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Article

Type 1 Diabetes: Disease Stratification

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Abstract
Type 1 diabetes, a disorder characterized by immune-mediated loss of functional pancreatic beta cells, is a disease continuum with specific presymptomatic stages with defined risk of progression to symptomatic disease. Prognostic biomarkers have been developed for disease staging and for stratification of subjects that address the heterogeneity in rate of disease progression. Using biomarkers for stratification of subjects at different stages of type 1 diabetes will enable smaller and shorter intervention clinical trials with greater effect size. Addressing the heterogeneity of the disease will allow precision medicine-based approaches to prevention and interception of presymptomatic stages of disease and treatment and cure of symptomatic disease.

Introduction

Type 1 diabetes (T1D) is a chronic, immune-mediated disease associated with destruction of the insulin-producing beta cells of the islets of the pancreas [1]. Approximately 40–50% of the risk of disease arises from genetics with the remaining risk arising from poorly defined environmental etiologies. The class I and II human leukocyte antigen (HLA) genes contribute about half of the genetic risk of disease with about 40–50 non-HLA genes accounting for the remainder of genetic risk [2–4]. The most prominent associated HLA genes are HLA class II

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haplotypes *DRB1*0301-DQB1*0201 (DR3-DQ2)* and *DRB1*0401-DQB1*0302 (DR4-DQ8)* with the highest risk occurring in the heterozygous DR3/4 genotype. Non-HLA genes include INS, CTLA4, PTPN22, and IL2RA in addition to multiple non-HLA SNPs that have been mapped to DNA regulatory sequences of immune cells [4, 5]. Several non-HLA susceptibility genes are expressed in human islets, and cytokines can alter their expression in the islet [6]. For example, the risk-associated GLIS3 gene product affects beta cell fragility through altering responses of beta cells to cytokines [7] or through the unfolded protein stress response [8] and thus enhances beta cell apoptotic and senescent fates. Environmental etiologies have not been well defined, but viral infections, the host microbiome, and food/diet have been invoked [9]. In contrast to genetics, environmental etiologies have not been validated and thus do not currently contribute to subject stratification in T1D prevention trials. However, some examples of gene-environment interactions include the interactions of the microbiome with the Fut-2 nonsecretor gene polymorphism, which increases risk of T1D and is associated with faster progression of presymptomatic T1D [10–12], and interactions of picornaviruses, which include enteroviruses, with polymorphisms of the innate immunity viral RNA receptor gene region IFIH1(MDA-5) [13, 14].

The highest prevalence of T1D is found in individuals of Northern European Caucasian backgrounds [4] and over the last 4–5 decades, the incidence of childhood-onset T1D has been increasing 2–4% in many countries in the developed world [15, 16], which demonstrates a major environmental contribution.

Why Stratification?

T1D has a high degree of disease heterogeneity based on its rate of progression from presymptomatic stages, progression from the time of clinical presentation, and the degree of glucose control and development of both short-term and long-term complications in established disease. Stratification of the disease at these various stages can take into account that heterogeneity, which has plagued multiple T1D clinical trials. Several T1D trials failed to reach their primary endpoint for the test population but demonstrated good responses in a subset of subjects [17, 18]. Effective subject stratification will permit the design of shorter and smaller trials and should result in greater effect size in trials [19]. As new tools and technologies to better characterize T1D are developed, T1D will be reclassified into subgroups of disease with unique, tailored preventive and therapeutic treatments.

Stages of T1D

Based on insights from multiple natural history studies conducted over the last 2 decades [20–23], distinct stages of T1D have been defined that reflect the underlying pathogenesis of the disease (Fig. 1) [24]. Early stages of T1D have been classified based on pathophysiology and prognostic outcomes that represent a continuum of the disease, including:

Stage 1: pancreatic beta cell autoimmunity+/normoglycemia/presymptomatic T1D. Stage 1 is characterized by the development of 2 or more T1D-associated islet autoantibodies directed to insulin/proinsulin, GAD, IA-2, or ZnT8, which reflects the occurrence of beta cell-specific autoimmunity. The development of multiple islet autoantibodies in children with HLA risk genotypes followed from birth is associated with a 5-year and 10-year risk of progression to symptomatic, clinical disease of approximately 44 and 70%, respectively, and a lifetime risk approaching 100% [25, 26].

