Breakthrough T1D Request for Applications

Advancing Genetic Risk Assessment for Type 1 Diabetes: Improving Prediction and Clinical Translation

May 2025

Summary

- The main goal of this funding opportunity is to enhance genetic risk assessment for type 1 diabetes (T1D), with a focus on improving prediction across ancestral backgrounds and advancing genetic risk scores (GRS) to support future use in real-world screening, and the detection and prevention of T1D.
- This Request for Applications (RFA) will award grants to non-profit and for-profit entities such as academic institutions and industry partners of up to $900,000.00 each and up to 3 years.

Background

Breakthrough T1D is the world's leading non-profit organization dedicated to curing and improving the lives of people with T1D by accelerating breakthroughs for T1D. The focus of the Early Detection Research Strategy portfolio is to develop a global approach for the early detection and prevention of T1D. This strategy aims to identify high-risk individuals—those at elevated genetic risk of developing T1D—and early stages of T1D as detected by autoantibodies allowing for early detection of autoimmunity, access to approved therapies, and prevention of diabetic ketoacidosis (DKA) at clinical diagnosis. Additionally, it opens doors to research opportunities and access to available disease-modifying therapies that may delay or halt the onset of symptoms, thanks to recent medical breakthroughs.

Early detection of T1D is increasingly being integrated into screening programs (e.g. Fr1da, ASK, ELSA, EDENT1FI, and TrialNet)[1-5] and through health policy initiatives such as the recently launched pilot program in Italy[6], with a primary focus on autoantibody screening in the pediatric population. Given the progress on these screening programs, and while we continue to support and advance autoantibody-based approaches, the field now aims to identify individuals at risk of developing T1D at even earlier stages – before the autoimmune process begins – by understanding and stratifying those at high genetic risk. While some pioneering feasibility studies are ongoing (TEDDY, Australian T1D National Screening Pilot, Early check, GPPAD, CASCADE and PLEDGE)[7-10], several gaps remain in the application of genetic risk scores (GRS, also referred as polygenic risk scores or PRS), in the general population, that must be

addressed prior to widespread implementation[11]. This RFA seeks to address these challenges, and the Funding Opportunity description that follows will outline the specific gaps and proposed research initiatives to resolve them.

Funding Opportunity Description

Despite substantial progress in the development of GRS/PRS for T1D, including HLA and non-HLA associated genetic variation, several critical gaps remain that limit their utility for broad equitable implementation. To date, most GRS models[12-16] have been developed and validated primarily in individuals of European ancestry and in pediatric-onset cases. This limited focus significantly reduces their predictive performance in identifying individuals who are at the highest risk of developing autoimmunity and progress to T1D clinical onset across diverse ancestral backgrounds and in adulthood[17]. While recent approaches have begun to identify genetic variants that are specific to several ancestries[18-19] — offering the potential to improve risk stratification — these variants have not yet been fully incorporated into existing GRS models. As a result, current tools may fail to capture the full range of genetic risk across populations.

Research areas of interest for this funding call include, but are not limited to, the following. Applicants are encouraged to address one or more of these areas within their proposals.

- **Identification of causal variants** that enrich T1D risk prediction in populations of non-European ancestry, including both common and rare variants, with a particular focus on HLA-associated and other risk loci across diverse genetic ancestral backgrounds and in individuals with adult-onset T1D. This may include DNA extraction and genotyping or sequencing of samples from individuals within these populations who have already been diagnosed with T1D and/or are part of existing cohorts, repositories, or biobanks.
- **Development of a common and more predictive trans-ancestry genetic risk score (GRS/PRS)** through the application of advanced models and interpretable AI approaches, with revised standardized reporting. This approach aims to increase the weighting of SNPs/SNVs associated with non-European ancestries while maintaining predictive accuracy (AUC) in European populations. The standardization of reporting and the integration of AI-driven methodologies should aim to enhance the robustness and applicability of the T1D GRS across diverse populations.
- **Advancement of T1D risk scores,** including array-based and sequencing alternatives, **to support clinical validation and regulatory approval through pathways such as 510(k) applications or similar regulatory frameworks.** This should aim to ensure that

these tools are rigorously tested and meet the necessary standards for widespread availability and use in early detection, facilitating their integration into clinical practice.

- **Evaluation of combined risk scores for T1D and type 2 diabetes (T2D) to refine disease classification** and improve risk assessment, leveraging existing, standardized, and validated T2D GRS to accurately predict T1D risk. This approach aims to improve T1D GRS by incorporating T2D data and minimizing T1D misdiagnoses.

