Complications

Vision

Prevent or delay progressive kidney decline and vision loss until we have a cure for type 1 diabetes (T1D).

Mission

The Complications program aims to accelerate therapies to prevent and treat diabetic kidney and eye diseases in people with T1D by:

- Identifying robust prognostic and surrogate biomarkers to recruit the 'right patient for the right trial'. Lack of effective biomarkers is the greatest barrier for developing new therapies, especially in early disease stages before overt clinical symptoms appear and damage becomes irreversible.
- Facilitating translation of therapeutic targets and pathways that show promise for people with T1D – especially where JDRF is uniquely positioned to drive progress
- Improve outcomes and care delivery by understanding and monitoring the 'real world' incidence of complications in T1D. Monitor the potential impact of new therapies in people with T1D through 'big data' approaches.

Rationale

Over 25 years ago, the landmark DCCT trial showed that the risk of complications could be reduced through intensive glucose control, however recent findings from various sources, including the T1D Exchange, an international meta-analysis, and US electronic health records, show that only 1/3 of people with T1D are actually achieving recommended blood glucose targets.

Indeed, 1/3 of ~300K with T1D in the international meta-analysis of 19 countries, spanning Australasia, Europe and North America, had HbA1c levels above 9%. Furthermore, the US-based SEARCH study which followed youth with T1D found a least one early-stage complication in 1/3 of adolescents and young adults and two or more complications in 6%. Minorities and lower socio-economic groups were disproportionately affected. In a UK-based study, diabetic retinopathy was identified in 1/3 of people with T1D who underwent checkups, while1/10 were found to reach vision-threatening levels.

Recent advances, such as artificial pancreas systems, will greatly reduce the daily burden and help many more achieve recommended targets and lessen the risk of complications. However, the global T1D population spans all ages and stages with varying levels of glucose control, diabetes awareness, susceptibility to complications and access to healthcare. In the United States alone, 1.25 million 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 - an estimated 85% are now in adulthood.

Although chronic hyperglycemia is the primary driver, other co-pathologies, such as high blood pressure and lipid abnormalities, as well as genetics and potentially other unknown factors contribute to the onset and progression of chronic complications. Susceptibility is highly variable and we still don't know why some people develop complications even though they may have lower HbA1c. JDRF's Complications program aspires to "Medalist-level" protection for everyone with T1D. Medalists are those individuals who have remained largely free from diabetic complications even after 50 years living with the disease — with many of those years prior to the advent of intensive insulin therapy. As such, there is a need and 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 – until a cure for T1D is found.

1/3

Of adolescents and young adults with T1D already show evidence of least one early-stage complication

Kidney failure, also known as end-stage renal disease (ESRD), is one of the most severe complications and continues to affect more than a quarter of individuals by 40 years of living with T1D. 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. Given the increasing prevalence of T1D and longer life expectancy, the number living with progressive kidney decline is actually anticipated to increase. Recent studies suggest a broad range in renal decline rates with some individuals progressing very slowly and others proceeding rapidly to ESRD. People living with chronic renal decline also have a substantially increased risk of cardiovascular disease such as stroke and heart failure. As such, there is an urgent need for therapies, beyond improvements in glucose control.

Similarly, progressive diabetic eye disease leading to 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. In contrast to DN which is clinically silent until later stages, DR can be detected, somewhat earlier, through direct observation of the retina using technologies such as fundus photography and optical coherence tomography, OCT, or OCT-A when combined with angiography.

Strategy

Identify and validate prognostic and surrogate biomarkers in DN and DR

People with diabetes develop complications at very different rates. The earliest stages are clinically silent making it difficult to reliably identify and treat those at greatest risk before irreversible damage can be prevented. As such, JDRF aims to identify robust prognostic biomarkers to more efficiently stratify patients into trials targeting earlier DN and DR stages. Surrogate biomarkers are also needed to substitute for hard clinical endpoints which are impractical for testing therapies targeting early disease stages. For example, the current DN endpoints of time to kidney failure or doubling of serum creatinine, limits testing of therapies to subjects who are within 3-4 years of kidney failure.

Heart disease is the most common cause of death in individuals with kidney disease. The FinnDiane T1D registry has reported a 2-fold increase in mortality with microalbuminuria, a 9-fold increase with macroalbuminuria and an 18-fold increase with ESRD that is largely due to cardiovascular disease. As such, JDRF is also considering cardiovascular biomarkers to the extent that these may increase prognostication in DN.

