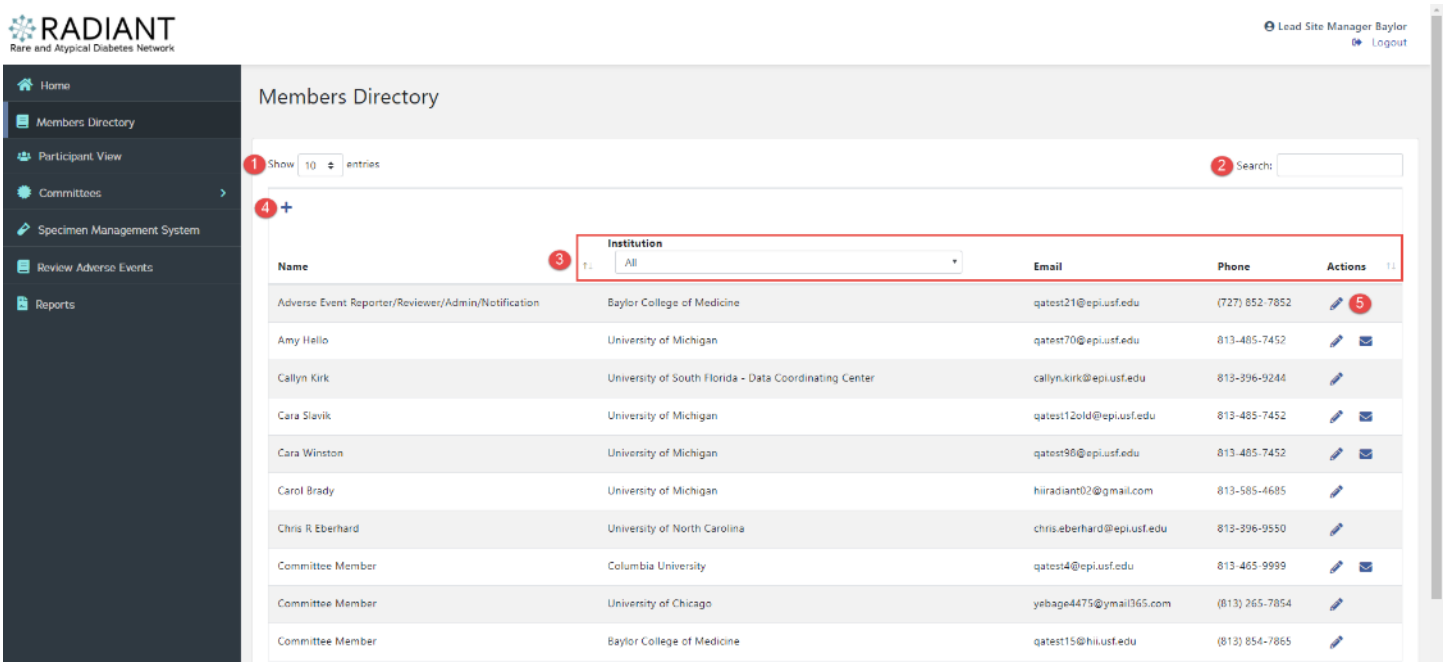


13.3.4 MEMBERS DIRECTORY#

The RADIANT Members Directory can be accessed from the left-hand navigation pane.



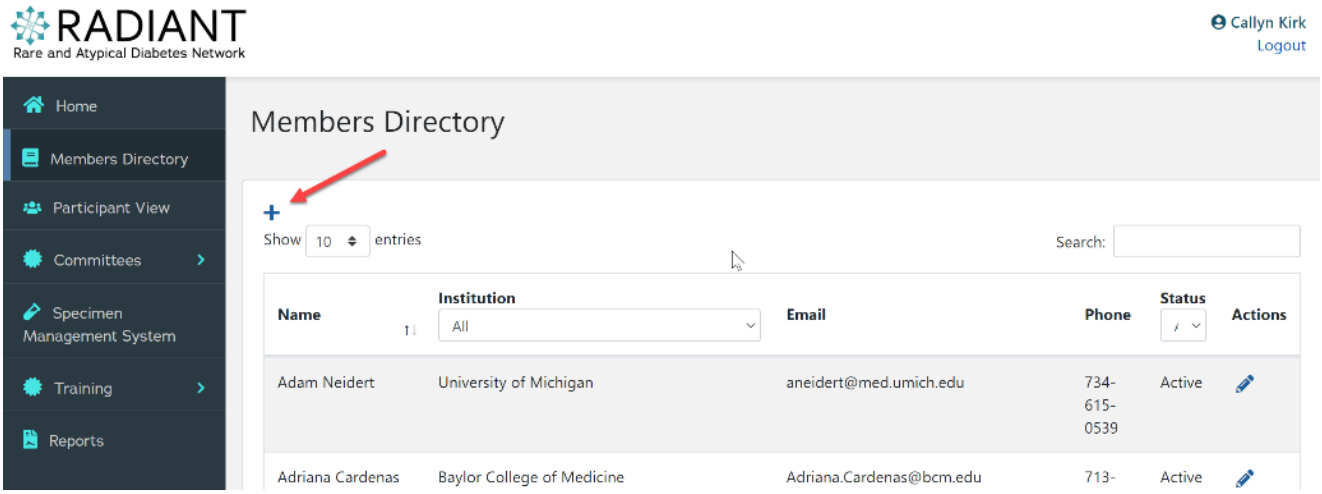
The Members Directory shows a list of each member with their Name, Institution, Email, and Phone. On this page, you have the ability to:



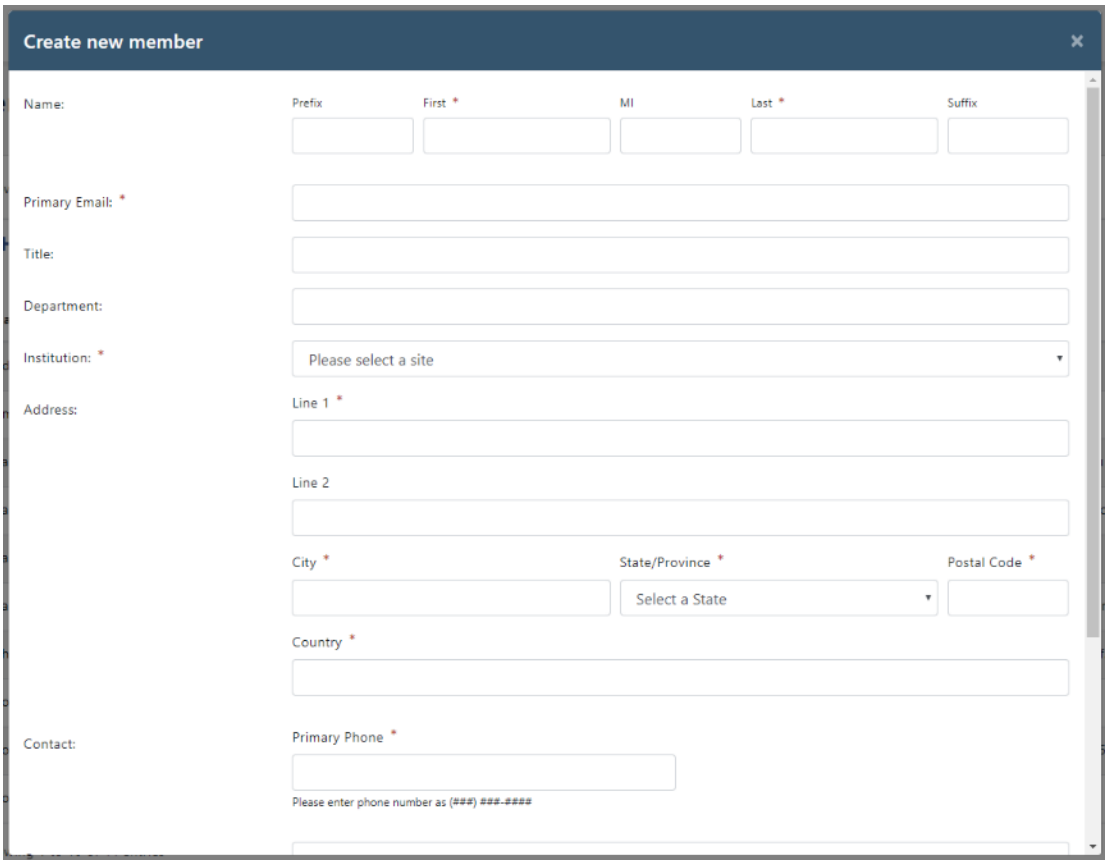
1. Show number of entries: This feature gives you the option of viewing 10, 25, 50, or 100 members listed at a time.
2. Search: This feature allows you to search for specific members.
3. Sort/Filter: This feature allows you to sort the members list by Institution or Actions. You can also filter by Institution.
4. Add new member: This feature allows you to add new members to the directory.
5. Edit member information: This feature allows you to edit/update member information.

How to Add a New Member:

- Click on the + icon.

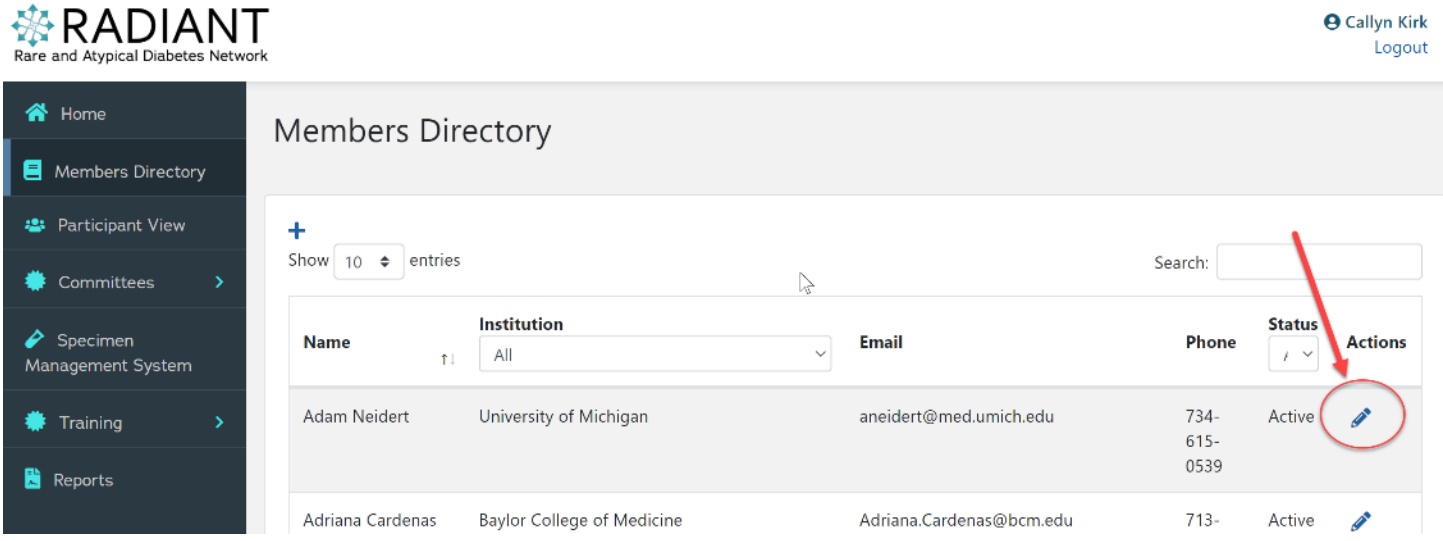


- The “Create New Member” Page will open. Enter the new member’s name and contact information. The following fields are required: First Name, Last Name, Primary Email, Institution, Address Line 1, City, State, Postal Code, Country, and Primary Phone. Click on ‘Add new member’ at the bottom of the page when you are done.