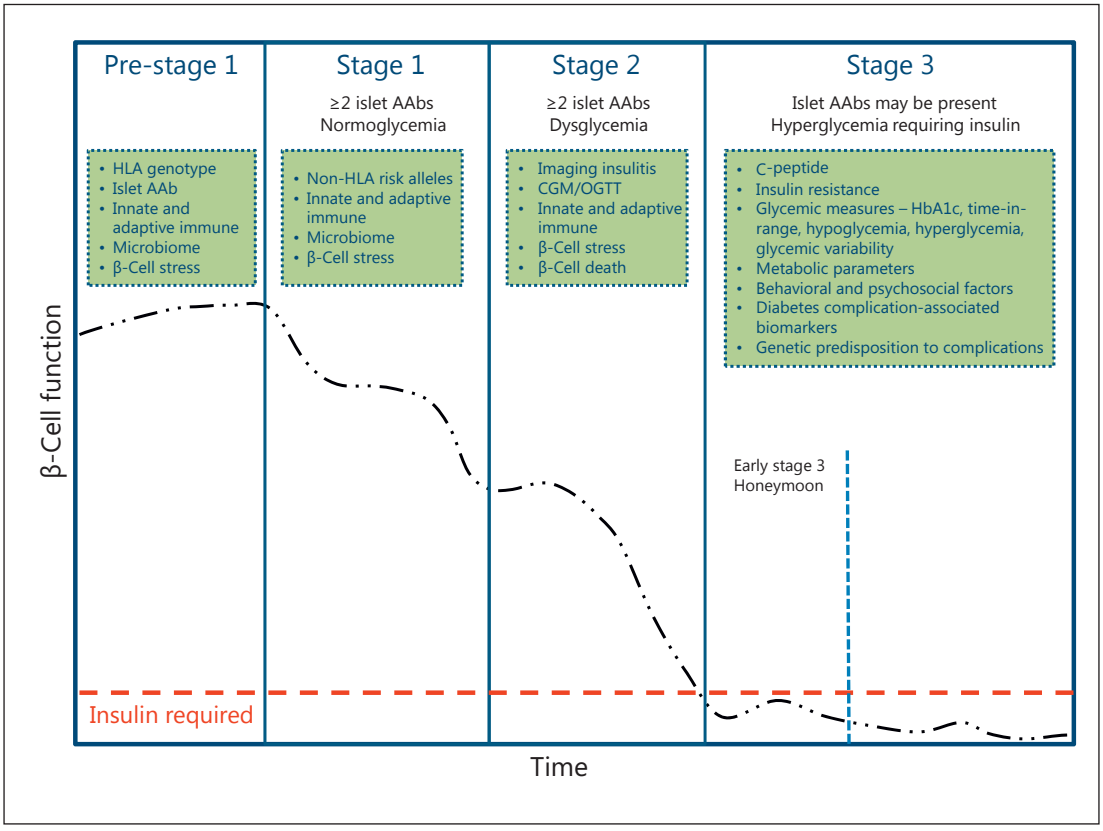

Fig. 1. Progression and staging of type 1 diabetes. Type 1 diabetes is characterized by a progressive loss of beta cell function (black dashed-dotted line) over time. As the disease progresses, beta cell function falls below the threshold (red dashed line) required to maintain glucose control creating a requirement for insulin replacement therapy. Type 1 diabetes may be staged over the course of its progression starting with stage 1 at which point 2 or more of the 4 commonly measured islet autoantibodies are detected with normoglycemia. Stage 2 is marked by the appearance of dysglycemia associated with loss of beta cell function in addition to the presence of autoantibodies. Stage 3 is defined by hyperglycemia requiring insulin. In the green boxes are categories of biomarkers which could be leveraged to refine the staging paradigm, improve prognostic predictions, or subset individuals within a given stage of disease. The specifics of these biomarkers are discussed in the text related to the relevant stage.

