

Precision Medicine for Type 2 Diabetes

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The study of type 2 diabetes (T2D) has been energized by advances in human genetics, epigenetics, biomarkers, mechanistic studies and large clinical trials, enabling new insights into disease susceptibility, pathophysiology, progression, and development of complications. Simultaneously, multiple new drug classes with different mechanisms of action have been introduced over the last two decades, accompanied by data informing on cardiovascular safety and non-glycemic outcomes. Here we critically examine the progress and integration of this new science into clinical practice, and review opportunities for enabling precision medicine in the diagnosis and treatment of T2D. We contrast the success in delivering personalised medicine for monogenic diabetes with the greater challenging of providing a precision medicine approach for type 2 diabetes highlighting gaps, limitations, and areas requiring further study.

Search strategy and selection criteria

We searched PubMed from January 1 2000-March 2 2018 for relevant journal articles published in English using query terms including diabetes, genetics, biomarkers, pharmacogenomics, precision medicine, and personalized medicine, from 2010 to 2018. We also searched reference lists of key articles. After reviewing ~100 papers, a smaller list of references was selected for inclusion based on quality of data, study sizes, and direct relevance to topic.

Conflicts of interest

DJD is a consultant to Intarcia, Merck, Novo Nordisk Inc, and Pfizer. Mt. Sinai Hospital receives funding for preclinical studies for work in the Drucker lab from GSK, Merck and Novo Nordisk Inc. ALG receives funding for preclinical studies from Novo Nordisk.

In recent years there has been much interest and it could be argued hype, in our increased ability to use human genetics, lifestyle and environmental information to individualise treatment decisions. Although not a novel concept, the technological advancements which have driven the omics revolution have provided impetus and expectation that a new dawn in “precision” medicine is approaching. In this review we use the term “precision medicine” to describe the stratification of patients into groups based on molecular and genetic biomarkers and clinical characteristics to optimise therapeutic outcomes. The scope of precision medicine has appropriately been broadened to not only include genetics, but to also include environmental and lifestyle factors, with recommendations targeting groups rather than individual patients. In this review we set out to examine the evidence for precision medicine in diabetes focusing on the success in monogenic diabetes, the emerging evidence for type 2 diabetes (T2D) and identifying challenges for enabling more individualized treatment recommendations in the coming years.

Precision medicine in monogenic vs. polygenic diabetes

The last ten years have seen unprecedented progress in our understanding of the genetic basis of diabetes. With this has come an expectation that our ability to diagnose, characterise and treat individuals with diabetes will be transformed. Given the well documented success in rapidly translating gene discovery efforts for monogenic varieties of diabetes into changes in clinical care pathways, this belief is understandable. Up to 3% of diabetes diagnosed in children has a monogenic basis with the most common cause mutations in the transcription factor gene hepatocyte nuclear factor 1 alpha (*HNF1A*)¹. Individuals with rare penetrant mutations in *HNF1A* typically present before the age of 25 years with non-insulin dependent diabetes, are slim and have a strong family history of diabetes. Clinical investigation usually reveals that they are autoantibody negative but C-peptide positive. An early case study highlighted that individuals with diabetes due to an *HNF1A* mutation had marked sensitivity to sulphonylureas (SUs), a finding that was elegantly substantiated in a randomised controlled trial providing the first example of personalised medicine in diabetes². The precise molecular mechanism for sensitivity to this class of oral hypoglycaemic agent remains elusive but it has been argued that closure of the K_{ATP} channel bypasses the major sites of β -cell dysfunction thus reigniting insulin secretion. SUs are also the first line treatment for individuals with neonatal diabetes due to activating mutations in the *KCNJ11* and *ABCC8* genes which cause failure of the K_{ATP} channels to close in response to ATP generated by glycolysis³⁻⁶. Closure of the channel by an ATP-independent mechanism circumnavigates the cause of the β -cell dysfunction, restoring insulin secretion in these individuals and remarkably improving their glycaemic control. Personalised medicine in monogenic diabetes extends beyond treatment response: for example individuals with loss-of-function mutations in the glucokinase (*GCK*) gene have stable fasting hyperglycaemia and are unlikely to develop diabetic complications⁷. For neonatal diabetes, non-selective genetic testing now informs on the future development of additional clinical features, disease management and likelihood of disease remission⁸.