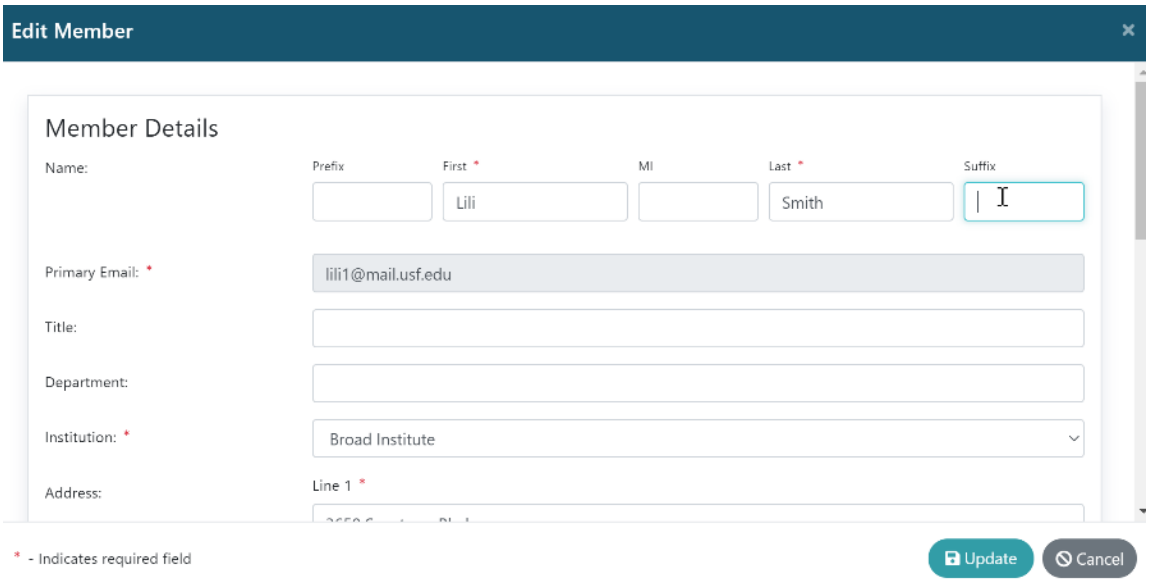


How to Edit/Update Member Information:

- Search for the member. (Tip: You may type the member's last name into the Search field.)
- Click on the icon next to name of the member.

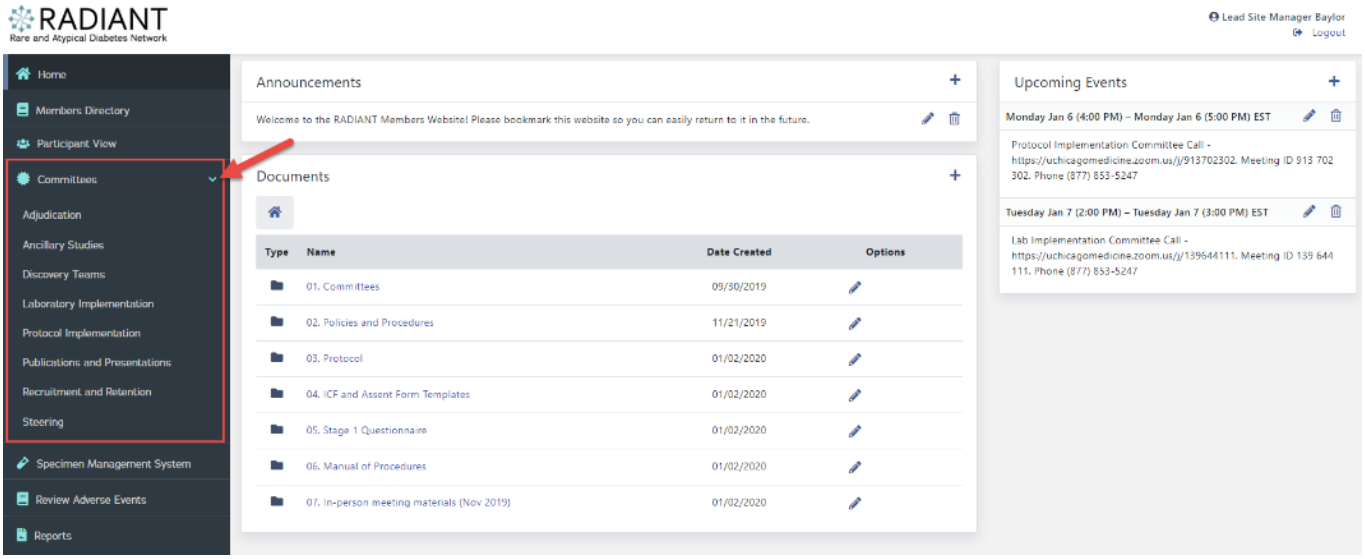


- The Edit Member page will open. Update the Member details as needed and click "Update" in the bottom right corner when you are done.



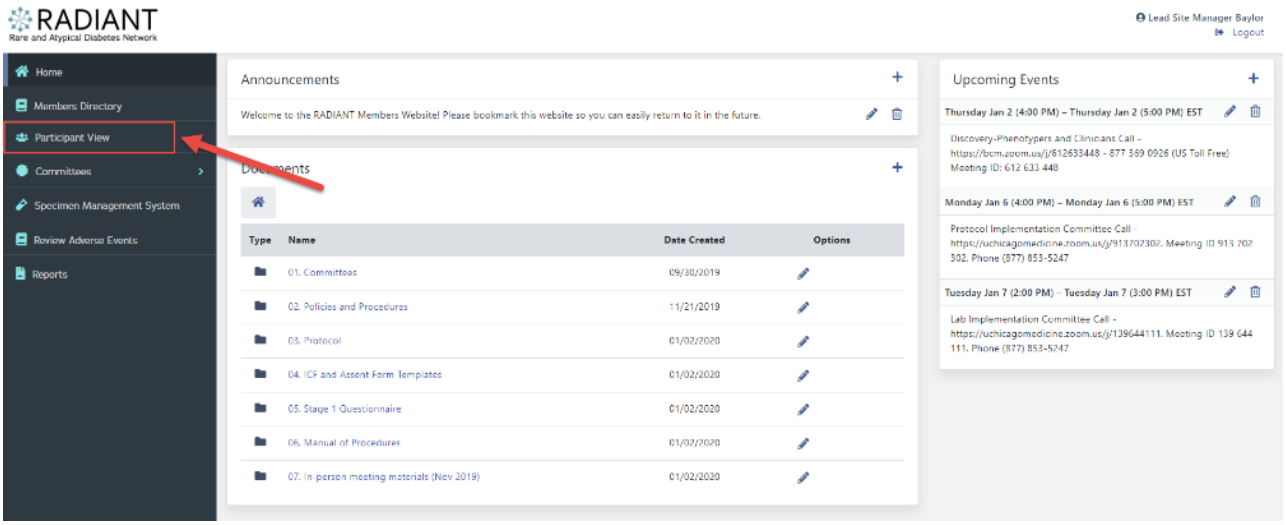
13.3.5 COMMITTEE PAGES

Committee pages can be accessed from the left-hand navigation pane. Special permission is needed to access some committee pages. Click on the name of the Committee to view the committee page.

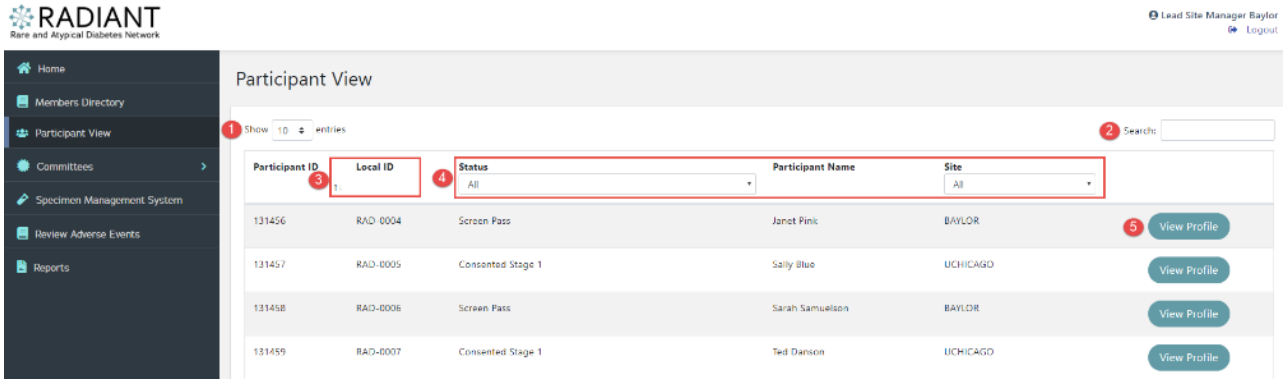


13.3.6 HOW TO VIEW ENROLLED PARTICIPANTS AND ENTER DATA#

On the RADIANT Members Website homepage, click “Participant View” in the left-hand navigation pane.