Stage 2: autoimmunity+/dysglycemia/presymptomatic T1D. With progressive loss of functional beta cell mass, the disease becomes associated with glucose intolerance, or dysglycemia, and this stage has a 5-year risk of symptomatic disease of approximately 75%, and lifetime risk approaching 100% [27].

Stage 3: symptomatic T1D. Stage 3 includes clinical symptoms and signs of diabetes (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis [DKA]) or is diagnosed in the presence of metabolic laboratory parameters established by the American Diabetes Association for a diagnosis of type 2 diabetes [28].

Established T1D. After diagnosis of stage 3 and with the initiation of insulin replacement therapy, a so-called "honeymoon" period may ensue associated with decreased insulin requirements until beta cell functional mass is further lost with increased insulin requirements. With established disease, subjects are at risk of short-term (hypoglycemia, DKA) and long-term (diabetic eye, kidney, neurologic disease) complications of the disease.

The order of this sequential progression of these stages is consistent, but the rate of progression from one stage to the next is variable. Biomarkers have been correlated with rate of progression (Fig. 1), and used in research studies [26, 29–31], but most have not been validated in longitudinal studies and none have reached a stage where they have become standard of care for informing treatment.

Several clinical trials have been designed that have taken advantage of the staging of T1D to preserve residual beta cell function in pre-stage 1, stage 1, stage 2, and stage 3 with a goal of delaying or preventing the onset of clinical, symptomatic disease and insulin dependence or improving glucose control in recent onset and established T1D. The TRIGR trial recruited subjects at pre-stage 1 with trial endpoints being progression to stage 1 in addition to progression to stage 3 [32]. An interception trial with CTLA-4-Ig (abatacept) has recruited stage 1 subjects with an endpoint of progression to stage 2 (NCT01773707), and a trial with anti-CD3 (tepluzimab) (NCT01030861) has recruited stage 2 subjects with an endpoint of progression to stage 3. Over the last decade, several stage 3 trials have been conducted to preserve residual functional beta cell mass at the time of onset of clinical disease [33], based on the evidence that preservation of residual beta cell mass is associated with decreased risk of the development of complications of T1D [34].

Progression from Pre-Stage 1 T1D

Multiple parameters and biomarkers have been investigated to better predict risk of progression to stage 1 T1D. Only approximately 10–15% of individuals newly diagnosed with T1D have a family history, but family history increases risk of disease ~10–100-fold higher than background population [24, 35]. Risk is higher for identical twins or with sharing of HLA genotype with the proband, is higher in offspring of fathers with T1D compared to offspring of mothers with T1D, and is ~14-fold higher in DR3/DR4-positive siblings if the proband develops symptomatic diabetes before age 10 years [35, 36]. As noted above, HLA genotype accounts for half of the genetic risk, and specific HLA alleles are associated with higher risk of disease and have been used to stratify a high versus moderate risk population [35, 37], or protection or resistance from developing disease, such as occurs with HLA class II *DRB1*1501* and *DQA1*0102-DQB1*0602* [38]. Both HLA genes [25] and non-HLA genotypes can be used to stratify subjects who have a faster rate of progression to stage 3 T1D [39, 40].

Several approaches beyond genetics are being investigated to predict early in life risk of developing T1D including: metabolomics and lipidomics [41, 42], type 1 interferon or inflammatory signature patterns with use of transcriptional profiling [30, 43–47], proteomics [48], and intestinal microbiome metagenomics and metabolites [49–53]. Epidemiological data can also be applied as illustrated by the risk of excessive weight gain in the first year of life, which is associated with increased risk of progression to stage 1 T1D [54, 55].

The environmental etiologies that trigger onset of islet autoimmunity are not well understood, but inflammation around the islets arising from various etiologies may lead to beta cell stress to precipitate immune-mediated beta cell dysfunction and destruction [56, 57]. Several candidate biomarkers (proinsulin/C-peptide ratio, hsp90, noncoding RNAs) for detecting beta cell stress in the periphery are being investigated, and although have not been studied at pre-stage 1 T1D, have been evaluated in later stages of presymptomatic or new onset T1D [29, 56, 58–61].

