JDRF REQUESTS LETTERS OF INTENT FOR:
IMPROVING RISK PREDICTION FOR T1D ONSET: MODELING AND ASSAY DEVELOPMENT FOR CLINICAL AND COMMERCIAL USE

BACKGROUND & PURPOSE

Currently 1.6 million people in the United States have a Type 1 Diabetes (T1D) diagnosis and this number is expected to increase to 5 million by 2050[1,2]. In the absence of approved disease modifying therapies to prevent or cure this disease, those with T1D are at dramatically increased risk of severe complications and an estimated 10-year reduction in life expectancy as compared to those without the disease. While some therapies have been demonstrated in clinical studies to delay the onset of or slow the progression of the disease after diagnosis, none are yet approved for use.

T1D risk is influenced by several factors including genetics, age, ethnicity, BMI, and environmental determinants. While almost 50% of the genetic contribution to T1D risk is associated with variation in the HLA alleles, many other genes have been shown to contribute to this and their relative contribution varies with age of diagnosis and ethnicity. Despite this variability, genetic predisposition to T1D has provided a valuable risk assessment tool with the most recent iterations of Genetic Risk Score (GRS) demonstrating very high specificity and sensitivity for detecting T1D risk in people of European descent[3].

The early stages of T1D can be detected by the presence of serum autoantibodies against the pancreatic beta cell and these are well correlated with the later development of symptomatic disease[4]. Persistent positivity to 2 or more of the most common T1D autoantibodies (insulin - IAA, glutamic acid decarboxylase - GADA, insulinoma-associated antigen-2 – IA2A, and zinc transporter 8 - ZnT8A) indicates active autoimmunity and is classified as Stage 1 T1D[5]. The presence of autoantibodies and signs of dysglycemia (Stage 2) is linked to a high risk of progression to symptomatic disease (Stage 3).

Multiple studies in both high-risk family members and the general population have demonstrated that screening for the risk of T1D followed by appropriate metabolic monitoring can dramatically reduce the rates of diabetic ketoacidosis (DKA) at diagnosis, which has been correlated with improvements in both near and long-term glucose control and health outcomes[6,7]. However, these programs still exist within the research setting and are not yet suitable to be integrated into the real-world health care setting. One of the major limitations preventing this integration is the utilization of research-grade genetics or autoantibody testing platforms by these programs. Integration of these programs into clinical care will require that these assays be adapted to platforms commonly used in hospital or commercial medical laboratories. In addition, as demonstrated by the recent COVID-19 pandemic, offering at-home or commercially available testing platforms has provided an important avenue for patients to get screened for disease and disease risk.

JDRF has a long-term goal of adoption of T1D risk screening into global standard healthcare practices. Improving current risk assessment tools and transitioning current assays to commercial platforms so as improve the availability of these tests to the clinical and patient population will be integral steps towards that goal.

JDRF, the world's leading non-profit organization with the mission to cure type 1 diabetes (T1D), invites Letters of Intent (LOI's) for projects to improve risk prediction of T1D onset in two specific areas:

> 1) in silico modeling using existing genetic data to improve identification of the at-risk population
> 2) Integration of T1D Genetics or autoantibody testing into assay platforms that are commercially available as direct to consumer products or routinely used in clinical/public health laboratories

OBJECTIVES

LOI's are sought for projects that will aid the translation of risk assessment tools for T1D into clinical use. The specific focus of this call is for the improvement of existing genetics and autoantibody risk assessment tools and their integration into clinically and commercially utilized testing platforms. Platforms/tools should aim to: (1) Decrease cost as compared to equivalent testing and/or (2) provide sensitivity and specificity superior to the consensus 'gold standard' or most advanced assays for the respective measure – radioligand binding assay for T1D autoantibodies[8] and GRS2 for T1D genetics[3].

in silico modeling using existing whole genome sequence data to improve identification of the at-risk population,