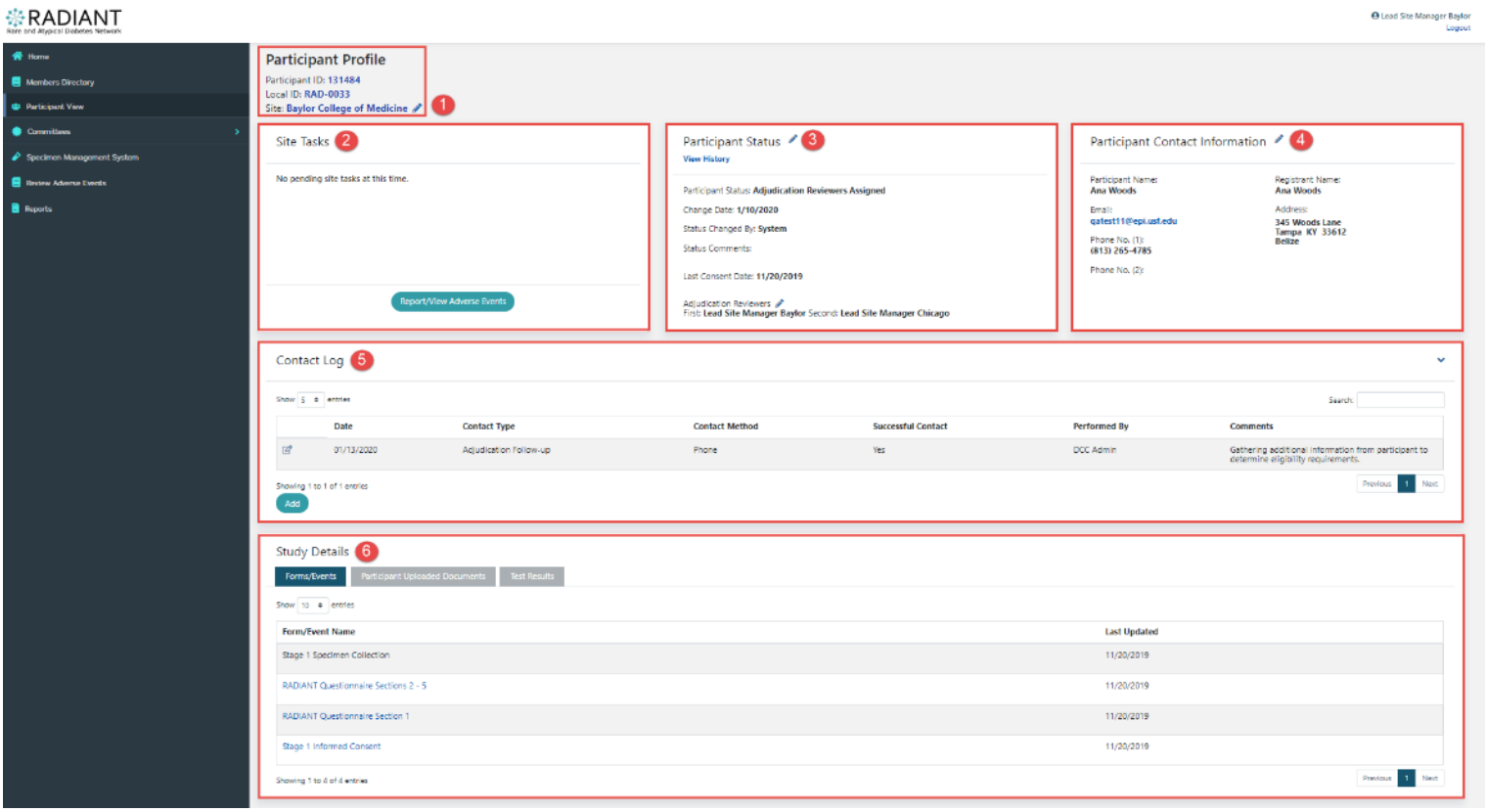
The Participant View page lists the study participants with their Participant ID, Local ID, Status, Name and Site. Depending on your role in the study, you may only see the participants assigned to your site. On this page, you have the ability to:



1. Show number of entries: this feature gives you the option of viewing 10, 25, 50, or 100 participants listed at a time.
2. Search: this feature allows you to search for specific participants.
3. Sort: this feature allows you to sort members list by ID
4. Filter: this feature allows you to filter participants by Status or Site.
5. View Profile: this feature gives you a more detailed view of a participant's profile.

Click "View Profile" to open the Participant's Profile. The Participant Profile is your central location for viewing information, data, and tasks relating to a specific participant and entering data.

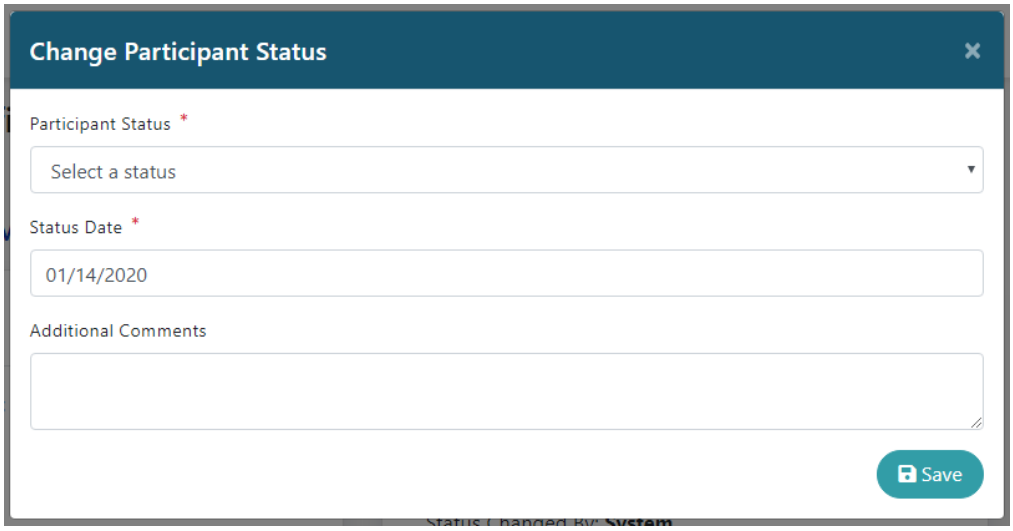
Participant Profile Page Features
The Participant Profile page consist of many features, including:



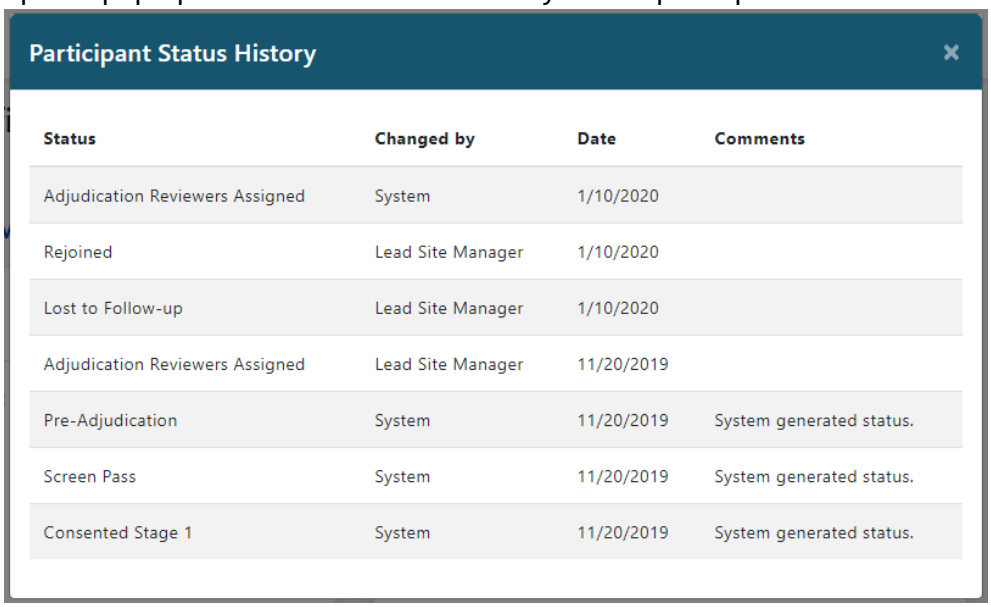
1. **Participant and Site Information:** This section specifies the Participant ID and Local ID assigned by the system for the participant and the current assigned site.

2. **Site Tasks:** This section lists pending tasks the site study team needs to perform. Examples include: Requesting a specimen kit shipment, completing a study form, etc. Click the site task to complete the task. This section also includes the button to “Report/View Adverse Events” (see section 10).

3. **Participant Status:** This section summarizes the participant’s current status and status history and last consent date. It also includes the ability to edit the participant status as the participant progresses through the study.
    a. *How To Edit Participant Status*: Click on the icon next Participant Status. A pop-up window will open like the one below. Participant Status and Status Date are required. Click ‘Save’ when you are done to save the participant’s new status.



b. *How To View Status History:* Click on “View History” under the Participant Status header to open a pop-up with an entire status history for the participant.

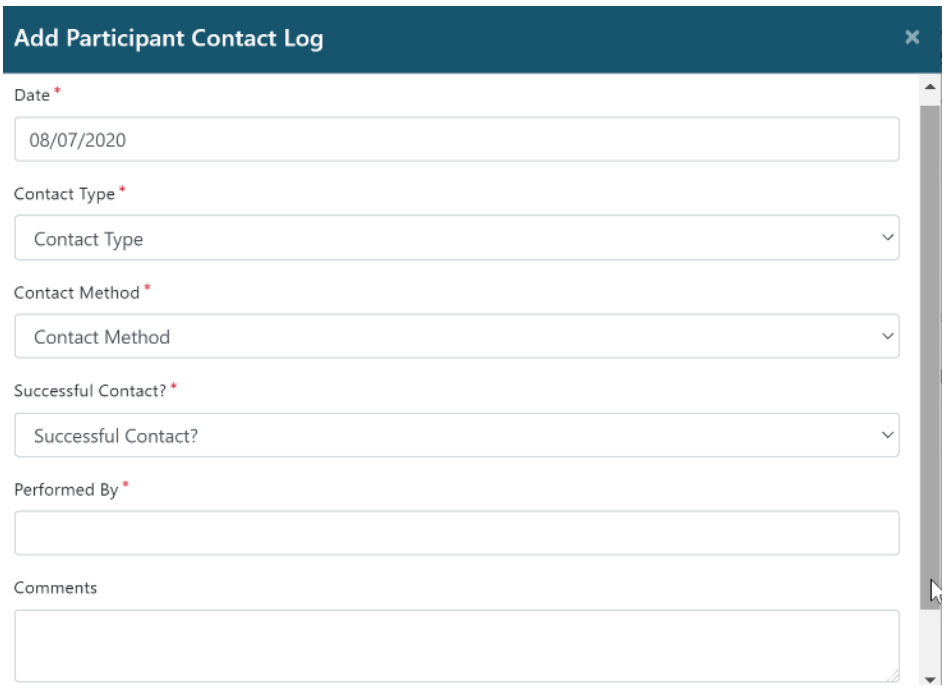


Status	Changed by	Date	Comments
Adjudication Reviewers Assigned	System	1/10/2020	
Rejoined	Lead Site Manager	1/10/2020	
Lost to Follow-up	Lead Site Manager	1/10/2020	
Adjudication Reviewers Assigned	Lead Site Manager	11/20/2019	
Pre-Adjudication	System	11/20/2019	System generated status.
Screen Pass	System	11/20/2019	System generated status.
Consented Stage 1	System	11/20/2019	System generated status.