At this point however, genetic discovery efforts for T2D have had limited translational benefits. Reconciling the very different “bench-to-bedside” trajectories for monogenic and more complex forms of diabetes can be achieved by appreciating the differences in the genetic contributions to the development of diabetes, which makes the eventual classification of T2D into multiple discrete subtypes

less likely (**Figure 1**). As the field has tried to wrestle with how genetics might be used to support precision medicine a number of theories have been proposed for complex diseases such as T2D or coronary artery disease. Two untested models which have garnered interest propose that individuals are very likely to have a diverse set of overlapping mechanisms for their failure to regulate their blood glucose or lipid levels and that these “blends” will be hard to tease apart into discrete subtypes. Both models propose that what matters is where an individual sits on a series of hypothetical “sliders” for particular pathophysiological processes (e.g. beta-cell mass, insulin sensitivity, incretin response)^{9,10}. The argument is that if we can understand the composition of the pallet or blend and where individuals sit on these sliding scales of intermediate phenotypes there is the potential to make more tailored treatment choices particularly with identifying patients who are unlikely to respond to a particular therapy. For example people with diabetes largely due to loss of β -cell mass are unlikely to respond to agents which potentiate insulin secretion. There is already evidence for this hypothesis from studies of the reduced efficacy of GLP-1 receptor agonists (GLP-1RAs) tested in insulin-treated patients with low C-peptide levels and auto-antibodies¹¹. Whilst encouraging evidence for the clinical utility of genetic risk profiling has also emerged from efforts to understand the frequency of T1D in individuals presenting with diabetes in adulthood. Distinguishing these people from those with T2D is important, as individuals with T1D will rapidly require insulin therapy¹².

Stratification of diabetes into multiple subtypes

A recent study from Scandinavia has provided support that identifying discrete subtypes of diabetes which have different compositions of pathophysiology may inform of disease trajectory. By performing hierarchical clustering in around nine thousand newly diagnosed individuals with diabetes, based on clinical variables (auto-antibodies, age at diagnosis, BMI, HbA1c, and estimates of β -cell function and insulin resistance) they were able to identify 5 sub-types of diabetes which replicated in independent cohorts¹³. In support of different pathophysiological features the clustering of established genetic associations differed between these classes. In line with different degrees of shared pathophysiology the risks of complications were different across the classes. Notably, diabetic retinopathy was identified earlier in subjects with relative insulin deficiency, whereas insulin-resistant individuals exhibited a greater risk of developing diabetic kidney disease¹³. These findings, if replicated in ethnically diverse populations across a range of ages, may be of potential value for clinical trial enrollment or for early treatment stratification, perhaps with agents such as SGLT2 inhibitors, that exhibit potential for modification of renal outcomes¹⁴. Future studies will now need to establish whether treatment response with different drug classes differs across these subclasses and whether they can further be improved and refined by additional prospective omic and clinical data

Pharmacogenomics and clinical trial data inform personalized treatment recommendations

Notwithstanding tremendous advances in application of genetics to the characterization of diabetes pathogenesis and treatment, the precise etiology of T2D is not currently informed by genetic testing or available biomarkers. Ideally, evidence would include a cost-effective genetic test, coupled with robust prospective validation of the predictive value of incorporating genetic information into the treatment algorithm. Presently, the extent to which genetic variation in the *G6PD* locus underestimates the

baseline HbA1c in some African Americans¹⁵, mandates consideration of routine genotyping at this locus for black subjects where interpretation of HbA1c values assumes clinical relevance. Despite tremendous progress in the integrated analysis of tissue and systemic metabolic networks perturbed in the setting of obesity, insulin, resistance, and T2D¹⁶, a uniform set of genetic information or biomarkers providing clinically useful information enabling individualized therapeutic choices has not yet been validated in randomized prospective clinical trials. Hence, a personalized approach to therapy requires consideration of the available clinical trial evidence, complemented by decisions surrounding affordability, patient goals and preferences.

