Breakthrough T1D™
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Breakthrough T1D Request for Applications: Studies addressing clinically relevant questions about ketones and the use of continuous ketone monitoring in type 1 diabetes

September 2025

Purpose

Circulating ketones are clinically relevant metabolites in type 1 diabetes (T1D). To date, most of our knowledge about ketones in T1D has come from point-of-care blood and urine ketone measurements, which provide only snapshots in time and lack the temporal resolution needed to fully understand ketone dynamics. Today, emerging continuous ketone monitors (CKMs) allow us to answer questions we never could before about the pathophysiology of T1D and its complications, DKA prevention, and other topics. Breakthrough T1D invites letters of intent for studies addressing clinically relevant questions about ketones and the use of CKM in T1D.

Background

Type 1 diabetes progresses through clinically defined stages. In stage one, the earliest stage of T1D, people have multiple autoantibodies and normal glycemia. This leads to stage two, where people exhibit dysglycemia. Stage three marks the onset of insulin dependence (and, usually, T1D clinical diagnosis). At this stage, diabetic ketoacidosis (DKA) at clinical onset is a common complication, occurring in approximately 30–60% of new diagnoses. Following stage three, people progress to "established T1D," and later, some will progress to the development of long-term complications including diabetic retinopathy, chronic kidney disease, and cardiovascular disease. Improved methodologies to predict when disease transitions will occur are needed.

DKA, an acute complication of T1D where insulin deficiency leads to hyperketonemia, metabolic acidosis and electrolyte imbalance, remains a risk of living with T1D, sometimes leading to hospitalization and life-threatening complications. Fortunately, the risk of DKA is modifiable; for example, early detection of autoantibody-positive individuals followed by glycemic monitoring has been shown to substantially reduce the frequency of DKA at the time of clinical diagnosis (stage three), and evidence suggests that continuous glucose monitor (CGM) use reduces the frequency of DKA in people with established T1D. However, despite these advances, the rate of DKA remains unacceptably high and a hindrance to the use of certain therapies in people with T1D. To address this unmet clinical need, Breakthrough T1D and others have supported the development of CKM technologies that can continuously measure ketones in the interstitial fluid and alert the user when ketones rise to a sub-clinical threshold. Today, multiple CKM devices are in clinical or preclinical development for diabetes care and other populations. We anticipate CKM sensors (integrated into a

CGM to avoid the burden of wearing multiple devices) reducing the risk of DKA in all people with T1D, including those at increased DKA risk such as adolescents, pregnant women, older adults, people using SGLT inhibitors, and others.

In addition to their promise to prevent DKA, CKMs will also unlock our ability to answer research questions about ketones in T1D that cannot be addressed with older methods of ketone measurement, such as blood and urine strips. In the same way that the dynamic data generated by CGMs transformed our understanding of glucose control, we anticipate research with CKMs revealing novel, clinically translatable insights into 1) the clinical meaningfulness of ketone patterns for individuals in various physiologic and therapeutic contexts across the natural history of T1D, and 2) the potential for CKM to prevent DKA and improve other acute or long-term outcomes.

Objectives

Letters of Intent (LOIs) are sought for studies that incorporate use of CKM to fill research gaps that will ultimately lead to improved outcomes and quality of life for people with T1D. Examples of research questions appropriate for this RFA include, but are not limited to, the following (Note that this list is not intended to be comprehensive):

- Can CKM reduce the incidence or severity of DKA in people with T1D?
- Can CKM data inform automated insulin delivery system algorithms for enhanced safety and glucose control?
- Can the addition of CGM-derived glucose data to CKM data improve algorithms or guidance for DKA prevention?
- How can education strategies, combined with CKM data, enhance recognition and timely response to elevated ketone levels?
- Can CKM metrics enhance the prediction of progression from early stages (stages one and two) to stage three T1D?
- Can CKM metrics help prevent DKA at the onset of stage three in individuals identified at early stages?
- Are CKM metrics associated with the development of (or, conversely, protection from) long-term diabetic complications?
- Do sub-clinical ketone patterns predict DKA or other clinical outcomes?
- Can CKM identify subpopulations of people with T1D at high risk for acute or long-term complications?
- Can CKM data elucidate poorly understood aspects of T1D pathophysiology?
- Can CKM be used to demonstrate risk of (or protection from) ketosis/DKA from adjunctive therapies besides SGLT inhibitors?
- Does wearing a CKM impact rates of ketosis and DKA, glucose control, and/or quality of life?
- Can CKM guide insulin dosing strategies around exercise to prevent ketosis and time out of glucose range during and after exercise?