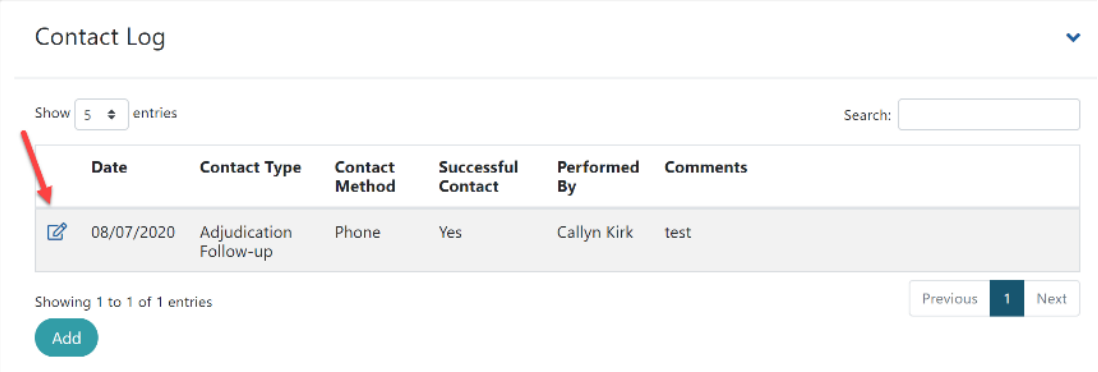
4. **Participant Contact Information:** This section summarizes the contact information provided by the participant.
    a. *How To Edit Participant Contact Information*: Click on the icon in the top right corner of the Participant Contact Information box. A pop-up window will open like the one below. Make the necessary updates and click ‘Save’ at the bottom when you are done.

b. *How to Edit Participant Email Address*: If the participant's email address is incorrect or needs to be updated, please email the DCC at radiantteam@atypicaldiabetesnetwork.org. Please note this email change will also affect the email address that the participant uses to log in to their Participant Portal account.

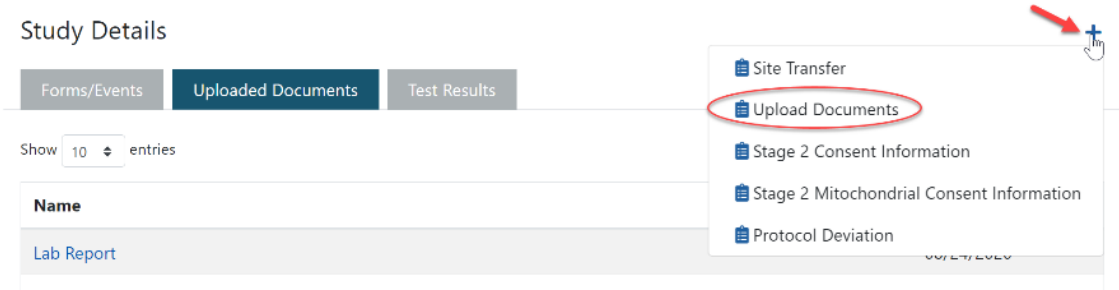
5. **Contact Log:** This section is where the study team will record contacts with the participant.
   a. *How to Record Contact with Participant:*
      i. Click the "Add" button in the Contact Log section of the Participant Profile. The "Add Participant Contact Log" module will open. Enter the information about the contact and click "Save" at the bottom when done.



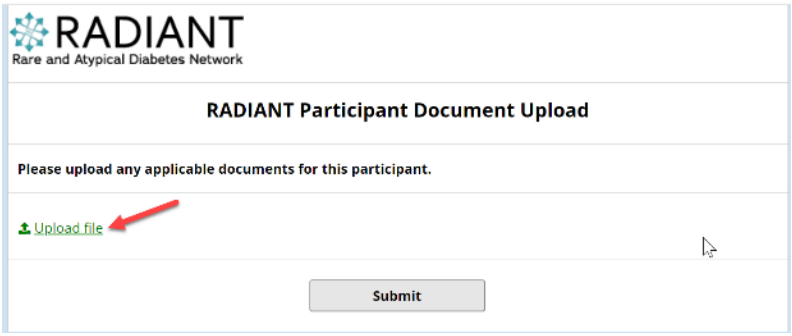
      ii. After the contact is saved, it will show in the Contact Log on the Participant Profile. If you need to edit the contact, click the edit icon as shown below.



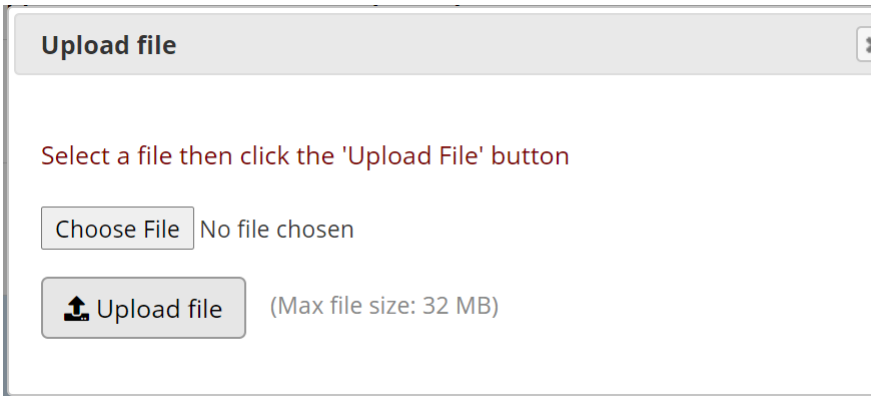
6. **Study Details:** This section includes the study forms, uploaded documents pertaining to the participant (ex. medical records), and the participant's test results. The information is organized across three separate tabs: Forms/Events, Uploaded Documents, and Test Results. Click on the tab name (ex. Uploaded Documents) to view the information in that tab. In the Forms/Events tab and Uploaded Documents tab, click on the name of the form/document to open the form/document.
    a. *How to Enter PRN Forms:* Click the plus sign in the top right corner of the Study Details section to open a dropdown list of available PRN forms. Click the name of the form to open the form and then complete the form. The completed form will then show in the "Forms/Events" tab.
    b. *How to Upload Documents:*
        i. Click the plus sign in the top right corner of the Study Details section to open a dropdown list of available PRN forms. Click "Upload Documents".



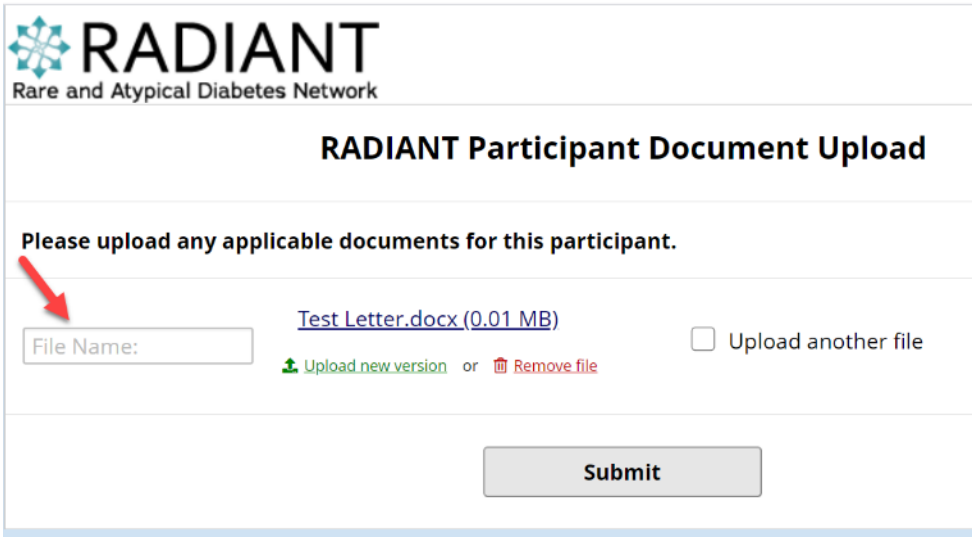
        ii. The RADIANT Participant Document Upload module will open. Click "Upload file".



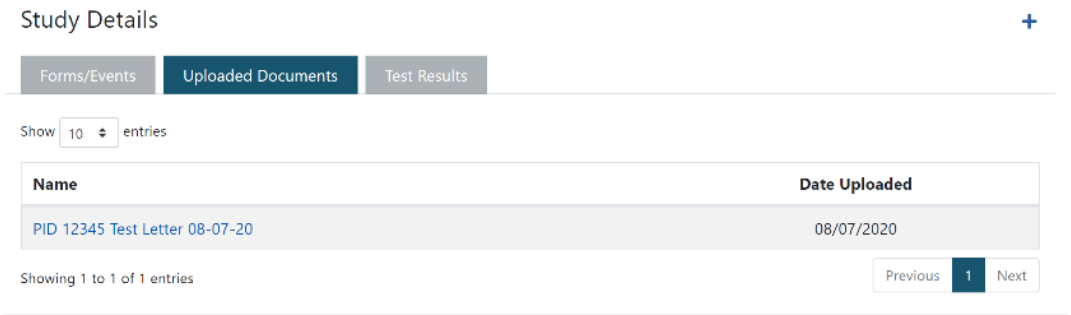
        iii. Select the file and then click "Upload file".



iv. Specify a filename for the uploaded document and click “Submit”.



v. Upload is complete. The uploaded file will then appear in the Uploaded Documents list in the Study Details section.