Prognostic and surrogate biomarkers that predict visual and anatomic outcomes are also critically needed to facilitate discovery and development of therapies for DR. Biomarkers are also needed to predict the likelihood of response to anti-VEGF therapy, the emerging standard of care, where up to 50% of patients do not show benefit. While most recent advances have focused on late stages, many pathological changes begin prior to clinical DR manifestation, including biochemical changes, leukocyte adhesion, basement membrane thickening, and altered retinal blood flow and neuro-electroretinogram changes. JDRF is prioritizing efforts to identify prognostic biomarkers for optimal patient stratification in clinical trials targeting earlier DR stages. Ideally, subjects would be enrolled into trials, based on retinal image (fundus, OCT, OCT-angiography etc.) or biomarker/s measurement in blood combined with relevant clinical parameters.

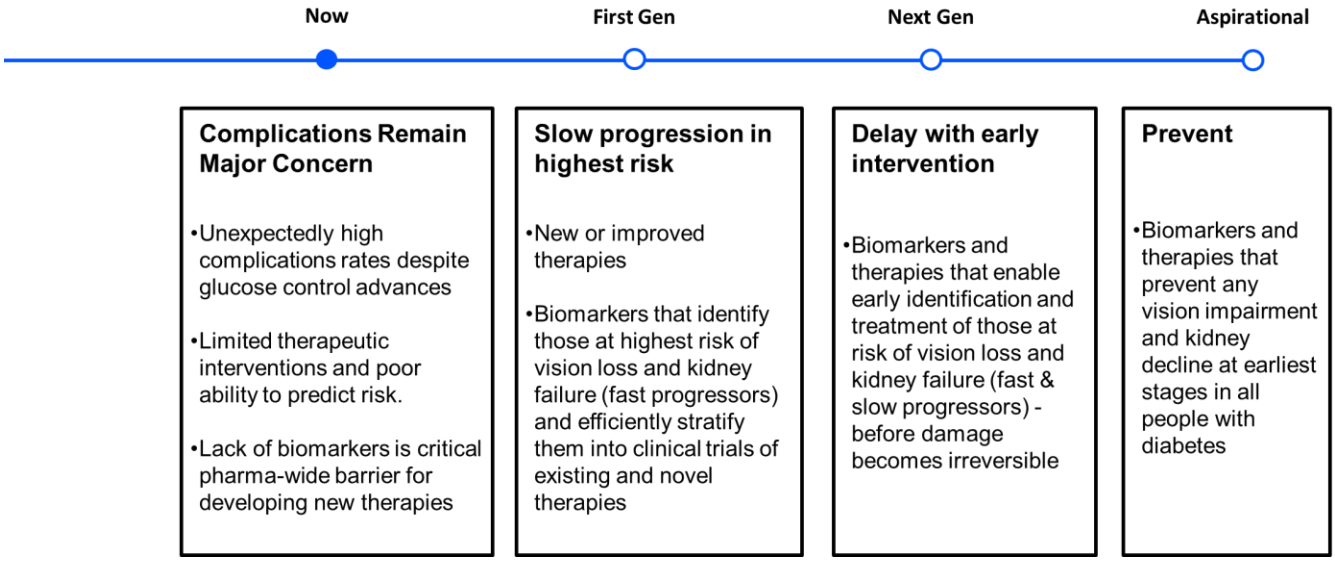
To ensure broad dissemination and use in clinical trials, prognostic and surrogate biomarkers will need regulatory qualification by the FDA. To achieve this, a comprehensive understanding of their relevance in the disease process will need to be demonstrated. For example, biomarkers relevant to early renal disease stages may reflect the initiation and progression of pathological processes such as inflammation and fibrosis whereas those appearing closer to the time of end organ failure may largely reflect the integrity of the kidney's filtration barrier.