It is important to be as critical of the emerging data for pharmacogenetics studies as we are now of association studies for T2D-risk and to recognise the importance of replication. The vast majority of the current literature is focused on small candidate gene and/or single nucleotide polymorphism (SNP) studies as opposed to unbiased genome-wide assessments of the impact of genetic variation on therapy response. Thus, whilst many studies report associations of T2D-risk alleles and response to treatment, the vast majority of these associations have not yet been replicated in larger prospective studies.

Metformin is the most widely used and intensively studied drug recommended for first line therapy in the treatment of T2D. Indeed, the study of metformin includes a large pharmacogenomics effort analyzing genetic determinants of metformin transport, and molecular targets transducing metformin action. Genetic determinants of variability in metformin pharmacokinetics, tissue uptake and clearance have been identified (*SLC22A1*, *SLC22A2* and *SLC47A*), however their clinical utility in predicting metformin responsivity in human subjects with T2D remains suboptimal¹⁷. Some studies have also identified genetic variation within *SLC22A1*, together with use of medications that inhibit the OCT1 protein, as factors predicting up to a 4-times higher rate of gastrointestinal metformin intolerance¹⁷. Genetic variation (rs11212617) near the *ATM* locus is associated with the glycemic response to metformin in some but not all populations however the effect size is modest, precluding current utility in the clinic. More encouraging data, including analysis of gene expression in human liver samples, implicated variation within an intron (rs8192675) of *SLC2A2* encoding GLUT2, together with hepatic *SLC2A2* expression informing the therapeutic response to metformin in study subjects of European ancestry (up to 0.33% (2.1 mmol/L) difference in HbA1c reduction)¹⁷. Nevertheless, no association of variation within *ATM* or *SLC2A2* and therapeutic metformin responsivity was detected in human subjects with prediabetes followed in the Diabetes Prevention Program (DPP) trial, highlighting challenges in extrapolating genetic findings from analysis of established T2D to different study populations and metabolic states¹⁸. Moreover, treatment with metformin or lifestyle improved insulin sensitivity in the DPP study independent of the genetic burden for insulin resistance, based on the presence or absence of 17 established genetic variants associated with insulin sensitivity¹⁹. Hence although considerable progress has been made in understanding the genetic basis underlying therapeutic responsivity to metformin, the predictive insights to date have been modest. Considering that metformin is inexpensive and associated with a very low risk of major side effects, broad implementation of pharmacogenomic analyses for clinical prediction of metformin efficacy and tolerability is not yet practical, nor cost effective. Continued efforts to understand genetic factors

underlying differences in therapeutic response between individuals may however shed light on the mechanisms by which metformin improves glycemic control, which continue to be debated²⁰.

The historical and ongoing extensive use of sulphonylureas (SUs) and insulin as second line glucose-lowering agents, recommended in many T2D guidelines, reflects decades of study and clinical experience. Moreover, intensive glucose control for several years in regimens including these agents is generally associated with reduction of microvascular outcomes over shorter time periods, with longer post-trial follow-up periods, out to 10 years, demonstrating reduction in cardiovascular events and in some trials, decreased all-cause mortality^{21, 22}. Nevertheless, the relative reduction in rates of microvascular disease may vary considerably depending on the population studied, the precise treatment regimens and duration of observation^{23, 24}. The use and benefits associated with SUs and insulin is offset by higher rates of hypoglycemia and weight gain²⁴⁻²⁶. Indeed the risk of severe hypoglycemia with these agents may be characterized by loss of consciousness, seizures, changes in mental status, and associated neurological and cardiovascular sequelae, resulting in increased rates of emergency room visits, hospitalization, morbidity and mortality, notably in older patients^{27, 28}.