Out of Scope for this request:

- Launch or follow-up of screening programs focused on the implementation of T1D GRS as an alternative to autoantibody testing.
- *De novo* recruitment of participants is not supported; only proposals that utilize samples from individuals with clinically defined T1D and appropriate controls, sourced from existing biobanks, repositories, or cohorts, will be considered.
- Development or validation of T2D GRS.

Eligibility

- Applications may be submitted by domestic and foreign non-for-profit organizations, public and private, such as universities, colleges, hospitals and laboratories, units of state and local governments, and eligible agencies of the federal government. Applicants 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.

- For-profit entities, or industry collaborations with academia, are welcomed to submit applications in response to this RFA. Please contact the Breakthrough T1D scientific contact below prior to submitting the application. Additional information will be requested from for-profit entities if invited to submit a full proposal.

- 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, Breakthrough T1D welcomes applications from all qualified individuals and encourages applications from persons with disabilities, women, and members of minority groups underrepresented in the sciences.

Funding Mechanism

In response to this announcement, LOI's can be submitted to Breakthrough T1D through the following two mechanisms (please refer to their respective website for further information):

- **Strategic Research Agreements (SRA)** are intended for support of research activities at non-for-profit entities such as academic institutions. SRA totals can include up to 10% indirect costs. For more information about our SRA and Clinical SRA grant mechanisms, please refer to our grant handbook.
- **Industry Development and Discovery Program (IDDP)** are intended for support of for-profit entities. They entail additional requirements and typically have a modest royalty payback to Breakthrough T1D. Please refer to our grant handbook for information on the IDDP grant mechanism and descriptions and contact the Breakthrough T1D scientific contact listed below before submitting your application. Indirect costs are not permitted on IDDP applications.

Proposed budgets for projects should not exceed $900,000.00 total costs for up to 3 years of duration. The level of funding or duration will vary depending on the scope and overall objectives of the proposal. Breakthrough T1D may consider applications with increased scope (time and/or budget) where there is a strong justification (e.g., additional budget for sequencing required to identify variants in individuals from diverse genetic ancestral backgrounds) and interested applicants should discuss with the Breakthrough T1D scientific contact below.

Consortium Participation Requirement

All SRA projects funded through this RFA will be expected to participate in the **T1D Genetic Risk Score (GRS) Consortium**, to be established with the intent to foster collaboration, harmonization, and knowledge exchange across all supported initiatives. Funded investigators will be expected to participate in quarterly Consortium meetings, share data and methodologies as appropriate, and contribute to joint efforts aimed at advancing the development, validation, and clinical integration of GRS-based tools. The overarching goal of the Consortium is to accelerate the translation of GRS discoveries into meaningful improvements in clinical care. **Participation in the Consortium is a pre-condition for funding any SRA project**. Any IDDP projects selected for funding through this RFA will be invited, but not required, to join the Consortium. All participants in this Consortium will be required to sign a separate Consortium policy, in addition to the standard terms and conditions.

Letter of Intent

Prospective applicants should submit a Letter of Intent (LOI) [2 pages maximum] online via RMS360 to be considered for a full proposal request. The LOI template provided through RMS360 must be used to complete the LOI application.

Proposal

An approved LOI is required prior to the submission of a full proposal. Upon notification of a request for a full proposal, the application must be completed using the templates provided in RMS360. Proposal section templates in Microsoft Word, [10 pages 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 a 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 section of our grant handbook.

Breakthrough T1D follows the U.S. National Institutes of Health (NIH) guidelines for studies including human subjects, including the Common Rule.

Review Criteria

Applications will be subjected to confidential external scientific review evaluated on the following:

- Significance
- Relevance
- Approach
- Innovation
- Environment
- Resource sharing plan

Informational Webinar and Q&A

Breakthrough T1D will hold an announcement introduction meeting via Zoom on **Tuesday, May 13, 2025, at 11 AM Eastern Time** to which all prospective applicants are invited. Breakthrough T1D scientists will give an overview of the goals of this initiative, explain the application process, and answer initial questions on applications. Recognizing that the scheduled time may not be convenient for participants in all time zones, the session will be recorded and made available upon request.

Please register for the webinar in advance:

https://breakthrought1d-org.zoom.us/webinar/register/WN_PG9fOQhLQGGI3G-usOe8gQ

After registering, you will receive a confirmation email containing information about joining the webinar.

Projected Timeline [no extensions will be given]

➢ Information webinar and Q&A	Tuesday, May 13, 2025
➢ Letter of Intent (LOI) deadline	Tuesday, June 10, 2025
➢ Notification of LOI outcome	Friday, June 20, 2025
➢ Full Application deadline	Thursday, July 17, 2025
➢ Award notification	December 2025
➢ Earliest anticipated start date	February 2026

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