

Complications

OVERALL VISION AND LONG-TERM OBJECTIVES

The overall vision of the JDRF Complications program is to accelerate delivery of drug-based approaches that prevent or delay progressive kidney decline and vision loss in people with type 1 diabetes (T1D). To achieve this long-term objective, the program is prioritizing the identification and qualification of prognostic and surrogate biomarkers to enable clinical trials of therapeutics targeting early stages in the disease process. Where feasible, the program also aims to facilitate the discovery and translation of highly promising disease targets and pathways that may emerge from these and other efforts.

Almost 25 years ago, the landmark DCCT/EDIC trial showed that intensive insulin therapy could significantly reduce the risk of diabetic complications, however only one-third are currently achieving the recommended blood glucose targets. Recent advances in diabetes technology, such as artificial pancreas systems, will dramatically reduce the daily burden of intense insulin therapy and help many more to achieve recommended glycemic targets. However, the global T1D population spans all ages and stages of the disease with varying levels of glycemic control, complications susceptibility and access to healthcare. In the United States alone, 1.25 million Americans are living with T1D and an additional 40K are being diagnosed with the disease each year. Healthcare advances have increased life expectancy and people with T1D are living longer and an estimated 85% are now in adulthood. Although chronic exposure to hyperglycemia is the primary driver, other co-pathologies, such as high blood pressure and lipid abnormalities, as well as genetic predisposition and potentially other unknown factors contribute to the onset and progression of chronic complications. Susceptibility is highly variable and it is still unclear why complications can develop even in those with lower HbA1c values, ostensibly reflecting good glycemic control.

The Complications program aspires to “Medalist-level” protection for people with T1D. Medalists are those individuals who have remained largely free from diabetic complications even after 50 years living with T1D—with many of those years prior to the advent of intensive insulin therapy. As such, there is great potential for new therapies, beyond management of glucose control, to protect those at increased risk and treat the millions already diagnosed with diabetes complications.

The Complications program focuses on the following areas to improve T1D outcomes:

1. Diabetic nephropathy (DN) in T1D.
 - a. Biomarkers to enable clinical trials targeting early DN disease stages.
 - b. T1D inclusion in DN clinical trials.
 - c. Translation of targets and pathways emerging from renal biomarker and genetics studies or other areas (where feasible).
2. Diabetic retinopathy (DR) in T1D.
 - a. Biomarkers to enable clinical trials targeting early DR disease stages.
 - b. T1D inclusion in DR clinical trials.

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Strategies to prevent and treat acute complications are included in JDRF's Metabolic Control Program.

DIABETIC NEPHROPATHY IN T1D

End-stage renal disease (ESRD) is one of the most severe complications in T1D and continues to affect more than a quarter of the population by 40 years of living with the disease. Given the increasing prevalence of T1D and longer life expectancy, the number living with progressive kidney decline is anticipated to increase. Although there are encouraging signs that ESRD specifically may be declining, this seems to reflect better glucose control and slower progression of established kidney disease rather than prevention of early renal disease per se. Recent studies suggest a broad range in renal decline rates with some individuals progressing very slowly and others proceeding rapidly to ESRD. As such, there is an urgent need for therapies, beyond improvements in glucose control, including intensive lipid and hypertension management as well as novel strategies that target disease mechanisms.

Biomarkers are Needed to Enable Clinical Trials Targeting Earlier DN Disease Stages

The lack of validated prognostic and surrogate biomarkers is probably the greatest barrier to the development of therapies to prevent or delay progression of DN. JDRF is prioritizing efforts to identify robust biomarkers to predict disease risk and progression, to facilitate subject stratification for less costly trials and to study interventions that target earlier stages in the disease process. JDRF is supporting collaborative academic research using 'omics' approaches (genetics, transcriptomics, proteomics, metabolomics) on large T1D cohorts as well as partnering with other funders, academia and industry to accelerate progress in this precompetitive space.

JDRF has supported the largest ever effort to identify genetic determinants of DN in T1D, and further genetic and functional validation is needed to confirm emerging candidates and their utility as biomarkers or potentially as therapeutic targets.