Probably the best studied example of genetics informing pharmacological responses is variation at the *TCF7L2* locus, where data from the GoDARTS study has shown that carriers of the *TCF7L2* T2D risk allele are less likely to achieve glycaemic goals in response to SUs than non-carriers, a treatment effect that was not observed for metformin²⁹. Other pharmacogenetic determinants contributing to SU responsivity and failure have also been studied, encompassing genetic variation within genes important for SU metabolism and the SU receptor, β -cell function, and insulin action, including *CYP2C9*, *ABCC8*, *KCNJ11*, *IRS1*, *CDKAL1*, *CDKN2A/2B*, *KCNQ1* and *NOS1AP*^{17, 30}. Of particular interest is the case of genetic variation at the SU receptor itself, where a number of studies have investigated whether coding variants in the *KCNJ11* and *ABCC8* genes which are themselves associated with T2D-risk also influence response to SU treatment³¹⁻³³. Supported by functional studies there is data to support pharmacogenetic effects on treatment for carriers of the *ABCC8* A1369AS variant with a particular subclass of SU (gliclazide, an A-site SU)³⁴. Nevertheless, the importance of determining these genotypes for guiding individual SU selection or dose to optimize achievement of clinical T2D outcomes, has not been sufficiently validated in prospective randomized studies.

Notwithstanding concerns surrounding relative benefit vs. risk of thiazolidinediones for glucose control in subjects with T2D, these drugs attenuate disease progression in subsets of subjects with non-alcoholic fatty liver and non-alcoholic steatosis in studies up to 24 months duration³⁵. Furthermore pioglitazone reduced the development of new T2D and decreased the rate of fatal or nonfatal stroke or myocardial infarction over 4.8 years in human subjects with insulin resistance and established cerebrovascular disease³⁶. Nevertheless, our understanding of the genetic determinants underlying beneficial or adverse therapeutic responses to thiazolidinediones, principally rosiglitazone and pioglitazone, remains limited. Variants within *SLCO1B1*, encoding the OATP1B1 (Organic Anion Transporting Polypeptide 1B1) transporter influenced glycemic response to rosiglitazone in 833 Scottish subjects assessed over 1-18 months of therapy, whereas variation within *CYP2C8*, encoding cytochrome P450 2C8 metabolizing enzyme, associated with glycemic response and weight gain³⁷. Surprisingly, the presence of these genetic variants did not similarly impact the response to pioglitazone therapy. Moreover, findings that

genetic variation with *PPARG*, specifically Pro12Ala, associate with decreased responsivity to thiazolidinediones in some small Asian cohorts, reviewed in¹⁷, have not been independently verified in larger heterogeneous populations followed for longer periods of time, hence the broad clinical relevance of these associations remains uncertain.

Acarbose, an α -glucosidase inhibitor widely used in some parts of Asia (particularly China), and to a lesser extent elsewhere, reduced development of new incident T2D in humans with impaired glucose tolerance (IGT), and a secondary analysis associated acarbose therapy in this population with reduction of cardiovascular events³⁸. Analysis of the STOP-NIDDM trial revealed associations between genetic variation in *PPARA*, *HNF4A*, *LIPC*, *PPARG2*, and *PPARGC1A* and the response to acarbose in subsets of subjects with IGT³⁹. Nevertheless, these associations were quantitatively modest, have not yet been confirmed in independent populations, and have not been examined in acarbose-treated human subjects with established T2D. Moreover, an independent study (6,522 subjects, median follow-up of 5 years) assessing the effect of acarbose vs. placebo in human subjects with IGT and established coronary artery disease did not reveal differences in rates of cardiovascular disease, all-cause mortality, hospital admission for heart failure, or impaired renal function⁴⁰.

The utilization of patient-appropriate HbA1c targets remains a cornerstone of T2D management, however personalized treatment goals beyond HbA1c based on available clinical evidence and expert opinion are increasingly within reach (**Figure 2**). The failure to achieve uniform benefit in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial provides a note of caution in regard to formulation of HbA1c targets and implementation of intensive treatment regimens for older subjects with T2D, notably those at risk for cardiovascular disease⁴¹. Analysis of common genetic variants from white individuals with T2D in the ACCORD trial identified two genetic variants significantly associated with cardiovascular mortality in response to intensive diabetes therapy⁴².