Proposals submitted for this objective will adapt existing genetic risk scores (GRS) or develop novel risk scores to determine T1D risk in a variable aged, multi-ethnic general population. Currently GRS for T1D risk are biased towards a European and Caucasian descent and rely on the detection of single nucleotide polymorphisms (SNPs). Increasing the number of SNPs represented by these GRS has been shown to broaden the applicability of these tools, however they are still limited in their ability to assess T1D risk in an ethnically diverse cohort. As genetic testing becomes more commonplace worldwide and the cost of whole genome and other advanced sequencing technology decreases, targeted assay approaches are being supplanted by whole genome or other advanced sequencing. LOIs submitted to this objective will develop novel or improved polygenic risk scores for T1D that capitalize on the increasing availability of whole genome sequencing data, improve on the sensitivity and specificity of previous GRS, and are applicable to a multi-ethnic population.

Integration of T1D Genetics or autoantibody testing into assay platforms that are commercially available as direct to consumer products or routinely used in clinical laboratories

To increase the availability of T1D risk screening, genetics and autoantibody assays must be deployable in a variety of settings: hospital offices, public health laboratories, commercial laboratories, and at home. Currently, these tests are largely restricted to the research setting and thus unavailable to most of the population. Proposals to this objective will address this hurdle by adapting T1D genetics and/or risk assessment testing to platforms suitable and commonly used in the hospital, office, commercial laboratory, and at home setting.

Overall Criteria:
- Priority will be given to LOIs that leverage existing data and sample sources
- Data use agreements must be in place before grant application
- Industry applicants and collaborations are welcomed
- LOI's must include a plan for validation towards regulatory qualification of the molecular diagnostic technology
- Priority will be placed on tools and assay platforms that are
    - commercially available
    - Applicable to established clinical/public health laboratory instrumentation and infrastructure
    - use small blood volumes
    - are amenable to automated handling
    - suitable to at-home sample collection
    - Low cost
    - Applicable to a multi-ethnic population
- Out of scope
    - Neoepitope discovery or assay development
    - Assay development for autoantibodies other than IAA, GADA, IA2A, or ZnT8
    - Clinical studies – observational or interventional

All applicants are encouraged to consult with JDRF Scientific Staff to discuss the alignment of their proposal to this RFA. Applications from for-profit entities are required to contact JDRF Scientific Staff prior to submission.

MECHANISM

Nonprofit organizations, public and private universities, colleges, hospitals, laboratories, units of state and local governments may apply under JDRF's **Strategic Research Agreement (SRA)** funding mechanism. For-profit entities may apply under JDRF's **Industry Discovery & Development Partnership (IDDP)** funding mechanism, which entails additional requirements and typically has a modest royalty payback to JDRF. For more information on SRA's or IDDP's can be found on our website (SRA: **Link**; IDDP: **Link**).

The level and length of funding will vary depending on the scope of the work proposed but is not to exceed $300,000.00/year for 2 years, including up to 10% indirect costs.

ELIGIBILITY

Applicants for SRA's must hold an M.D., D.M.D., D.V.M., Ph.D., or equivalent and have a faculty position or equivalent at a college, university, medical school, or other research facility. Please note that applications from for-profit entities or industry collaborations with academia may be submitted to this LOI; however, additional information will be requested from for-profit entities if a full application is invited.

For clinical studies, applicants must hold an appointment or joint appointment in a subspecialty of clinical medicine and conduct human clinical research.

There are no citizenship requirements for this program. To assure continued excellence and diversity among applicants and awardees, JDRF welcomes applications from all qualified individuals and encourages applications from persons with disabilities, women, and members of minority groups underrepresented in the sciences.

LETTER OF INTENT

Prospective applicants should submit a Letter of Intent (LOI) online via RMS360 (http://jdrf.smartsimple.us) to be considered for a full proposal. The LOI template provided through RMS360 must be used to complete the application. Applicants will be notified approximately four weeks after the LOI deadline date if they have been approved to submit a full application.

