INTRODUCTION

The overall goal of the workshop was to bring advances in identifying individuals at risk for T1D and disease modifying therapy to clinical practice. The aims were to engage stakeholders in discussion of shared goals, strategies, and approaches, identify gaps in bringing screening and disease modifying therapy to clinical use and describe specific topic areas and projects for further development by cross-stakeholder working groups. The NIH has been congressionally mandated since 1997 to study T1D, and the Special Diabetes Program (SDP) has provided ~$150,000,000 of annual funding to support T1D initiatives overseen by NIDDK. This level of investment has enabled large, ambitious initiatives investigating each stage of T1D development and provides a long-term commitment to T1D research, much of which is accomplished through the support of TrialNet.

SESSION 1: MAY 14, 2021

Session 1 **focused on identification of individuals "at-risk" for T1D – 30 panelists discussed 4 questions:**

Question 1: How do goals such as preventing diabetic ketoacidosis (DKA), enrolling trials, and assuring market for therapy compete and complement each other?

- These goals complement each other.
- While preventing DKA is beneficial, screening itself does not prevent DKA. It is the follow-up actions that matter.
- We need to enroll patients in clinical trials to make progress toward the other two goals.
- However, not all individuals will want treatment or to participate in trials; thus, DKA prevention is an important part of the benefit-risk ratio that can be presented to individuals.
- Assuring a market for new therapies is critical to sustain investment and engagement from industry. When therapies become available, we will learn more about who can benefit from them. This enhances our screening, which can, in turn, help improve DKA prevention.

Question 2: What are scientific gaps – populations, algorithms, assays?

- There are significant gaps in all of these topics. The question is which gaps can we live with and which must be closed?
- While general population testing is the long-term goal, this will be challenging to accomplish. Population level assays ideally need to be feasible in large laboratories and considered in the context of their positive and negative predictive value.
- Perhaps a staged approach would be more palatable, focusing on addressing essential scientific and implementation issues on those at highest risk to inform approaches to broader population testing.
- Regarding algorithms and assays, we need to develop a consensus about criteria for the use of algorithms and assays for screening in different populations. Similar efforts will be needed to guide follow-up in those identified as antibody positive in different populations. This will require exploratory and confirmatory data that will support that consensus, particularly in general population screening.

Question 3: What are the knowledge gaps for clinicians and individuals?

- There are significant knowledge gaps for clinicians and for the individuals that are to be targeted for screening, and the gap is greater for those without personal experience with T1D. The general population knows less about risk than relatives, and general physicians know less than pediatric endocrinologists.
- Research has been done by some in industry to understand the knowledge gaps of regulators, payors and patients, and this information may be available to share with others.
- There is also a need to educate decision makers within industry on the opportunities available in embracing the concept of prevention – what prevention means and the value of prevention.
- The points that need to be explained include: why do we need to screen, who do we need to screen and when do we need to screen?
- There is a lack of clarity about how to describe autoantibody positivity – as a disease such as hypertension, or as a risk factor?
- Education alone is insufficient – we must also evaluate ways to facilitate participation in screening for prevention and address other implementation gaps including the use of clinical time to discuss testing and interpret results. It was

generally agreed that we need to contest the perception that T1D is adequately treated with insulin. T1D is thought of as a treatable disease, but it really is not. This area readily lends itself to cross-stakeholder working groups.

Question 4: What information is needed by regulators/insurers/clinical practice guidance groups to bring screening and monitoring to clinical use?

- The essential questions are: 1) Who pays for the screening and monitoring? How can it be implemented into clinical practice? 2) How can cost effective screening and monitoring be made feasible in the general population?
- Payors need to be involved early and need to see an economic argument for T1D prevention therapies or DKA prevention. This is a challenge because of the time lapse between when costs are incurred and when benefits are seen.
- Some payors have also said that they will follow the guidelines set by the American Academy of Pediatrics and the US Preventative Services Task Force. Yet some of the data that are needed by regulators and those that develop clinical practice guidelines are lacking. Recommendations will need to consider age-specific guidelines.
- It will be important to identify meaningful clinical benefits that balance patient risk. If you are screening to prevent DKA in a population where the risk of T1D is low, or there is no clinical and psychosocial support for individuals found to be at risk, there will be a chance of harm due to low T1D positive predictive values. In contrast, a benefit that would outweigh potential harm of screening would be a significant delay in T1D onset if risks from therapy itself does not outweigh benefits.

General Discussion

While the ultimate goal may be a preventative therapy to forestall T1D forever, getting the first drugs that delay T1D onset to market could be catalytic to that goal. Industry participants made clear that their goal is to have a therapy for T1D prevention; this goal is complementary to but different from the public health aim of decreasing DKA. We could take an interim step, such as making it standard of care to screen relatives. This would also identify a population to which clinical trial participation could be offered, for example. That would be an interim goal towards the ultimate goal of therapy. It currently takes a lot time to do a prevention trial, so expanding screening could help.