A genetic risk score based on these variants was further validated using the clinical care T2D population at the Joslin clinic, and subjects studied in the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial²⁶. Remarkably, a 22% increase in plasma GLP-1 levels in a subset of intensively-treated subjects in ACCORD harboring the C/C variant of rs57933 was associated with a favorable GRS and cardiovascular benefit⁴³. The implications of these findings and applicability of this risk score to individualization of T2D therapy for younger subjects utilizing treatment regimens that minimize hypoglycemia remains uncertain and requires prospective validation.

Three new classes of glucose-lowering agents, GLP-1RAs, dipeptidyl peptidase-4 (DPP4) inhibitors and sodium glucose cotransporter-2 inhibitors (SGLT2i) have been introduced which extend our ability to treat T2D with reduced rates of hypoglycemia, less frequent self-blood glucose monitoring, simplified dosing regimens, and without weight gain. These drugs were initially developed based on understanding of metabolic physiology⁴⁴⁻⁴⁶, with mechanism of action and safety of SGLT2i and GLP-1RA subsequently informed through analysis of genetic variation at these loci in individuals⁴⁷ and large population studies⁴⁸. Reinforcing the ability of human genetics to identify safe and effective therapeutic targets, array-based studies focused on assessing coding variation exome-wide identified a low-frequency nonsynonymous variant A316T in the receptor for GLP-1 which associates with fasting glucose levels⁴⁹.

⁵⁰. The glucose-lowering allele is also associated with decreased T2D risk yet a paradoxical reduction in the early β -cell response to glucose, quantified by insulinogenic index⁵⁰. Furthermore, and pertinent for therapeutic response, the glucose-lowering allele is associated with protection against coronary heart disease⁴⁸. Nevertheless, the extent to which genetic variation within the *GLP1R* contributes to glycemic or non-glycemic outcomes in clinical trials employing GLP-1R agonists is not yet known. Even less is known about the pharmacogenetic determinants underlying the glycemic response to DPP4 or SGLT2 inhibitors. Genetic variation at rs7202877 near *CTRB1/2*, a known diabetes risk locus, associated with differential insulin secretory responses to acute GLP-1 infusion and also associated with a lower A1C response to DPP-4 inhibitor treatment⁵¹. Genetic variation and clinical biomarkers associating with declining β -cell function also predicts the response to GLP-1R agonist therapy in some populations¹¹. Recent findings from the Predicting Response to Incretin Based Agents (PRIBA) study, validated independently using case records from the Clinical Practice Research Datalink, support the use of baseline clinical characteristics in decisions on incretin based therapies. Individuals with markers of insulin resistance such as higher fasting C-peptide, HOMA2 insulin resistance and triglycerides responded less well over a 6 month treatment period to DPP-4 inhibitor treatment but their response to GLP-1 RA was unaffected⁵².

Considerable effort has been expended, using genetics, biomarkers, metabolomics, and gut microbial profiling to prospectively identify ideal candidates for metabolic surgery with a greater likelihood of achieving sustained diabetes remission. Development of a Diabetes Remission (DiaRem) scoring system (age, HbA1c, use of specific glucose-lowering medications) was followed by introduction of an Advanced DiaRem (Ad-DiaRem) score, refined through addition of diabetes duration and number of glucose-lowering agents. Ad-DiaRem enhanced predictive accuracy for diabetes remission at 1 year in severely obese individuals⁵³. These clinical tools, while promising, require further validation in longer prospective clinical trials, as the rate of T2D remission after surgery drops progressively with follow-up beyond 1 year. Moreover, extending these analyses from Roux-en-Y (RYGB) Gastric Bypass to vertical sleeve gastrectomy, potentially incorporating indices reflecting β -cell function, tissue fibrosis, and additional metabolic profiling data, may enhance the performance and utility of emerging predictive scoring systems. The available observational data support a sustained improvement in blood pressure and control of dyslipidemia and a 51% rate of T2D remission assessed 12 years after RYGB⁵⁴. RYGB surgery reduced the rates of cardiovascular death in obese subjects followed over time in the Swedish Obese Subjects study, however study subjects were at least 37 years old at the time of surgery, and only 7.4% of individuals had T2D⁵⁵. Nevertheless, the incidence of myocardial infarction, but not stroke, was reduced in obese subjects with T2D⁵⁶.