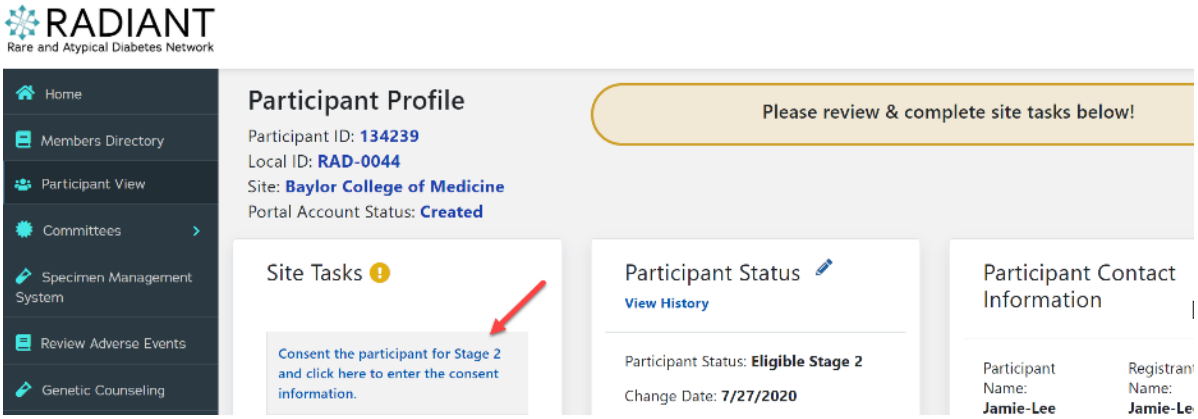


13.3.6.1 Documenting Stage 1 paper consent information in RADIANT Members Website#

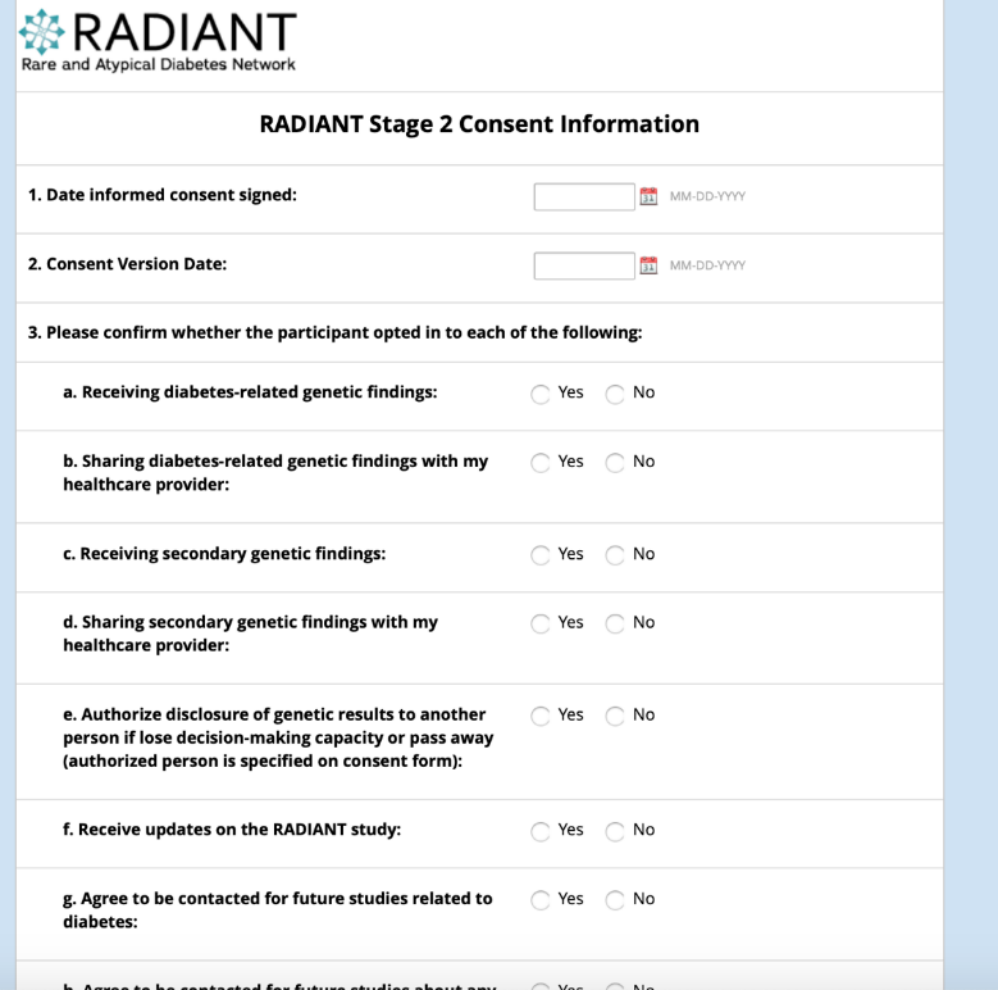
1. Login to the RADIANT Members Website
2. Click on “Participant View” in the left navigation menu.
3. Click on “Register new participant who consented for Stage 1 on paper” button, located on top right corner of page.
4. Enter Stage 1 consent information. A participant ID and local ID will then be assigned to the participant. The participant will be assigned to the site that entered the consent information.
5. Navigate to the Participant Profile in the RADIANT Members Website for the participant (i.e. look up the Participant ID in the Participant View, see section 13.3.6).
6. Click on the Stage 1 Section 1 Form, and enter the responses provided by the participant on paper to determine participant screen pass or fail status.

13.3.6.2 Documenting Stage 2 consent information in RADIANT Members Website#

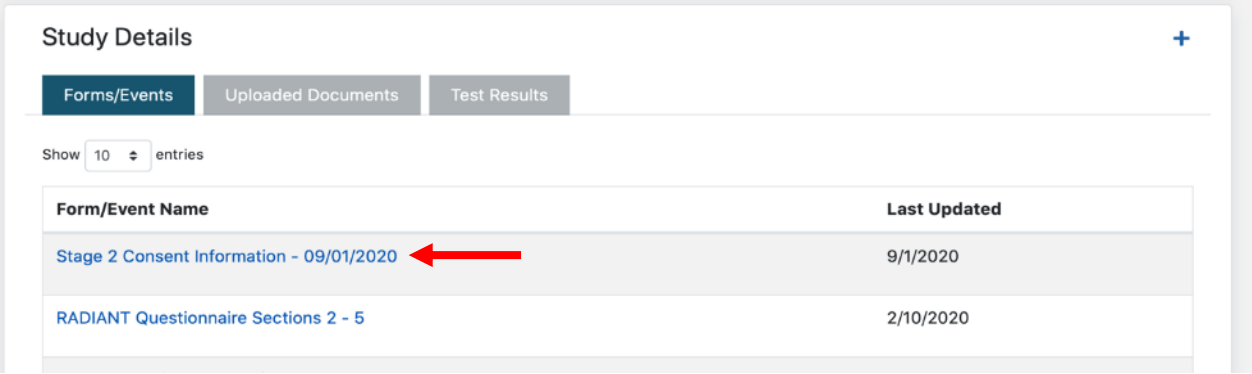
7. Login to the RADIANT Members Website
8. Navigate to the Participant Profile (section 13.3.6)
9. Click on the site task “Consent the participant for Stage 2 and click here to enter the consent information”.



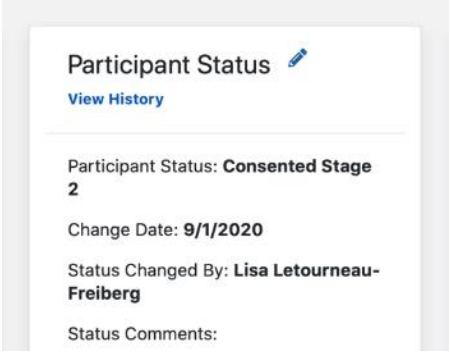
10. The Stage 2 Consent Information Form will open. Complete the form and click “Submit” at the bottom of the form.



11. Upon submission, a copy of the completed Stage 2 Consent Information Form will appear in the 'Study Details' section on the Participant Profile.

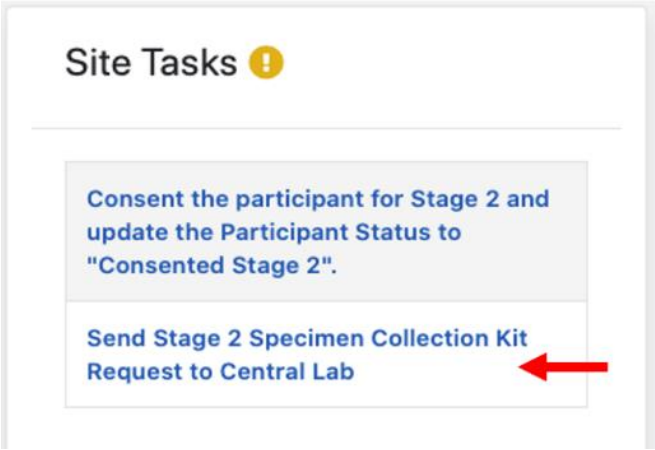


12. The Participant Status will automatically update to 'Consented Stage 2' (see Participant Status section of Participant Profile in RADIANT Members Website).

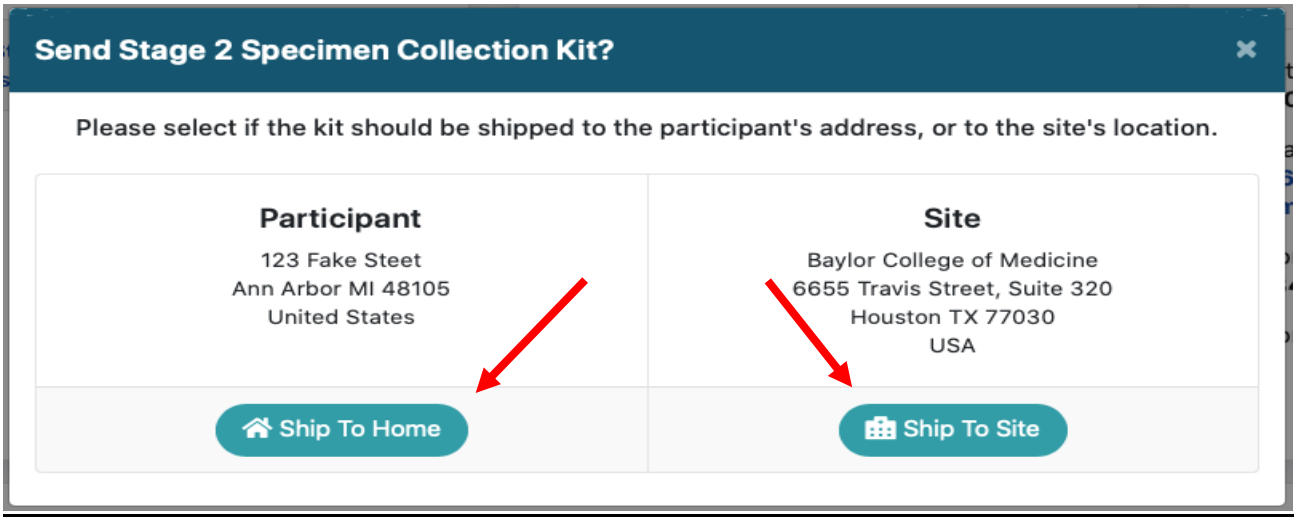


13.3.6.3 Requesting a Proband Stage 2 Specimen Collection Kit in the Members Website#

1. Login to the RADIANT Members Website
2. Navigate to the Participant Profile (section 13.3.6)
3. Click on the site task “Send Stage 2 Specimen Collection Kit Request to Central Lab”.



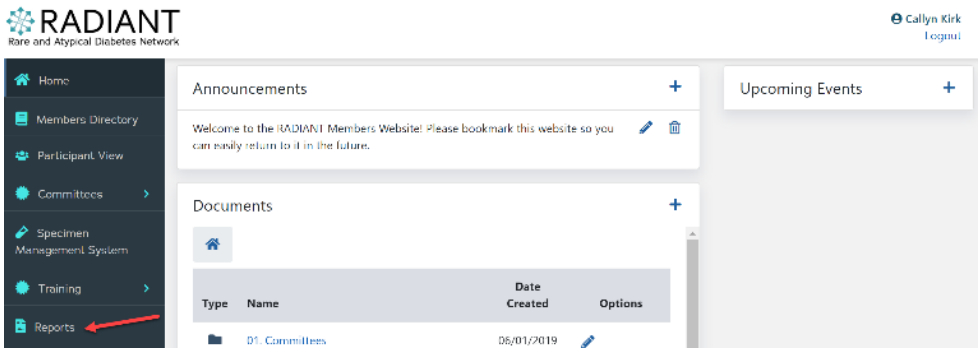
4. A pop-up window will open. Select whether the kit should be shipped to the participant’s address (Stage 2 remote visit) or to the site’s location (Stage 2 in-person visit). If any changes to the participant’s address are needed, please update the participant address in the Participant Profile BEFORE submitting the kit request.