Beta cell stress has been demonstrated to generate modifications (posttranslational modifications, generation of hybrid proteins arising from fusion of beta cell peptides, defective ribosomal proteins with altered reading frames) of beta cell proteins that elicit either antibody or T cell responses in established T1D [62–66]. Of interest to stratifying subjects at risk

of progressing to stage 1 T1D is detection of antibodies to beta cell protein modifications prior to detection of antibodies to native beta cell epitopes. Antibodies to a modified form of insulin – oxidized insulin – have been demonstrated in at-risk children, occur in islet autoantibody-negative subjects, precede autoantibodies to native insulin, and can identify at an early stage risk of at-risk children progressing to stage 3 T1D [67]. It is possible that immune responses to beta cell protein modifications catalyze the breaking of immune tolerance to native beta cell epitopes and lead to autoimmune responses to native beta cell self-antigens [62, 68].

Alteration in islet-specific adaptive immunity in addition to innate immunity is observed in pre-stage 1 T1D. A specific gene signature is observed in altered naïve, beta cell antigen responsive CD4+ T cells that resembles a pre-T helper 1 (TH1)/TH17/T follicular helper cell response and occurs prior to the development of beta cell-specific antibodies or memory helper T cells [69].

Progression from Stage 1 T1D

The presence of multiple islet autoantibodies characterizes stage 1 T1D and the number of antibodies and their specificity, titer, and affinity as well as the age when first detected are associated with rate of progression to symptomatic disease. Faster rates of progression are observed with 3 or 4 versus 2 islet autoantibodies [25, 70, 71]. The presence of antibodies to IA-2 and ZnT8 as well as higher titers of antibody to Insulin and IA-2 are associated with a faster rate of progression [10, 70, 72–74]. Islet autoantibody seroconversion at a young age is associated with a faster rate of progression [25], and disease progression is also accelerated in children at stage 1 T1D with an increased BMI [75] and markedly accelerated in Hispanic children younger than 12 years of age who are overweight or obese [76]. A declining rate of progression is observed with increased age in stage 1 T1D relatives of individuals with T1D [77, 78].

HLA [25] and especially non-HLA genes [36, 79–81] are associated with a faster rate of progression from stage 1. There are differences in age and genetic predisposition for specificity of antibodies – insulin antibodies occur at an earlier peak age incidence (9–24 months) than GAD antibodies (~36 months), with IA-2 and ZnT8 tending to occur later and rarely as the first autoantibody. Insulin antibodies have a higher association with HLA-DR4-DQ8 and GAD with HLA-DR3-DQ2 [35, 82, 83].

The presence of only a single islet autoantibody is associated with progression in approximately only 15% of subjects, with progression occurring more frequently at a younger age [84, 85], if associated with HLA-risk genotypes [85], when the autoantibody is directed to IA-2 [25], or if higher affinity single autoantibodies are generated [86–89]. In young children with HLA risk of T1D, progression from a single to multiple autoantibodies occurs usually within 2 years [84]. Reversion of single islet autoantibodies over time is common, but complete reversion in the presence of multiple islet autoantibodies is relatively rare [90], though loss of insulin autoantibodies in the presence of multiple autoantibodies is associated with delayed progression [91].

Progression from Stage 2 T1D

Most, if not all, of the immune and beta cell biomarkers relevant in stage 1 will presumably be relevant in stage 2 as the underlying autoimmune process is not likely to differ in substantial ways. Instead, stage 2 of T1D is distinguished from stage 1 by the presence of dysglycemia signifying that the pancreatic islets are no longer capable of maintaining normal glucose control. The

dysglycemia observed in stage 2 is likely the result of both the loss of beta cell mass and a decline in beta cell dysfunction [56]. Of note, emerging evidence suggests that beta cell mass may in fact be maintained until near the time of stage 2 to stage 3 transition [60]. There is also evidence that insulin resistance is present in at least a subset of stage 2 individuals [92–95].