Evidence guiding therapeutic recommendations for T2D

Optimization of diet and exercise remain key initial therapeutic recommendations for virtually all patients with T2D, together with treatment of co-existing blood pressure, dyslipidemia, and consideration of anti-platelet therapy. Despite the explosion of genetic and biomarker information refining our understanding of the underlying characteristics of T2D in different populations, regulatory guidance for T2D currently embodies only a single precision medicine recommendation. Health care providers should consider genetic testing for glucose-6-phosphate dehydrogenase (G6PD) deficiency

prior to the use of some SUs⁵⁷, given the risk of hemolytic anemia. Hence, a personalized medicine approach to T2D mandates extensive consideration of clinical trial data, in the context of individual patient goals and characteristics.

In the absence of robust comparative effectiveness data, and limited insights from prospective use of genetic and biomarker studies to inform long term therapeutic efficacy, evidence-based formulation of personalized treatment recommendations for patients with T2D is challenging. Randomized controlled trials comparing individualized treatment regimens vs. traditional sequential therapy based on HbA1c targets are limited. Clearly, each patient is unique, with different goals, medical history, and expectations (Figure 2). Moreover, medication access and cost vary widely, and substantially influence individual treatment recommendations. Although some expert guidance advocates initial therapy with two or more glucose lowering medications for individuals with higher levels of HbA1c to counteract clinical inertia, long term studies and evidence supporting early initial combination therapy vs. sequential addition of medications is lacking⁵⁸.

Application of Cardiovascular Outcome Trials (CVOTs) to Clinical Practice

Two classes of drugs, the SGLT2 inhibitors (SGLT2i), and GLP1R agonists (GLP-1RAs), notably liraglutide, have been associated with reduction of major adverse cardiac events (MACE) and reduced mortality in subjects with T2D studied in randomized cardiovascular outcome trials (CVOTs). The EMPA-REG OUTCOME trial enrolled subjects > 18 years of age with established cardiovascular disease (CVD)⁵⁹. The population studied in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial was at least 50 years old at the time of study enrollment, with ~80% of enrolled subjects exhibiting prior CVD⁶⁰. Subgroup analyses of EMPA-REG OUTCOME revealed that as a group, African-American subjects, or individuals <65 years old, or those with a BMI > 30kg/m² did not exhibit reductions in the primary cardiovascular outcome, but all three subgroups exhibited a reduced rate of cardiovascular death⁵⁹. Less than 4% of subjects enrolled in the Canagliflozin Cardiovascular Assessment Study (CANVAS) program were black or African American, and individuals less than age 50 were not included in the primary prevention cohort, limiting direct application of evidence from CANVAS to patient C⁶¹. Nevertheless, the reduction in cardiovascular events detected with canagliflozin provides reassuring evidence for the cardiovascular safety associated with SGLT2i therapy.

Although results of CVOTs have provided substantial insight into the benefits and safety of newer anti-diabetic agents, extrapolation of results from CVOTs to broader T2D populations is problematic. It is currently unknown whether initiation of therapy with SGLT2 inhibitors or GLP-1R agonists in healthier subjects with T2D earlier in the course of the disease will provide substantial cardiovascular benefit with chronic therapy. Indeed subgroup analysis in LEADER revealed lack of benefit in the cohort of subjects > 60 years of age without established CVD⁶⁰. Many CVOTs enrolled relatively few female subjects over the age of 75 and small numbers of subjects over the age of 80. Ideally, treatment recommendations and targets for elderly subjects need to be adjusted based on life expectancy and individualized based on the relative risk of developing new diabetes complications over defined time periods⁶². The development of polygenic risk scores enabling identification of individuals at high risk for development of coronary artery disease⁶³ may prove useful for selecting individuals without known CVD for earlier treatment with

SGLT2i or GLP-1R agonists; however information on the predictive value of these scores in large populations of subjects with T2D, independent of aggressive treatment of blood pressure and dyslipidemia, is currently limited.