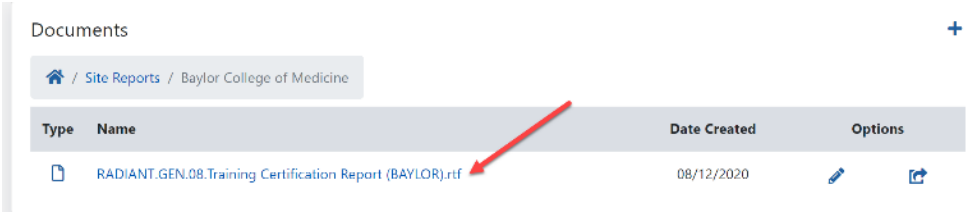
13.3.7 REPORTS#

Reports are available on the RADIANT Members Website for study team members to view.

1. Login to the RADIANT Members Website
2. On the homepage, click “Reports” in the left-hand navigation pane.



3. Click the “Site Reports” folder to view site-specific reports. Click the “General Reports” folder to view general reports for the study. Reports accessible to study team members will vary based on the study team member’s role in the study.
4. Click the name of the report to open and view the report. Example:



14 RADIANT TRAININGS, SUPPLIES, AND ADMINISTRATIVE TASKS FOR SITES

14.1 ADDING OR UPDATING STAFF AT RADIANT CLINICAL CENTERS

If sites have a new staff member to add to their local RADIANT team, the following steps should be taken:

1. Add new staff member to local IRB, per local IRB guidelines
2. Add new staff member to RADIANT Site Delegation Log (see Section 14.2) and send updated copy of Site Delegation Log to the DCC at radiantteam@atypicaldiabetesnetwork.org
3. Add new staff member to the RADIANT Members Website (see Section 13.3.4).
4. The new staff member can then complete their RADIANT Members Website account set-up and complete the online training modules (see Section 14.3).
    - If the staff member will be involved with Stage 3 Standard Visits (S3SV), they may need to complete additional S3SV trainings. Please see the S3SV MOP for more information.
5. If the new staff member is a study coordinator, email radiantteam@atypicaldiabetesnetwork.org to request that they be added to the RADIANT Study Coordinator Committee call invitations.

14.2 MAINTAINING SITE DELEGATION LOG (SDL)#

All sites are responsible for maintaining an accurate Site Delegation Log. This document notes which staff members are working on the project, their specific roles and responsibilities, and their start/end dates. An accurate Site Delegation Log should be maintained locally and a copy of it should be shared with the DCC any time a change occurs – please email the copy to radiantteam@atypicaldiabetesnetwork.org.

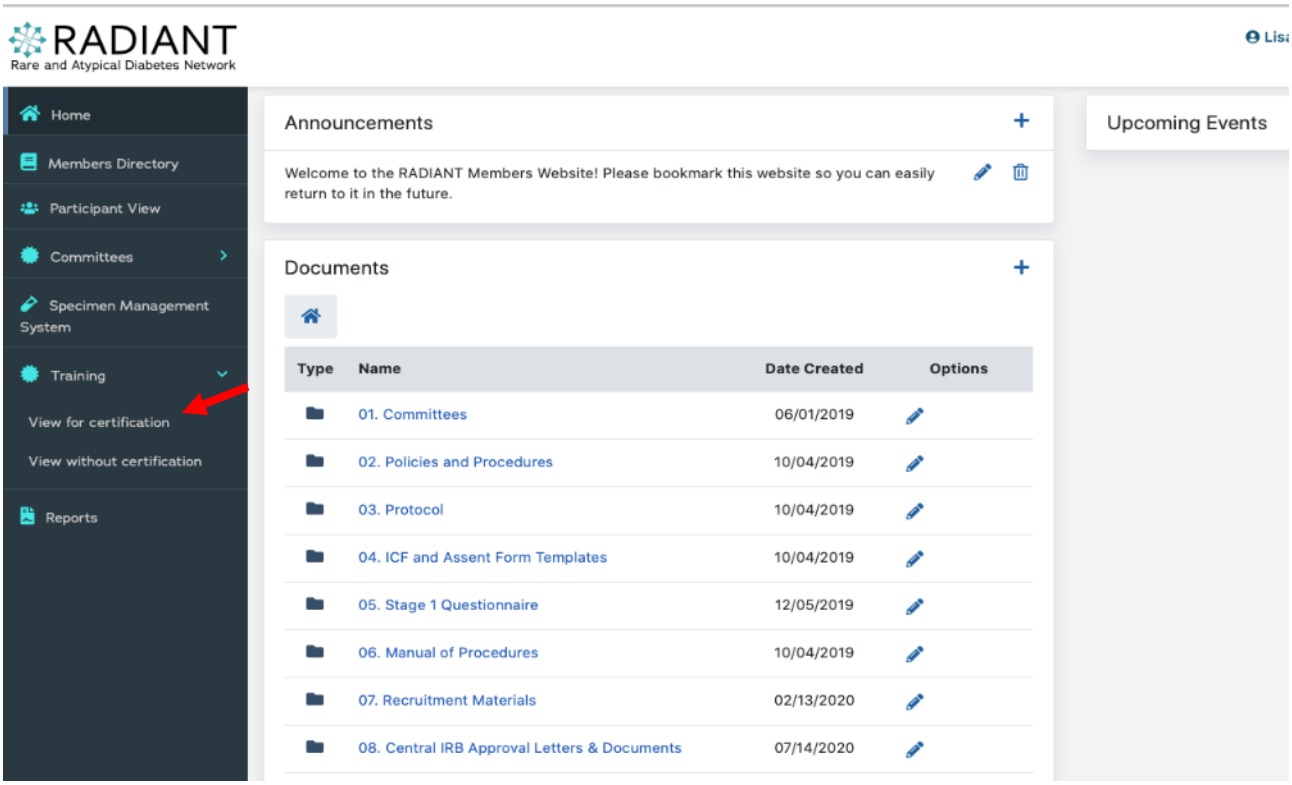
A RADIANT Site Delegation Log template can be found on the Members Website in the Study Documents section, Manual of Procedures folder.

T and U designations may only be held by licensed independent practitioners. T = Manages Adverse Events that occur for local site participants (i.e., review, provide intervention direction). U = Medication Management (e.g., administering medications; adjusting/holding medications)

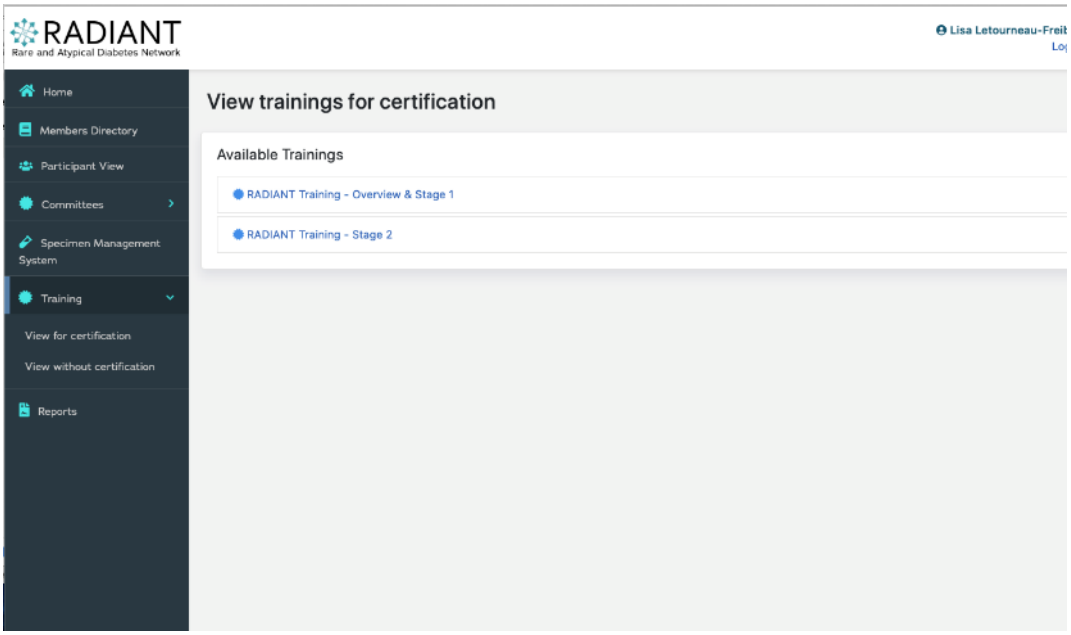
14.3 RADIANT TRAININGS#

RADIANT staff are required to complete trainings prior to participating in the study. All trainings can be found on the Members Website.

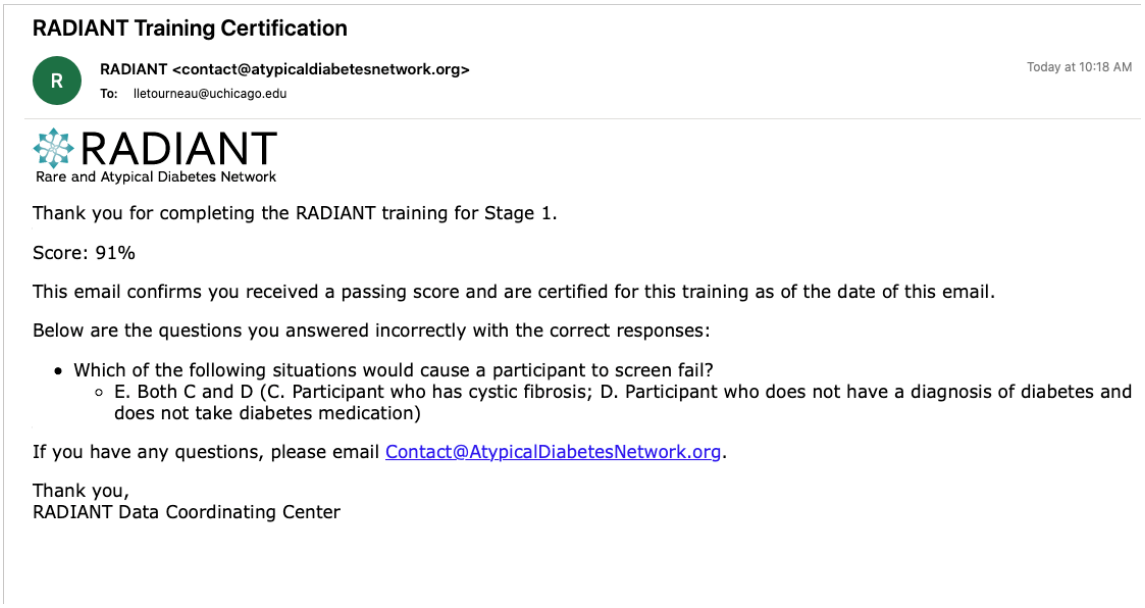
i. Select 'Training' on the left side of the screen. Then select 'View for certification'. You may click on 'View without certification' if you want to view the training materials later without being re-certified.



ii. All available trainings will show on the screen. Select any training module to continue.



iii. After a module is completed, you will receive an email which includes your overall score and any questions you may have gotten incorrect, along with the correct answers. If you received a score of 75% or higher, you passed:



RADIANT Training Certification

R **RADIANT <contact@atypicaldiabetesnetwork.org>** Today at 10:18 AM

To: lletourneau@uchicago.edu

RADIANT
Rare and Atypical Diabetes Network

Thank you for completing the RADIANT training for Stage 1.