While the current staging concept relies on oral glucose tolerance test (OGTT)-based definitions of dysglycemia, the detection of elevated HbA1c, elevated fasting glucose, and impaired first-phase insulin response (FPIR) on an intravenous glucose tolerance test, which can be abnormal up to 5 years before stage 3 with an accelerated decline in the 1.5 years in progressors, have all been used to detect dysglycemia with impaired FPIR, the latter providing perhaps the earliest indicator of failing glucose control [96]. The OGTT can be analyzed for 2-h glucose levels, sum of glucose values every 30 min, peak C-peptide, C-peptide area under the curve, or 30-0 min C-peptide, which correlates with the FPIR on an IVGTT and is an earlier predictor of progression than the other OGTT parameters with changes 1–2 years before Stage 3 [31]. In addition, stimulated C-peptide, which changes later than the OGTT, may also be reduced in late stage 2 individuals, with an accelerated decrease beginning 6 months prior to stage 3 [97, 98]. Fasting C-peptide usually does not change during this period. As a given individual progresses toward the need for exogenous insulin, elevated HbA1c and/or abnormal fasting glucose measures may be observed [97]. In Stage 2, many individuals do not develop an increased HbA1c, but a HbA1c increasing by 10% or an HbA1c ≥5.9% on consecutive samples are associated with rapid progression to stage 3 [27, 99].

The possibility of relapsing-remitting disease (discussed below) and inherent variability in OGTT measures make this method of detecting dysglycemia somewhat unreliable, and repeated abnormal values may be required to be certain that someone has progressed to stage 2. It is possible that the use of continuous glucose monitoring could replace OGTT as a monitoring standard and would have several advantages over the use of OGTTs including convenience and lower overall costs [100–103].

To improve stratification of stage 2 trials, composite predictive risk scores that integrate diverse data (genetics, immunologic, metabolic, age, etc.) have been used to predict rate of progression as well as onset of stage 3 T1D [31, 104].

Identification of Active Disease in Stage 1 and Stage 2 T1D

The ability to stratify subjects at stage 1 and stage 2 T1D who have ongoing active disease is important because of the likely possibility that presymptomatic T1D can be relapsing and remitting [105] and the requirement that certain types of interventions will only show efficacy in the face of active immune beta cell pathology. Several approaches should be considered. Changes in islet antibody titers do not directly correlate with active disease [26]. Subject-specific, expanded clones of islet antigen-reactive CD4+ memory T cells can be detected in the peripheral blood of individuals with T1D [106], and may prove to be an approach applicable to detecting active presymptomatic T1D in an individual. Circulating CXCR5+PD-1+ICOS+-activated circulating follicular T helper cells increase in the periphery in stage 2 T1D that has advanced close to Stage 3 T1D and may prove to be a useful biomarker of active disease [107]. Exhaustion of peripheral blood T cells associated with cellular unresponsiveness and loss of effector function with expression of a T-cell exhaustion signature correlates with clinical remission in several autoimmune diseases [108] and is being evaluated for correlation with both spontaneous remission in presymptomatic T1D and in therapy-induced remission in T1D [109]. Other immune assays are being developed to better predict active disease and rate of progression [29].

Active disease in stage 1 and stage 2 T1D could also be identified by detecting cellular infiltration in and around islets, so-called insulitis. Autopsy specimens from human new-

onset T1D have shown that the degree of insulitis is quite variable, is not as prominent as in mouse models of the disease, and is often not detected in multiple islet autoantibody-positive cadaveric pancreata [110, 111]. Insulitis in younger, new-onset T1D subjects (less than 7 years of age) is associated with a more prominent CD20+ B cell infiltration response and with more marked loss of residual insulin-positive beta cells, suggesting a more aggressive loss of beta cells [112]. The infrequency of detection of insulitis in presymptomatic T1D may reflect a relapsing-remitting pattern of the disease and further reinforces the importance of detecting disease activity for stratifying for trials in the presymptomatic setting. Imaging of islet inflammation based on vascular leak, which allows leakage of the imaging agent into the pancreas, and accumulation of antigen-presenting cells, which retain the imaging agent, has been used to detect inflammation in the pancreas in new-onset T1D [113], and could be applied to presymptomatic stages of T1D to detect active insulitis. Imaging of insulitis based on detection of infiltrating T cells is also being investigated [114].