Monitor real-world complications rates in T1D by leveraging electronic health records (EHRs)
JDRF is monitoring emerging 'big data' and other novel approaches for gaps where strategic support may be feasible and accelerate progress. Mining of de-identified images, blood, urine and other relevant data, combined with machine learning approaches, has the potential to uncover novel biomarkers that may facilitate development of new therapies and improved clinical decision-making in both diabetic nephropathy and retinopathy. Indeed, the prospect of predicting which individuals are at risk for rapid progression to renal failure or which eyes may not respond to therapies such as anti-VEGF may lie in leveraging these innovative approaches. To complement these efforts, the complications program also aims to better understand and monitor the 'real world' incidence of complications in T1D through 'big data' approaches. This will enable population-based studies on the effectiveness of existing and novel therapies, a deeper understanding of the factors contributing to progressive end organ failure and ensure a more strategic approach to care delivery.

Facilitate translation of targets and pathways – where feasible and JDRF is uniquely positioned
Adverse outcomes remain disturbingly high among people with T1D, and as the largest patient voice and foundation supporting T1D research worldwide, it is JDRF's Mission to improve the lives of our stakeholders. Contingent on resources, and where JDRF is uniquely positioned, we aim to partner with pharma, and similar organizations, with aligned patient-driven goals to assess highly-promising therapies in people with T1D. For example, there have been no new drugs for DN in the last 20 years and, with the exception anti-VEGF therapies, no new drugs for DR in the last 50 years. Disturbingly, T1D has largely remained an exclusion criteria in most sponsor-initiated clinical trials in diabetic nephropathy. Hence a strategic goal of JDRF is to understand and reduce the barriers to trials in T1D with the eventual approval of therapies for this population. There is also a critical need for innovation in DR. While anti-VEGF therapies have been transformational this has been the only new therapy for DR in the last 50 years.

Roadmap

The Complications program has outlined a roadmap from the current state where complications rates, although decreasing, remain unacceptably high despite technologies to improve glucose control. The greatest urgency is to prevent or slow progression of in those at greatest risk of rapid decline. The next step would be to delay complications in all people with T1D and then ultimately prevent progression and/or disease onset at the earliest possible stage.



Current Status

Diabetic Nephropathy Biomarkers

Extensive efforts are underway to identify novel prognostic and surrogate biomarkers to effectively stratify patients and measure therapeutic response in diabetic nephropathy clinical trials. JDRF is supporting academic collaborative efforts leveraging 'omics' approaches (genetics, transcriptomics, proteomics, metabolomics) blood and urine samples from large T1D cohorts as well as actively partnering with other funders, academia and industry to accelerate progress in this precompetitive space. These include the JDRF-funded DNBio collaborative group, partnership with NIH in the Kidney Precision Medicine Project (www.kpmp.org), and with the EU-based Innovative Medicines Initiative in the BEAt-DKD project (www.beat-dkd.eu).

JDRF-funded 'omics' efforts in blood and urine have led to the identification of prognostic biomarkers in late stage diabetic nephropathy and the identification of a multi-protein signature of inflammatory circulating proteins. However, the detection of early stage prognostic biomarkers remains a critical gap.

To complement 'omics' in blood and urine, T1D kidney biopsies are being profiled to correlate progressive structural and molecular changes in the kidney with the appearance of new biomarkers in urine and blood. These tissue-based 'omics' efforts are also anticipated to uncover pathways in the pathogenesis of disease and lead to new drug targets. Towards these objectives, JDRF is supporting the collection of kidney biopsies in the PERL trial and also partnering with NIH to ensure T1D is included in the kidney atlas being developed in KPMP.

JDRF also supported the largest ever effort to identify genetic determinants of DN in T1D. The project successfully identified kidney-relevant disease genes and further genetic and functional validation is underway on emerging candidates to assess utility as biomarkers or potentially as therapeutic targets. This valuable dataset is now publically accessible via the Accelerating Medicines Partnership knowledge portal (www.type2diabetesgenetics.org/informational/data)

JDRF is optimistic that eGFR slopes will emerge as the first-ever surrogate endpoint in diabetic nephropathy. A recent comprehensive meta-analyses of clinical trials and observational studies has now provided robust supporting evidence and FDA and EMA guidance is anticipated in 2019. If endorsed, this would enable trials of therapies targeting earlier disease stages. This would also reinforce JDRF-supported biomarker discovery efforts which all use eGFR slope to define rate of progressive renal decline.