Also, what is the key thing we are trying to do for patients? We need to make clinical trials part of a public health campaign while at the same time explaining and demonstrating that the benefits (reduction in DKA by screening and monitoring for those that will not be interested in or able to use therapies) will exceed potential harm.

There is a large education gap that we need to tackle. We will ultimately need these ideas to make sense to all for there to be progress towards therapies. We need to collaborate to make sure that our messages are consistently accurate and aligned with our goals. We also need to communicate, stay open to new ideas and to keep things simple!

SESSION 2: MAY 21, 2021

Session 2 **focused on disease modifying therapies** – **30 panelists discussed 4 questions:**

Question 1: How do we bring understanding of disease progression into discussions for drug approval?

- Both the concept of stages and the use of tools for trial enrichment, such as autoantibodies, have been helpful, particularly in explaining the concept of disease prior to overt clinical symptoms. Nonetheless, there is a need to assure that the concept of stages does not become limiting as advances in understanding specific pathways become more actionable.
- More understanding of when to treat through increased biological understanding of progression would be helpful.

Question 2: What are the challenges and opportunities of using a network to gain efficiencies in conduct of trials?

- While TrialNet is the acknowledged leader in the conduct of prevention trials of disease modifying therapies in T1D, from an industry perspective, their funding and scope is currently too limited to overcome the challenges of time. It simply takes far too long for the recruitment of at-risk individuals. There may be opportunities to more effectively partner with industry and other stakeholders to expand this work while capitalizing on the experience and efficiencies of conducting trials.
- Key issues from industry in working with TrialNet and NIDDK include working out agreements on items such as intellectual

property, data sharing and others. Other models of private-public partnerships may be better able to address these issues up front and may be better situated to develop data in support of clinical care guidelines and the economics needed for clinical implementation.

Question 3: How can data and samples be most effectively used to identify targets and understand response to therapy?

- All stakeholders emphasized the importance of data and samples for target identification and understanding response to therapy.
- There may be opportunities to share the effort and cost to interrogate TrialNet samples to identify questions of common interest to multiple stakeholders, while recognizing that other data may be linked to proprietary drug discovery investigation and would require separate agreements and assurance that appropriate consent was obtained.
- Regarding data, issues include assuring data is available, usable and useful. Many were unaware that TrialNet data is available via the NIDDK repository. Others noted, however, that additional effort is needed before it is readily usable. Some in industry noted the data would be most useful if there is opportunity for confidential engagement with TrialNet investigators in interpretation of the data.
- There are other successful examples of sharing and understanding data that meet the needs of industry and academics that should be considered as a model, including projects through the Foundation for the National Institutes of Health (FNIH), such as the Accelerating Medicines Partnership (AMP).

Question 4: What are the opportunities and challenges in understanding disease and pathways that can lead to novel trial designs?

- A multi-stakeholder coalition involving patients, FDA, academics and industry in alignment could be very impactful.
- Key for industry is timeliness; mechanistic studies or outcomes that allow for early decisions before committing to larger trials can be useful as well as helpful in understanding trials with negative clinical outcomes. However, these efforts must not impact development timelines.
- An important cross-stakeholder issue is how a greater scientific understanding of disease and pathways may allow for a different paradigm than enrolling adults before enrolling children in early stage trials.
- While the science should drive trial designs, practical issues including risks of novel approaches and timelines are challenges for industry.

Cross-stakeholder projects for further consideration and development:

1. Develop and recommend Consensus Guidelines using currently available data and expert opinion for screening and follow-up of first-degree relatives or other high-risk individuals to the American Diabetes Association Professional Practice Committee.
2. Develop and test population tailored education materials for (a) primary care and specialty clinicians (b) individuals and families living with T1D and those with no knowledge of T1D, and (c) use within industry.
3. Collaborative design and implementation of research study (studies) to obtain additional data to meet evidentiary needs for recommendations for screening and monitoring including the general population in clinical practice.
4. Develop and recommend consensus criteria for antibody assays to be used to identify individuals at risk.
5. Explore ways to maximize efficient cross-stakeholder use of TrialNet data and samples to address common questions and specific topics.
6. Explore other models for cross-stakeholder interaction in recruitment and the conduct of clinical trials in at-risk individuals.

We wish to acknowledge the work of Cate Speake PhD, Megan Smithmyer PhD and Sandra Lord MD, all from the Benaroya Research Institute in Seattle, WA, for providing notes in support of this summary document.