Targeting glycemic outcomes and complications beyond HbA1c

Current evaluation of therapeutic effectiveness remains predominantly focused on a single glycemic measure, HbA1c, however it seems likely that this will change. The expanding use of CGM to refine understanding of the importance of glycemic parameters beyond HbA1c, including rates of hypoglycemia, and proportions of time within target glucose ranges, is receiving increasing attention in the management of both T1D and T2D. Notably, HbA1c may not always reflect or predict the burden of disease, and CGM may be particularly useful for individuals with unexplained recurrent hypoglycemia or marked glycemic variability. A limited assessment using several capillary blood glucose determinations each month correlated the extent of glycemic variability with rates of severe hypoglycemia in the Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events (DEVOTE)⁶⁴. Moreover, the development of severe hypoglycemia correlated temporally with rates of all-cause mortality in subjects studied in DEVOTE⁶⁵. More information on the potential clinical importance of severe hypoglycemia is likely forthcoming from imminent results of the CARdiovascular Outcome Trial of LINAgliptin Versus Glimepiride in Type 2 Diabetes (CAROLINA) trial⁶⁶, which may, depending on the results, further shift the T2D treatment paradigm away from medicines associated with an increased risk of severe hypoglycemia, most notably in elderly individuals and subjects at high risk for cardiovascular events (**Figure 2**). Hence future precision diabetes initiatives will likely encompass newer goals and non-glycemic targets, once these become prospectively validated.

Individualization of therapeutic options beyond metformin, as outlined in **Figure 2**, largely reflects expert opinion, not prospective validation in randomized trials. The demonstration that several SGLT2i and at least one GLP-1RA reduced MACE events further refines current options for reduction of heart failure (SGLT2i) and MACE-related complications (GLP-1RA and SGLT2i) in subjects with T2D. Although heart failure has not been a traditional focus for adjudication of CVD events in CVOTs undertaken in subjects with T2D, a reduction in hospitalization for heart failure was reported in both the EMPA-REG OUTCOME and CANVAS trials, highlighting the importance of heart failure as an independent outcome in subjects with T2D^{59,61}. Moreover, a reduction in progression of diabetic nephropathy, including doubling of serum creatinine and time to renal replacement, was detected in subjects treated with empagliflozin in the EMPA-REG OUTCOME trial¹⁴. Similarly, a numerical reduction of renal events, although not statistically significant, was demonstrated in canagliflozin-treated subjects in the CANVAS trial⁶¹.

Less compelling, but equally intriguing, are exploratory studies demonstrating reduction of liver fat and attenuation of liver inflammation and fibrosis in subjects with prediabetes or T2D treated with 45 mg daily of pioglitazone for 18-36 months⁶⁷. Moreover a smaller, double-blind, randomized controlled trial of liraglutide 1.8 mg daily for 48 weeks, including 35% of subjects with T2D, revealed a reduction in the extent of NASH and fibrosis in liraglutide-treated subjects⁶⁸. While much larger registration studies will

be needed to validate the preliminary findings for these putative non-glycemic indications, it seems likely that therapeutic recommendations for the management of T2D will increasingly be based on a personalized combination of goals encompassing both glycemic and non-glycemic targets (**Figure 2**), based on accumulating evidence from outcome and registration studies.

Mind the Gap in Personalized Medicine

Despite the introduction of multiple new drug classes for the treatment of T2D, data from real world health care audits demonstrates that population HbA1c levels have failed to decline as much as might be expected based on analysis of clinical trial data. Although many explanations, encompassing barriers to medication and health care access, contribute to this discrepancy, poor medication adherence underlies the challenge in achieving target HbA1cs for many patients⁶⁹. Despite substantial differences in HbA1c outcomes favoring GLP-1RAs over DPP-4 inhibitors in multiple clinical trials, retrospective claims analysis revealed comparable (and disappointing) HbA1c reductions of ~0.51 % for both classes, with very low rates of medication adherence (29-37% for GLP-1RAs vs. DPP-4 inhibitors, respectively) underlying the results achieved⁷⁰. The introduction of medications taken once weekly or even less frequently may theoretically improve compliance with diabetes therapies, however this concept requires rigorous prospective validation in real world studies.