Kidney damage is largely irreversible at later stages of DN. As such, there is an urgent need to intervene earlier in the disease. Late biomarkers may reflect the integrity of the filtration barrier, whereas biomarkers for earlier disease stages may reflect the initiation and progression of pathological processes such as inflammation and fibrosis.

Prognostic biomarkers enabling stratification into trials at earlier DN disease stages will need to be accompanied by novel validated surrogate biomarkers of efficacy as the currently FDA-accepted trial endpoints, doubling of serum creatinine or time to dialysis, would require unacceptably long clinical studies.

Clinical Trials in DN Should Include Subjects with T1D

T1D continues to be an exclusion criterion in the majority of pharma-sponsored clinical trials. Currently, the PERL trial assessing the uric acid-lowering generic drug, allopurinol, is the only clinical study underway that includes subjects with T1D. Excitingly, recent cardiovascular outcomes trials in T2D suggest that drugs in the SGLT2 and GLP-1 classes could act as renal protective agents in their own right. All three SGLT-2 inhibitors on the market have dedicated renal outcomes trials planned or ongoing. Such trials should include subjects with T1D and JDRF aims to facilitate this wherever feasible.

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DIABETIC RETINOPATHY IN T1D

Blindness is a feared complication of T1D. Almost all experience vision loss over a 15- to 20-year period, and approximately 20–30% advance to the blinding stage of the disease. DR begins with mild nonproliferative abnormalities, characterized by increased vascular permeability and progresses to moderate and severe nonproliferative diabetic retinopathy (NPDR), characterized by vascular closure and then to proliferative diabetic retinopathy (PDR), characterized by the growth of new blood vessels on the retina and posterior surface of the vitreous. Macular edema, characterized by retinal thickening from leaky blood vessels, can develop at all stages of retinopathy. Pregnancy, puberty, blood glucose control, hypertension can accelerate these changes. In addition, the progression of microvascular complications in the retina may be useful in diagnosing or screening for DR.

Biomarkers are Needed to Predict Therapy Response and Target Earlier DR Stages

Molecular understanding of the pathogenesis of DR uncovered the role VEGF in the growth and permeability of retinal blood vessels and in causing diabetic macular edema (DME) and led to the development of anti-VEGF drugs for treating DME and NPDR. Unfortunately up to 25% of patients do not respond or under-respond and therefore alternate therapies are urgently needed. Potential therapies include plasma kallikrein inhibitors and fenofibrate.

Most recent advances have focused on late stages of DR but many changes begin prior to clinical manifestation of the disease, including biochemical changes, leukocyte adhesion, basement membrane thickening, altered retinal blood flow and neuroelectroretinogram changes. As such there is an urgent need to preserve vision by intervening at earlier stages of the disease.

The development of treatments targeting earlier DR disease stages will require prognostic and surrogate biomarkers that can predict visual and anatomic outcomes. Biomarkers are needed to accurately determine the risk of disease, identify those at risk of vision loss, monitor disease progression, identify patients likely to respond to treatments, monitor treatment response. Retinal biomarkers may also have the potential to serve as biomarkers of DN and vice versa.

SHORT-TERM OBJECTIVES AND PRIORITIES

Diabetic Nephropathy in T1D

1. Identification, validation and regulatory qualification of prognostic and surrogate biomarkers in DN with emphasis on early disease stages.
2. Identification of factors associated with rapid progression or protection from DN.
3. Inclusion of T1D subjects in DN clinical trials (e.g., renoprotective effects of SGLT2 inhibitors or other drugs).

Diabetic Retinopathy in T1D

1. Identification, validation and qualification of prognostic and surrogate biomarkers in DR with emphasis on early disease stages.
2. Leveraging “big data” approaches to identify biomarkers from retinal imaging data.

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3. Understanding the molecular basis of anti-VEGF non-response to facilitate patient stratification/personalized medicine.
4. Inclusion of T1D subjects in DR clinical trials (e.g., fenofibrates, plasma kallikrein inhibitors).