Diabetic Nephropathy Therapies

JDRF is partnering with the NIH on the multi-site international PERL trial which anticipated to report results in mid to late-2019. This study is testing whether the generic drug, allopurinol, can prevent or delay progression of kidney disease in people with T1D and is anticipated to report results in mid to late-2019 (perlstudy.org).

Although no new therapies for diabetic nephropathy have been developed in the last 20 years, a number of very promising candidates exist that have glucose control as well as cardiorenal protective benefits. For example, recent T2D cardiovascular outcomes trials suggest that SGLT2 and GLP-1 drugs act as renal protective agents in their own right. Notably, the CREDENCE trial of the SGLT2 inhibitor (SGLT2i) Cannagliflozin was halted a year early because it had already demonstrated renal protective efficacy. SGLTi drugs have now been approved in T1D for glucose control in both Europe and Japan and are under review by FDA. It is essential that these drugs be evaluated for renoprotection in T1D clinical trials so that people with T1D may realize the full benefits of this therapy. Other developments include significant eGFR improvement in a small cohort of T1D subjects in the phase 2 PHOENIX trial of bardoxolone methyl.

Diabetic Retinopathy Biomarkers

Diabetic eye disease begins with mild non-proliferative abnormalities, characterized by increasingly leaky blood vessels. This progresses to moderate and then severe non-proliferative diabetic retinopathy (NPDR). New blood vessels grow on the retina and posterior surface of the vitreous to compensate. This is called proliferative diabetic retinopathy (PDR). Macular edema, characterized by retinal thickening from leaky blood vessels, can develop at any stage of retinopathy. Pregnancy, puberty, blood glucose control, and hypertension can accelerate these changes. In addition, the progression of microvascular complications in the retina may be useful in diagnosing or screening for DR

Molecular understanding of the disease pathogenesis uncovered the role VEGF in the growth and permeability of retinal blood vessels and in causing diabetic macular edema (DME). This led to the development of anti-VEGF drugs for treating DME and NPDR. Unfortunately up to 50% of patients do not respond or under-respond and so new therapies, and biomarkers to inform clinical decisions, are critically needed. Although pan-retinal photocoagulation and the more recent Anti-VEGF therapies have greatly reduced the risk of progression to the blinding stage, there is an urgent need for biomarkers to predict who may or may not benefit from these therapies and for novel more effective therapies to prevent visual impairment.

Significant progress has been made using 'big data' approaches by applying deep learning to large fundus photo databases of retinal images. This recently led to the commercialization of a screening device that automatically detects 'more-than-mild diabetic eye disease' in the primary care setting for referral to expert ophthalmological care. JDRF anticipates next-generation screening devices will provide a more comprehensive risk assessment such as "X percentage chance of developing Y stage in Z years".

Diabetic Retinopathy Therapies

Therapy for diabetic retinopathy largely depends on the type and severity. Mild or non-proliferative diabetic retinopathy is primarily closely monitored and an emphasis is placed on maintaining good glucose control. As the condition advances to proliferative diabetic retinopathy or macular edema, treatments include photocoagulation, pan-retinal photocoagulation, vitrectomy and intravitreal anti-VEGF injections. Novel, more effective therapies, are needed to prevent and delay the disease progression, especially in those individuals who don't respond to Anti-VEGF.

Critical Gaps

Identify and validate biomarkers of diabetic nephropathy and retinopathy

- Develop prognostic biomarkers to enable stratification of patients for clinical trials – "right patient for right trial"
- Develop surrogate biomarkers to substitute for hard clinical endpoints and enable testing of therapies early in disease stage
- Develop predictive biomarkers that predict response to therapy

Understand 'real world' rates of complications in people with T1D

- Mine electronic health records (EHRs) to better understand 'real world' complications rates and guide JDRF strategies to improve outcomes in T1D. These may include uncovering associations between disease variables that may lead to better prognostication and clinical decision making.
- Monitor "real world" benefits of novel complications therapies in T1D . For example, leveraging of national T1D registries to determine whether the effects of therapies on HbA1c, and other variables including safety outcomes, in clinical trials are obtained in real world practice.
- Identify and address regional and demographic 'complications hotspots' in people with T1D

Facilitate translation of therapies for people with T1D – where feasible and JDRF is uniquely positioned

- Facilitate translation of promising generic drugs that show strong rationale for working in T1D but no company will develop
- Facilitate translation of promising brand-name drugs that show strong rationale for working in T1D but limited pharma interest because small size of T1D market.