Score: 91%

This email confirms you received a passing score and are certified for this training as of the date of this email.

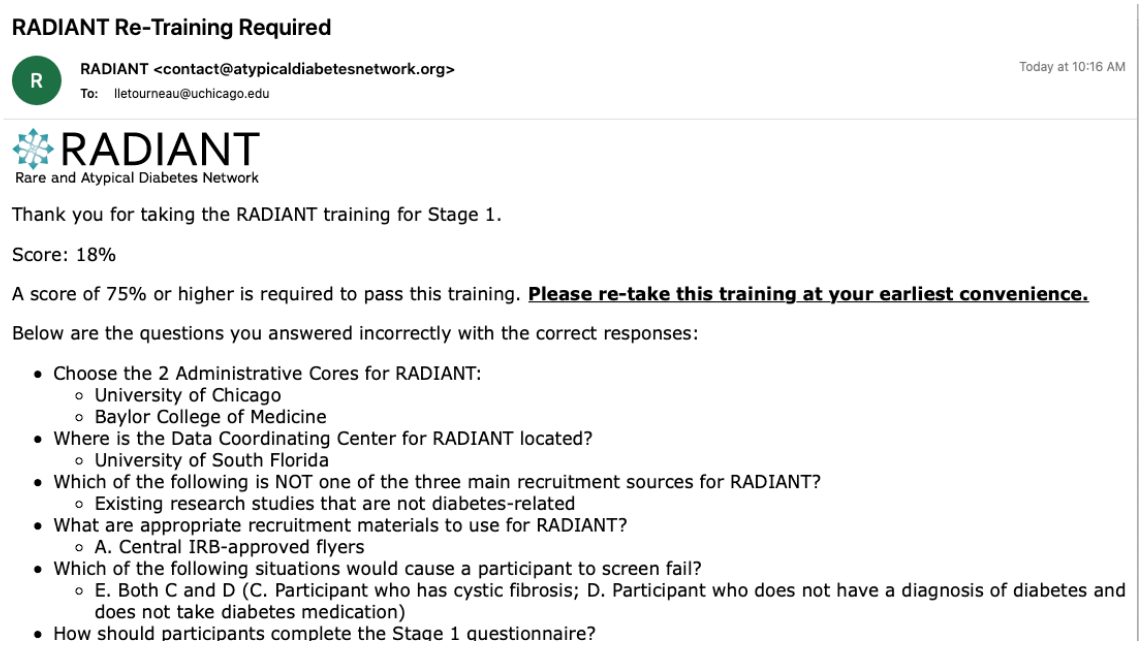
Below are the questions you answered incorrectly with the correct responses:

- Which of the following situations would cause a participant to screen fail?
  - E. Both C and D (C. Participant who has cystic fibrosis; D. Participant who does not have a diagnosis of diabetes and does not take diabetes medication)

If you have any questions, please email Contact@AtypicalDiabetesNetwork.org.

Thank you,
RADIANT Data Coordinating Center

iv. If you received a score less than 75%, you will be asked to retake the training:



RADIANT Re-Training Required

R **RADIANT <contact@atypicaldiabetesnetwork.org>** Today at 10:16 AM
To: lletourneau@uchicago.edu

RADIANT
Rare and Atypical Diabetes Network

Thank you for taking the RADIANT training for Stage 1.

Score: 18%

A score of 75% or higher is required to pass this training. **Please re-take this training at your earliest convenience.**

Below are the questions you answered incorrectly with the correct responses:

- Choose the 2 Administrative Cores for RADIANT:
  - University of Chicago
  - Baylor College of Medicine
- Where is the Data Coordinating Center for RADIANT located?
  - University of South Florida
- Which of the following is NOT one of the three main recruitment sources for RADIANT?
  - Existing research studies that are not diabetes-related
- What are appropriate recruitment materials to use for RADIANT?
  - A. Central IRB-approved flyers
- Which of the following situations would cause a participant to screen fail?
  - E. Both C and D (C. Participant who has cystic fibrosis; D. Participant who does not have a diagnosis of diabetes and does not take diabetes medication)
- How should participants complete the Stage 1 questionnaire?

14.3.1 RADIANT STAGE 1 AND STAGE 2 TRAININGS#

Training topic + content	Required to complete	Re-certification	Method of completion
General RADIANT training – Overview & Stage 1 Est time to complete: 30-60 min	• Study coordinators • Site PIs • Co-Investigators • Central Lab personnel • Genetic Core personnel	Complete baseline training. Re-train as needed (e.g., significant changes in site Stage 1 responsibilities; retraining required by Steering Committee, etc).	Complete training on Members Website. Must watch videos, read text, and complete quiz questions (Pass rate: 75%) Completion is documented at DCC. Auto emails sent after training completed. Re-certification emails will be sent as needed.
General RADIANT training – Stage 2 Est time to complete: 15-30 min	• Study coordinators • Site PIs • Co-Investigators • Central Lab personnel • Genetic Core personnel	Complete baseline training. Re-train as needed.	Complete training on Members Website. Must watch videos, read text, and complete quiz questions (Pass rate: 75%) Completion is documented at DCC. Auto emails sent after training completed. Re-certification emails will be sent as needed.
RADIANT Lab training Est time to complete: 30 min	• Study coordinators* • Site PIs • Co-Investigators • Central Lab personnel • Genetic Core personnel	Complete baseline training. Re-train as needed based on feedback from Central Lab regarding site performance,	Complete training on Members Website. Must watch videos, read text, and complete quiz questions (Pass rate: 75%)

		protocol changes, site personnel changes.	Completion is documented at DCC. Auto emails sent after training completed. Re-certification emails will be sent as needed. *Study coordinators are also required to participate in a Zoom call with Central Lab after completion of videos/quiz platform to discuss the videos and answer questions

14.3.2 LOCAL SITE TRAININGS#

All RADIANT staff must also abide by local training requirements, as applicable, including bloodborne pathogens training, chemical hygiene training, HIPAA training, etc. It is the responsibility of the local site PI and study coordinators to ensure their staff are appropriately trained.

14.4 RADIANT REGULATORY BINDER#

All RADIANT Clinical Centers will prepare and maintain a regulatory binder for this study per ICH GCP and local site requirements. This should include, but may not be limited to, the following documents:

Provided by DCC (to be posted on RADIANT Members Website):

- ☐ Central IRB Approval Letters
- ☐ Central IRB-approved Protocol (all versions)
- ☐ Central IRB-approved consent and assent forms (all templates & site-specific versions)
- ☐ Central IRB-approved Recruitment Materials and Questionnaires
- ☐ Central IRB Roster
- ☐ NIDDK OSMB Letters
- ☐ CAP/CLIA certification for central lab

Provided by Sites:

- ☐ Local IRB Approval/Acknowledgement Letters (as applicable to your site)
- ☐ Site Delegation Log (SDL)
- ☐ Local Staff and Contact Information
- ☐ Investigator and Sub-investigator CVs
- ☐ Investigator and Sub-investigator clinical licenses, as applicable
- ☐ Documentation of human subject protection training, GCP training, and other local trainings as applicable for study staff
- ☐ Site Recruitment and Retention Plan

14.5 RADIANT SUPPLIES AND EQUIPMENT#

14.5.1 LABORATORY EQUIPMENT AND SUPPLIES#

RADIANT staff will ensure that their sites are properly equipped to handle any laboratory testing. Before sites begin scheduling participants for blood collection visits, they must obtain the following equipment (or equivalents, where noted):

Local lab has all required equipment and calibrations

- ☐ -80 freezer temperature logs

☐ -20 freezer temperature logs
☐ Centrifuge calibration

Site has all required supplies for Blood Collection
These are suggested supplies only; clinics may use equivalent substitutions, if desired.

☐ Alcohol wipes
☐ Ammonia spirits ampules
☐ Arm boards
☐ Band-Aids
☐ Cold compresses
☐ Disposable gloves (powder-free, to avoid possible cross-contamination from powder)
☐ Needle (Vacutainer) holders – adult and pediatric
☐ Paper and/or other dermatological tape
☐ Sterile and non-sterile gauze pads
☐ Sterile, 19, 21, 23 & 25 gauge, 1” needles (multiple-sampling)
☐ Sterile, 21, 23, 25 gauge butterfly needles (multiple-sampling)
☐ Tourniquets
☐ Tegaderm
☐ Topical Anesthetic (EMLA, lidocaine/prilocaine)

Site has all required supplies for Blood Processing/Shipping/Storage
These are suggested supplies only; clinics may use equivalent substitutions, if desired.

☐ Tube racks
☐ Plastic-backed table covers
☐ Waterproof pens (such as laundry markers, fine-point, for scribing on labels)
☐ Centrifuge: refrigerated swinging-bucket type with Microtainer holding capability
☐ Freezer: -20°C, non-cycling for freezing shipment cold packs
☐ Freezer: -80°C, for freezing metabolomics batched samples
☐ Wide (3”) packing tape for sealing shipping containers

Site has all required supplies for Specimen Handling
These are suggested supplies only; clinics may use equivalent substitutions, if desired.

☐ Lab coat
☐ Goggles or face shield
☐ Paper towels
☐ Bleach decontaminant -1 part Clorox to 9 parts water, stored in a labeled bottle
☐ Biohazard waste containers with orange or red-plastic liners
☐ Sharps/biohazard containers - rigid red or orange plastic containers for sharps waste

15 LOST TO FOLLOW UP PLAN

Participants become 'lost to follow up' if they are no longer reachable to actively participate in the study. For RADIANT, the following guidance has been developed on when to classify a participant as lost to follow up:

Study staff will follow up with participants at least 4 times within 180 days of a study timepoint, such as Stage 1 questionnaire start, Stage 1 antibody kit being mailed out, attempt to consent for Stage 2, etc. For example, if a participant has not yet completed their Stage 1 questionnaire, study coordinator should follow up at least 4 times within 180 days. If the participant has not responded to any of the coordinator's communication attempts, they can then be marked as lost to follow up.