Alternative approaches to detect active disease include detection of pancreatic beta cell stress [56], using assays described above, or detection of beta cell death. Multiple beta cell death assays are under development that are based on detection in peripheral blood of circulating beta cell DNA (insulin, amylin, and others) that is differentially methylated/demethylated [115–118]. Some of these assays have been shown to be able to detect beta cell death at stage 2 of T1D [115], but have not been well studied to date in longitudinal samples collected from subjects with presymptomatic T1D.

Early Stage 3 T1D

The distinction between stage 2 and early stage 3 is really a matter of degree. Currently, the proposal for stage 3 is to use the broad definition of diabetes that was developed for the use of insulin in the setting of type 2 diabetes and which may not be appropriate for T1D. T1D is rarely screened outside the research setting and because early symptoms are subtle, individuals can persist in a state of hyperglycemia for some time before stage 3 T1D is recognized. Unfortunately, this frequently means that the diagnosis of stage 3 is often made with the patient in a state of DKA. Emerging evidence suggests that the DKA that results from failure to recognize the disease in earlier stages may carry lasting consequences for the affected person's ability to achieve good glucose control [119], and may even predispose to additional DKA episodes.

Early stage 3 is characterized by a partial remission, or a so-called "honeymoon" phase, that is often observed after a newly diagnosed individual is placed on insulin for the first time. During this period of partial remission, insulin requirements decrease, sometimes so much that the use of basal insulin is all that is required. The typical honeymoon period, if observed, may last from a few months to more than a year. Predicting who will or will not enter a honeymoon period and the rate of decline of residual beta cell function in recent onset T1D is important for stratification for stage 3 T1D clinical trials. With insulin administration in new-onset T1D, beta cell dysfunction recovers with increase in stimulated C-peptide levels for ~6 weeks [120], and then proceeds to decrease with a faster rate of decline in the first 12 months compared to the second year after onset of stage 3 [121]. The decline in C-peptide is more rapid in children than adults, with about 11% of subjects showing no decline from a baseline at 2–3 months to 2 years after onset of stage 3 [121]. Residual C-peptide can be detected in some individuals years to decades after diagnosis but more commonly with adult-onset versus childhood-onset T1D [122, 123]. Several biomarkers and genes have been identified and modeled that predict a lack or presence of a honeymoon/remission in stage 3 T1D [124–127].

Established T1D: Progression from Stage 3

With the clinical presentation of frank insulin dependence, all forms of T1D are treated with combinations of rapid-acting (bolus) and long-acting (basal) insulins to compensate for the loss of endogenous insulin production. Better understanding of the etiopathogenesis of T1D is demystifying various assumptions, while several others remain unsolved. To list a few, it is now established while genetic predisposition is a critical factor, the majority of T1D occurs with no known family history; almost half of the newly diagnosed cases occur in adults; the epidemic of obesity has not spared T1D, thus invoking metabolic syndrome-like characteristics; insulin resistance – a less studied culprit – affects T1D even in the lean phenotypes; about a third of individuals retain up to a third of insulin production despite long-standing disease; and many other facts and findings [122, 128]. Additionally, psychosocial factors and family dynamics that often influence disease management and outcomes in significant ways, but are out of scope of this review. Some of these include, but are not limited to, socioeconomic status and awareness and access to treatments, ethnicity, and cultural considerations influencing disease perspective, key lifestyle factors including stress, diet, and exercise, family dynamics and partners, and several individual psychosocial and behavioral issues such as inherent fear of devices, lack of peer-to-peer networking, or under- or overcorrection for fear of severe hypoglycemia or long-term complications from hyperglycemia.

With the onset of stage 3 and throughout the duration of diabetes, all of the above affect glucose control to varying degrees among individuals and often in an individual from day to day – thus underscoring the often underappreciated heterogeneity in established T1D. Furthermore, the protracted glycemic insult and any genetic predisposition render individuals vulnerable to the development of long term vascular complications of the disease, again to varying degrees of severity in their manifestation. This is evidenced in many epidemiologic and observational study cohorts, most recently from the T1D Exchange [129].