Regulatory

An assessment of the regulatory landscape for diabetic nephropathy (DN) has been completed. The findings showed that there is a regulatory pathway for DN therapies. Given the fact that there were endpoints such as the doubling of serum creatinine and ESRD used for approval in previous and current clinical trials there is a body of information to build on for future drug development programs for DN. Development of a sound study design in conjunction with communication with FDA especially around endpoints could lead to approval of a DN specific therapy.

In the diabetic retinopathy space, a workshop was held in June 2015, "NEI/FDA Diabetic Retinopathy Clinical Trial Design and Endpoints Public Workshop" sponsored by NEI, JDRF, ARVO and FDA that explored expanding endpoints beyond use of visual acuity. FDA presented at the workshop and is open to considering additional endpoints if the community wants to pursue.

Therapeutic and Biomarker Concepts

The therapeutic and biomarker concepts described below are the main projected requirements for anticipated future products based on the current status and direction of the field and input from key opinion leaders.

Diabetic Nephropathy – Biomarker Concepts

Prognostic biomarker for highest risk, late stage DN	
Context of Use Statement	Single or panel of serum (or urine) markers, measured at baseline, used as a prognostic enrichment biomarker to stratify patients with DN who are at ***high risk for ESRD within 3-4 years*** for inclusion in interventional clinical trials.
Conditions for Qualified Use	**Patient Population:** T1D or T2D Patient Selection: Baseline measurements can be used as an enrichment factor in combination with diabetes duration, blood pressure, HbA1c, BMI, albuminuria status and baseline eGFR

Prognostic biomarker for highest risk, early stage DN	
Context of Use Statement	Single or panel of serum (or urine) markers, measured at baseline, used as a prognostic enrichment biomarker to stratify patients with DN who are at ***high risk for progressive decline in renal function*** for inclusion in interventional clinical trials.
Conditions for Qualified Use	**Patient Population:** T1D or T2D Patient Selection: Baseline measurements can be used as an enrichment factor in combination with diabetes duration, blood pressure, HbA1c, BMI, albuminuria status and baseline eGFR

Surrogate (Predictive) biomarker for DN	
Context of Use Statement	Single or panel of serum (or urine) markers, that when measured in a clinical trial can ***substitute for hard clinical outcomes*** (eg. time to ESRD or doubling of serum creatinine) to assess therapy response.
Conditions for Qualified Use	**Patient Population:** T1D or T2D Patient Selection: Baseline measurements can be used as an enrichment factor in combination with diabetes duration, blood pressure, HbA1c, BMI, albuminuria status and baseline eGFR

Diabetic Nephropathy – Therapeutic Concept

Diabetic nephropathy drug	
Primary Indication	Prevent, delay or reverse progressive renal decline in CKD
Target Population	T1D (and T2D) with diabetic nephropathy CKD stages 1, 2 or 3
Features	Minimally burdensome administration
Efficacy	Reduced proteinuria, ESRD risk, risk of CV events
Risk/Side Effect	None

Diabetic Retinopathy – Biomarker Concepts

Predictive biomarker of anti-VEGF response	
Context of Use Statement	Biomarker (imaging or blood-based) measurement used to predict response to intravitreal anti-VEGF therapy
Conditions for Qualified Use	**Patient Population:** T1D or T2D who are candidates for anti-VEGF therapy

Surrogate (Predictive) biomarker of visual acuity	
Context of Use Statement	Use of biomarker as a surrogate of visual acuity that is equivalent to measurement based on standardized eye chart
Conditions for Qualified Use	**Patient Population:** All patients

Diabetic Retinopathy – Therapeutic Conept

Drug to prevent, delay or reverse progressive decline of visual acuity	
Primary Indication	Prevent, delay or reverse progressive decline of visual acuity
Target Population	All stages of diabetic retinopathy in T1D and T2D
Features	Oral tablet, topical or other minimally burdensome administration
Efficacy	Clinically significant improvement in ETDRS Best Corrected Visual Acuity (BCVA)
Risk/Side Effect	None

For more information:
Please contact the program lead, Marlon Pragnell, Ph.D.
mpragnell@jdrf.org; Tel: 212-479-7690

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