Poor adherence is not limited to glucose-lowering agents, but extends to therapies directed at reduction of blood pressure, platelet aggregation, and dyslipidemia. As poor adherence is associated with increased rates of hospitalization and all-cause mortality in subjects with T2D⁷¹, understanding the myriad causes underlying adherence in different individuals is critical for successful application of personalized diabetes therapy. Intensification of efforts directed at identifying key factors underlying the success of RCTs (frequent interaction with health care providers, finite, time-limited and incentivized commitments to clinic visits and compliance, unencumbered access to medications, extensive provision of resources and regular support) and implementing best practices in the clinic represents a major challenge and opportunity for improved delivery of effective diabetes care in the real world.

Multiple international studies investigating patient stratification or predictors of response to therapy in treatment naïve individuals are underway including the Innovative Medicines Initiative funded DIRECT study (<http://www.direct-diabetes.org/>), the MASTERMIND and SUGAR-MGH studies^{72, 73}. These efforts will help address some of the current gaps in our knowledge regarding the impact of metabolic state on response to treatment. Indeed recent results from the SUGAR-MGH study demonstrate a role for the *TCF7L2*-T2D risk alleles in the acute responses to both glipizide and metformin in people without diabetes⁷⁴. Whether determination of these risk alleles provides similarly useful information on the chronic response to therapy in subjects with T2D remains uncertain.

Future Directions, Limitations, Recommendations, Areas of Uncertainty

The available evidence strongly links early and sustained control of T2D with long term benefit and reduction of complications. Greater use of electronic medical record-generated information for monitoring achievement of blood pressure, glucose, weight, and lipid targets, together with timely reminders for frequency of eye exams and foot care, should reduce the morbidity and mortality

associated with T2D. It is early days in our understanding of how genetic information can be used to stratify individuals for treatment response and it is almost certain that this information will need to be considered in concert with the clinical status of each individual along their disease progression path. The increasing availability and decreasing cost of human genetic analysis makes it likely that precise genome analyses will become routine in clinical medicine, and utilized for diagnosis and therapeutic recommendations in multiple subspecialties beyond the diabetes clinic. Refinement of algorithms incorporating predictive genetic variation and biomarkers for drug responsiveness and the risk of complications, prospectively validated by clinical trial outcomes data in multiple populations with different ethnic backgrounds, should progressively enhance our ability to transform diabetes care. Although there is much more progress to come, it is not farfetched to anticipate gradual implementation of cost-effective precision-based personalized medicine in T2D treatment centers.

Successful deployment of a precision medicine approach to T2D requires attention to gaps in our current knowledge base, including a paucity of clinical trial data guiding treatment in adolescents, the elderly, and during pregnancy. Moreover, the majority of study subjects in trials informing the safety and cardiovascular benefit of new medications for T2D were recruited with established cardiovascular disease. Our outcomes data for recommending T2D therapy directed at primary prevention of macrovascular complications in younger healthier individuals is insufficient. It seems certain that the increasing availability, and improved accuracy and utility of genomic and clinical biomarkers, will further enable precision diabetes. Simultaneously, information technology will continuously improve our capacity to conduct global, large scale and cost-effective clinical trials. Nevertheless, given the staggering numbers of subjects with T2D, critical evaluation of the cost vs. benefit for utilization of genomics, biomarkers, new technologies, and specific medications will be needed to support recommendations for clinical use in specific populations. Given the tremendous progress made over the last decade, it is reasonable to predict greater adoption of precision medicine approaches in the T2D clinic in the years to come.

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Figures

Figure 1: Illustration of current status of precision medicine approaches for treatment of individuals with selected monogenic subtypes of diabetes (left panel) vs. individuals with complex genetic determinants of T2D (right panel)

Figure 2: Evolving clinical considerations underlying personalized medicine recommendations for intensification of therapy after metformin in subjects with T2D. Clinical characteristics influencing medication selection (left panel) vs. recent evidence from clinical studies examining the non-glycemic actions of glucose-lowering therapies on complications associated with T2D (right panel). OAD Orally administered anti-diabetic drugs; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; HF=heart failure; CAD, coronary artery disease; CVA, cerebrovascular accident; CKD, chronic kidney disease.

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