Please see below for complete instructions. Letters of intent should use the template provided and include the following information:

- Background/Rationale and Specific Aims of overall project
- Uniqueness about the approach and advantages over other approaches explored in the field
- Overview of hypotheses, goals, deliverables, and collaborative framework if applicable
- Impact of the expected deliverables of the proposed study with potential next steps
- Timelines/timetable
- Intellectual Property or commercial efforts associated with the current application
- Estimated total and annual budgets
- Biosketches for all Principal Investigators

PROPOSAL

An approved LOI is required prior to submission of a full proposal. Upon notification of a request for a full proposal, the application must be completed using the templates provided on the RMS360 portal (http://jdrf.smartsimple.us). Proposal section templates in MS Word [**10 page maximum**] should be type-written, single-spaced and in typeface no smaller than 10-point font and have no more than six vertical lines per vertical inch. Margins, in all directions, must be at least ½ inch. Complete information should be included to permit review of each application without reference to previous applications.

Note that all applications involving human subject research must include supplemental information to address subject safety, study design and investigational product information. More details can be found in the Human Subject Research Guidelines: (link **here**).

REVIEW CRITERIA

Applications will be evaluated based on JDRF's standard confidential award policy and according to the following criteria:

- Significance
- Relevance to T1D
- Approach
- Innovation and level of differentiation
- Investigator experience
- Environment

DEADLINES

- **RFA Release Date**   November 15, 2021
- **Letter of Interest (LOI) Deadline**   December 15, 2021
- **Notification of Full Application Request**   January 12, 2022
- **Application Deadline**   February 16, 2022
- **Response to Applicants**   June, 2022
- **Earliest Anticipated Start Date**   August, 2022

CONTACTS

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If you have any grant-specific questions as you work within RMS360, please contact the administrative contact listed above.

For any **non-grant-specific** inquiries or issues, please contact SmartSimple Support Services via email support@smartsimple.com or phone (866) 239-0991. Support hours are Monday through Friday between 5:00am and 9:00pm US Eastern Standard Time.

1. CDC. National Diabetes Statistics Report, 2020. Centers for Disease Control and Prevention. Published February 11, 2020. Accessed October 27, 2021. https://www.cdc.gov/diabetes/library/features/diabetes-stat-report.html

2. Dabelea D, Mayer-Davis EJ, Saydah S, et al. Prevalence of Type 1 and Type 2 Diabetes Among Children and Adolescents From 2001 to 2009. *JAMA*. 2014;311(17):1778-1786. doi:10.1001/jama.2014.3201

3. Sharp SA, Rich SS, Wood AR, et al. Development and Standardization of an Improved Type 1 Diabetes Genetic Risk Score for Use in Newborn Screening and Incident Diagnosis. *Diabetes Care*. 2019;42(2):200-207. doi:10.2337/dc18-1785

4. Ziegler AG, Rewers M, Simell O, et al. Seroconversion to Multiple Islet Autoantibodies and Risk of Progression to Diabetes in Children. *JAMA*. 2013;309(23):2473-2479. doi:10.1001/jama.2013.6285

5. Staging Presymptomatic Type 1 Diabetes: A Scientific Statement of JDRF, the Endocrine Society, and the American Diabetes Association | Diabetes Care. Accessed October 27, 2021. https://care.diabetesjournals.org/content/38/10/1964

6. Fredheim S, Johannesen J, Johansen A, et al. Diabetic ketoacidosis at the onset of type 1 diabetes is associated with future HbA1c levels. *Diabetologia*. 2013;56(5):995-1003. doi:10.1007/s00125-013-2850-z

7. Aye T, Mazaika PK, Mauras N, et al. Impact of Early Diabetic Ketoacidosis on the Developing Brain. *Diabetes Care*. 2019;42(3):443-449. doi:10.2337/dc18-1405

8. Yu L, Zhao Z, Steck AK. T1D Autoantibodies: Room for Improvement? *Curr Opin Endocrinol Diabetes Obes*. 2017;24(4):285-291. doi:10.1097/MED.0000000000000348