With the advent of improved insulins and delivery systems such as insulin pumps, technology to measure glucose levels in real time such as continuous glucose monitors (CGMs), approval of the first automated hybrid closed loop systems (USA), emerging data from the use of adjunct therapies such as GLP1 analogs, SGLT inhibitors, and fixed dose and fixed ratio combinations of therapeutics with or without insulin, it behooves the research and clinical communities to exploit all options to understand the benefit/burden profiles of treatments and optimize care of patients [130–132]. This calls for deep phenotyping of individuals, including assessment of critical markers of disease onset and progression, such as age at onset, disease duration, body weight, insulin sensitivity, C-peptide level, adiposity, metabolic syndrome parameters, time in and out of desirable glucose range, glycemic variability, and plasma and urine markers suggestive of vascular diseases.

Clinical studies over the last decade have shown promising effects with use of devices such as insulin infusion pumps and CGMs; however, efficacy has been correlated with adherence to the therapies [133]. CGM is a powerful and the only technology that can measure exposures to various glucose levels and its variability at any point of time and for entire periods of use – which can be advantageous in monitoring effects of therapies and self-management, as well as avoidance of extremes of high and low blood glucose levels that often lead to devastating acute consequences [100, 134]. However, CGM use and data interpretation requires training and experience, has had slow adoption, and its potential remains to be fully realized. Likewise, use of therapies currently approved for the treatment of type 2 diabetes have improved outcomes in T1D such as body weight and insulin dose reductions, insulin sensitization, lowering HbA1c, increasing time in desired glucose range and even reducing glycemic variability; however, most studies have shown responses span the gamut from nonresponders to super-responders [135–139], thus emphasizing the need for strat-

ified, precision medicine approaches. The novel class of SGLT inhibitors, both mono SGLT2 and dual SGLT1/2, are currently in pivotal T1D label expansion studies by manufacturers. Encouraging safety and efficacy results have been recently reported, and stratified analyses of all individuals will certainly enrich our understanding of T1D heterogeneity and facilitate the development of customized treatment approaches.

Tailoring the right therapy at the right dose to the right individual at the right stage is the Holy Grail for personalized medicine approaches. This has to be achieved in a standardized and simplified manner for easier adoption by health-care professionals and providers. There has been some success; however, current knowledge gaps for stratification of individuals for clinical trials and treatments will have to be addressed. Perhaps the need for prognostic and predictive markers to enable smart clinical trial design and develop stratified treatment is most urgent for diabetic long-term complications, which have a high degree of heterogeneity, protracted period with variable rates of progression toward end organ failures, and are often confounded with comorbidities. Not surprisingly, therapies to prevent or treat micro- and macrovascular complications have largely yielded mixed results in clinical studies with subsequent discontinuation of development by manufacturers, especially in diabetic nephropathy and neuropathy [140].

Recent success from various groups has been encouraging. For example, the use of a composite of levels of serum tumor necrosis factor receptor isotype 1 with or without the gold standard albumin-to-creatinine ratio significantly increased sensitivity and prognostic values, thus reducing the size of diabetic nephropathy clinical trials required to achieve statistical power in detecting treatment responses [141]. Furthermore, the rate of decline in estimated glomerular filtration rate (eGFR) has been suggested as a reliable marker for loss of renal function and for facilitating differentiation between rapid, moderate, and slow progression of diabetic nephropathy [142]. More studies such as these are required to enroll the appropriate individuals in trials as well as to predict response to therapies.

Another remaining gap in the field is the need for surrogate endpoints to accelerate drug development. Current clinical trials in diabetes complications require 2–4 years to observe primary treatment effect, which adds to the current barriers of entry. Fortunately, the JDRF and other funding organizations have invested significant resources for the discovery, development, and validation of prognostic and predictive biomarkers from longitudinal cohorts and interventional studies, as well as for understanding the natural history of disease progression, to ultimately de-convolute disease heterogeneity and lead to development of specific therapies and companion diagnostics for precision medicine approaches.

Disclosure Statement

The authors declare no conflict of interest.

Author Contributions

All authors contributed substantially to the work reported.

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