- While general guidance is given above, the specific frequency of follow up attempts within the 180 day period is left to the discretion of the local site, as long as at least 4 attempts are made.
- A combination of phone and email attempts is recommended.
- At least one attempt should include a certified mailed letter via United States Postal Service.
    - An IRB-approved letter template can be found on the Members Website

If a change to lost to follow up is indicated, the study staff will change the participant status to lost to follow up – see section 13.3.6 for information on how to change a participant's status. All attempted communications should be documented in the Contact Log.

No further contact should be made with the participant after the participant is marked as lost to follow up.

- If the participant reconnects with study staff after they have been marked as lost to follow up, their status can be changed back to active participation without a reconsent (unless participant has turned 18 years old, consent has been revised with reconsent required, or eligible to consent for next stage of study).

16 APPENDIX 1. CONSENT FORMS AND OTHER DOCUMENTS NEEDED BY STAGE[#]

STAGE 1

1. Stage 1 consent (online module; or paper version)
2. Other documents:
    - Online medical record release form (as needed to obtain records for Adjudication Committee)
    - Online Stage 1 questionnaire sections (paper versions also available, if needed)

STAGE 2

- Stage 2 consent
    a. In-person consent – use printed consent forms as needed by age/affected status
    b. Phone/video consent – use printed consent forms as needed by age/affected status
- Other documents:

STAGE 2 FAMILY MEMBER SANGER

- Stage 2 Family Member Sanger Consent
    - Phone/video consent – use printed consent forms as needed by age (assent is available)
        - See Section 6.3.1 for possibilities regarding in-person consent

STAGE 2 FAMILY MEMBER WGS-TRIO

- Stage 2 Family Member WGS Trio Consent
  - Phone/video consent – use printed consent forms as needed by age (assent is available)
    - See Section 6.4.1 for possibilities regarding in-person consent

17 APPENDIX 2. LETTER FOR PARTICIPANTS WHO ARE LIKELY TO HAVE MONOGENIC DIABETES, LIPODYSTROPHY, SYNDROMIC/MITOCHONDRIAL DIABETES, OR SECONDARY DIABETES

(Version 20200520, approved by cIRB July 2020)

RADIANT
Rare and Atypical Diabetes Network

[Date]

[Participant Name]

Dear [Participant Name],

Thank you for participating in RADIANT – Stage 1.

As you know, the goal of RADIANT is to identify people with rare and atypical forms of diabetes. Stage 1 of the study involved completing online questionnaires and obtaining diabetes autoantibody testing at Quest Laboratories. Before proceeding to Stage 2, where whole genome sequencing is done, the RADIANT Adjudication Committee meets to review your questionnaire information, medical information, and lab testing. This committee is comprised of physicians who have expertise in genetic forms of diabetes, and the committee determines whether you are eligible to proceed to Stage 2.

The RADIANT Adjudication Committee reviewed your case on [Date of Adjudication Committee call]. The Committee's consensus was that you may have [Insert type here – ex: monogenic, lipodystrophic, syndromic, steroid-induced, etc.]. This is a previously identified form of diabetes. You may be eligible to continue participating in RADIANT, but a RADIANT Adjudication Committee team member would like to schedule a phone call with you to discuss this further. If you would like your healthcare provider to be involved in this phone call, we can set up a conference call to accommodate that.

We'd be happy to answer any questions you may have and recommend additional resources if you are not eligible to continue on in RADIANT.

Thank you for your participation and we look forward to speaking with you.

Sincerely,

RADIANT Adjudication Committee
contact@atypicaldiabetesnetwork.org

18 APPENDIX 3. RADIANT STAGE 1 SPECIMEN MANUAL OF PROCEDURES (STAGE 1 CENTRAL LAB MOP)

This appendix was created by the Central Lab and details the specimen collection, processing, and shipping procedures for Stage 1.

19 APPENDIX 4. RADIANT STAGE 2 SPECIMEN MANUAL OF PROCEDURES (STAGE 2 CENTRAL LAB MOP)

This appendix was created by the Central Lab and details the specimen collection, processing, and shipping procedures for Stage 2.

20 APPENDIX 5. AUTOMATED PARTICIPANT-FACING EMAILS

RADIANT Automated Participant Emails Summary

Email Short Description	Email Subject line	Audience	Purpose	Time Point
Stage 1 Online Consent Confirmation Email	Thank You for Agreeing to Participate in RADIANT!	Participants who consented for Stage 1 online	To give participant a copy of Stage 1 consent form after online consent submitted	Stage 1; upon submission of online Stage 1 consent in real time
Section 1 Questionnaire Reminder Email	RADIANT Questionnaire Reminder	Participants who consent for Stage 1, but do not complete Section 1 of the questionnaire	To remind participants to complete section 1 of the questionnaire and give them a link to the questionnaire.	Stage 1; send 1 day, 7 days, and 14 days after consent submission if Section 1 not completed
Participant Portal Verification Code Email	RADIANT account email verification code	Screen Pass Participants who initiate Portal set-up process	To verify participant's email address and provide code for participant to enter during portal set-up (authentication) process	Stage 1; upon beginning portal set-up (authentication) process
Participant Portal Set-up Confirmation	RADIANT Participant Portal	Screen Pass Participants who complete Portal set-up process	To confirm participant portal set-up complete and provide the link to the Participant Portal for the future	Stage 1; upon completion of portal set-up (authentication) process
Participation Next Steps / Portal Set-up Reminder	RADIANT Participation Next Steps	Screen Pass participants who haven't yet set-up a Participant Portal account; Participants whose status have been changed from Screen Pause to Screen Pass	For participant to follow the link to set up their portal account and complete the questionnaire	Stage 1; send 1 day, 7 days, and 14 days after "Screen Pass" status assigned in system
Pre-adjudication Screen Fail/Ineligible Notification Email	RADIANT Participation Decision	Participants determined to be Screen Fail or Ineligible prior to Adjudication Review	To notify participants that based on their questionnaire responses they are not eligible for the study	Stage 1; upon RADIANT PM selecting "Screen Fail" status (if making determination on section 1 responses before rest of questionnaire is completed) or "Ineligible" status (if making determination upon completion of questionnaire) prior to Adjudication Review
Questionnaire Section 2-5 Questionnaire Reminder Email	RADIANT Questionnaire Reminder	Screen Pass Participants who completed Portal account-set-up, but have not completed Sections 2-5	To remind participant to complete questionnaire and provide link to Portal to login	Stage 1; send 3 days, 10 days, and 17 days after portal account set-up if Sections 2-5 not completed

Stage 1 Sample Collection Reminder Email	RADIANT Sample Collection Reminder – Stage 1	Participants who are in Screen Pass status and have Stage 1 samples InTransit/Not Received state	To remind participants to complete Stage 1 Sample Collection	30 days and 45 days after Stage 1 kit is sent, if blood sample not yet received by the lab; For those >45 days since Stage 1 kit sent and sample not yet received, send email reminder once after promotion.)
Stage 2 Sample Collection Reminder Email	RADIANT Sample Collection Reminder – Stage 2	Participants who have Stage 2 samples InTransit/Not Received state	To remind participants to complete Stage 2 Sample Collection	30 days and 45 days after Stage 2 kit is sent, if blood sample not yet received by lab. (For those >45 days since Stage 2 kit sent and sample not yet received, send email reminder once after promotion.)
Adjudication Review Ineligible Decision Notification	RADIANT Adjudication Decision	Participants reviewed by Adjudication Committee (AC) who the AC determined should NOT continue to Stage 2	To notify participants that they will not be continuing to Stage 2	End of Stage 1; after Adjudication Reviewers decide the participant should not continue to Stage 2 and RADIANT PM enter that determination in the Members Website
Test Results Available	RADIANT Test Results Available	Participants only if they consented to view their test results	To notify participants that they have new test results available to view in the portal	Stage 1 and Stage 3; after test results are processed, email will be sent to participant
Critical Test Result Value	ABNORMAL RADIANT Lab Test Result	Participants if they have critical results	To notify participants that they have critical results available to view in the portal	Stage 3; after test results are processed, email will be sent to participant if there are critical values
Genetic Counseling Appointment Scheduled	RADIANT Genetics Counselor Appointment Scheduled	Participants who appointment was scheduled for	To notify participants of their appointment date and time	Stage 2; after staff contacts participant to schedule appointment and selects appointment in Members Website
Genetic Results Available Email	RADIANT Genetics Results Available	Participants whose WGS results were uploaded to participant portal	To notify participants that their results are avalible for viewing in participant portal	Stage 2; after genetic counselor uploads genetic counseling letter
S3SV Portal Questionnaires to Complete Within 2 Weeks	RADIANT Online Questionnaires - Please Complete Within 2 Weeks	Participants who consented to Stage 3 Tier 1 (S3T1)	To notify participants that they have questionnaires available in their portal to complete	Stage 3; after Stage 3 Standard Visit Consent
RADIANT Online Questionnaires Reminder	RADIANT Online Questionnaires Reminder	S3T1 participants who have not yet completed all questionnaires in portal	To remind participants to complete all questionnaires in portal	Stage 3; 10 days after Stage 3 Standard Visit Consent
Family History Questionnaire Email	RADIANT Online Family History Questionnaire - Please Complete	Participants who consented to Stage 2	To notify participants to complete the questionnaire in the portal	Stage 2; after Stage 2 Consent entered
Family History Questionnaire Reminder Email	RADIANT Online Family History Questionnaire Reminder	Participants who consented to Stage 2 and have not yet completed the questionnaire in the portal	To remind participants to complete the questionnaire in the portal	Stage 2; 14 days after Stage 2 Standard Visit Consent

Family Member Participant Portal Set-up Notification	RADIANT Participation Next Steps	Family members recommended for Sanger or WGS Trio who have been consented by a RADIANT site	To notify family members of next steps to sign up for the participant portal	After the first Family Member Sanger or WGS Trio Consent Information Form is entered by the site for the family member
Family Member Participant Portal Set-up Reminder	RADIANT Participation Next Steps Reminder	Family members recommended for Sanger or WGS Trio who have been consented by a RADIANT site and have not yet completed their portal set-up	To remind family members of next steps to sign up for the participant portal	7 days after the first Family Member Sanger or WGS Trio Consent Information Form is entered by the site for the family member, if Family Member has not yet completed portal set-up
Family Member Questionnaire Reminder Email	RADIANT Questionnaire Reminder	Sanger/WGS-Trio family members who completed Portal account set-up, but have not completed the Family Member Questionnaire	To remind participant to complete questionnaire and provide link to Portal to login	Family Members; Send 3 days after portal account set-up if Family Member Questionnaire not completed