Examples of research not covered by this RFA include:

- Studies that are not clearly differentiated from ongoing CKM research that assess ketone dynamics and explore the frequency of ketosis episodes (including DKA) under free-living conditions in the general population of adults and children with T1D.
- Studies investigating the use of CKM to mitigate the risk of DKA in people with uncomplicated T1D using SGLT inhibitors, unless proposed studies are well differentiated from other efforts in the field. Applicants are encouraged to check NIH RePORTER, ClinicalTrials.gov, and other resources documenting ongoing and planned trials.
- Studies that evaluate CKM accuracy or performance.
- Studies focused entirely on non-T1D populations.
- Pre-clinical development of novel CKM technologies.

Applicants are encouraged to consult with the Breakthrough T1D Scientific Staff below to discuss the alignment of their proposal to this RFA and to develop the projected study concept.

Critical Considerations

- Breakthrough T1D will support interventional clinical trials, observational studies, and if appropriate, analysis of existing data.
- We encourage proposals that seek to leverage ongoing or planned studies (For example, Breakthrough T1D will consider requests to provide CKM and support for associated analysis to ongoing trials).
- Funded studies may use either blinded or unblinded CKMs.
- It is the responsibility of the applicant to obtain drugs for their study. Breakthrough T1D funding will be contingent on a written commitment from the manufacturer to provide study drug, devices, and placebo, as applicable.

CGM-CKM Procurement

- Successful proposals may be eligible to receive donated Abbott CKM devices if their study plan involves use of Abbott technology, contingent upon review by Abbott.
- Devices provided by Abbott will be dual glucose ketone continuous monitors. Depending on the study, glucose readings from the device may or may not be relevant.
- In the Letter of Intent, applicants will be required to indicate whether they give permission to share LOI and application materials with Abbott.
- For applicants who give permission to share LOI and application materials with Abbott, possible application outcomes may include: funding by Breakthrough T1D with donation of devices from Abbott, co-funding by Breakthrough T1D and Abbott, and/or trial sponsorship by Abbott.
- Proposals utilizing other CKM devices or prototypes will likewise be considered by Breakthrough T1D.

Regulatory Requirements

- Breakthrough T1D follows the U.S. Department of Health and Human Services (HHS) regulations for the protection of human subjects in research (45 CFR 46). All projects with human subjects will be required to provide Breakthrough T1D with ethical approval documentation at all times.

Budget

Applications for SRAs and IDDPs may request up to a total of $1,500,000 over a maximum of three years. Breakthrough T1D may consider applications with increased scope (time, budget) where there is a strong justification, and applicants interested in such should discuss with the Breakthrough T1D scientific contact below. Note that the above budget figures are maximums, and Breakthrough T1D will also consider projects with substantially smaller budgets. In all cases, the level of requested funding should be commensurate with the studies proposed and non-Breakthrough T1D resources (funds, personnel, other) available to successfully complete the project. Appropriateness of budget in relation to scope will be considered as part of the review criteria.

Mechanism

In response to this announcement, Letters of Intent (LOI) can be submitted under the following mechanism(s):

Strategic Research Agreement (SRA)

Strategic Research Agreements are intended for support of research activities at not-for-profit entities such as academic institutions. For more information on the SRA grant mechanism please refer to the Grant Handbook. SRA applications may include up to 10% indirect costs as part of the total request.

Industry Discovery and Development Partnerships (IDDPs)

For-profit entities may apply under Breakthrough T1D's Industry Discovery & Development Partnership (IDDP) funding mechanism, which entails additional requirements including company matching funds. If you would like to submit an Industry Discovery and Development Partnership (IDDP) project LOI to this RFA, please review the IDDP guidelines available in the Grant Handbook. Indirect costs are not permitted on IDDP applications. IDDP applications that are invited to a full proposal will receive their own timeline for completion of due diligence and finalization of an agreement.

Eligibility

Applications may be submitted by domestic and foreign non-profit organizations, public and private, such as universities, colleges, hospitals, 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., D.O., 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 RFA; however, additional information will be requested from for-profit entities if a full application is invited.

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.

Letter of Intent (LOI)

Prospective applicants should submit a Letter of Intent (LOI) using the template provided online via RMS360. The LOI should be 2 pages and submitted online to be considered for a full proposal invitation.

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. Complete information must 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 in the Grant Handbook.

Review Criteria

Applications will be evaluated based on Breakthrough T1D's standard confidential award policy and according to the following criteria:

- Significance
- Approach
- Innovation
- Investigator Experience
- Environment

Projected Timeline

Milestone	Date
LOI deadline	November 12, 2025
Notification of LOI outcome	December 10, 2025
Full proposal deadline	January 21, 2026
Award notification	May 2026
Earliest anticipated start	July 2026

Program Contacts

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