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## **Precision medicine in diabetes: a consensus report from the ADA and EASD**

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## **Abstract**

The convergence of advances in medical science, human biology, data science and technology has enabled the generation of new insights in the phenotype known as “diabetes”. Increased knowledge of this condition has emerged from populations around the world, illuminating the differences in how diabetes presents, its variable prevalence, and how best practice in treatment vary between populations. In parallel, focus has been placed on the development of tools for the application of precision medicine to numerous conditions. This Consensus Report presents the ADA Precision Medicine in Diabetes Initiative, its mission, current state of the field, and prospects for the future. This report provides expert opinions on areas of precision diagnostics and precision therapeutics (including prevention and treatment), as well as highlighting key barriers and opportunities to implementation of precision diabetes medicine around the globe in a way that enables better care and outcomes for all those in need. There are clear cases where precision diagnosis is already feasible and effective (monogenic forms of diabetes) and others where major hurdles remain for global implementation (in complex forms of diabetes). The situation is similar for precision therapeutics, in which the appropriate therapy will often change over time owing to the manner in which diabetes evolves within individual patients. This report describes a foundation for precision diabetes medicine, while highlighting what remains to be done to realise its potential. This, combined with a subsequent, detailed evidence-based review (due 2022) will provide a roadmap for precision medicine in diabetes that helps improve the quality of life for all those with diabetes.

## Rationale for Precision Medicine in Diabetes

The practice of medicine centers on the individual. From the beginning, the physician has examined the patient suffering from illness, ascertained his/her signs and symptoms, related them to the medical knowledge available at the time, recognized patterns that fit a certain category and, based on the practical wisdom accumulated *via* empirical trial and error, applied a given remedy that is best suited to the situation at hand. Thus, the concept of *precision medicine*, often defined as providing the right therapy, for the right patient at the right time, is not novel. What has changed radically is our ability to characterize and understand human biological variation through 1) assessment of the metabolic state, 2) leveraging data to inform disease categories, and 3) science-guided preventive and treatment decisions tailored to specific pathological conditions. Coupling these with detailed information accessible through digital devices and technologies about lifestyle and the environment, as well as data abstracted from electronic medical records, present unparalleled opportunities to optimize diabetes medicine.

Diabetes mellitus is diagnosed by the emergence of hyperglycemia, the crossing of a threshold of blood glucose concentration beyond which, if chronically unchecked, results in microvascular and macrovascular end-organ complications. However, hyperglycemia is the end-product of numerous pathophysiological processes that often emerge over many years and converge on the inability of the pancreatic beta cells to secrete enough insulin to meet the demands of target tissues, often because the amount of available insulin is no longer effective. In clinical practice, absolute insulin deficiency can be detected from the autoimmune destruction of beta cells in type 1 diabetes (T1D), which comprises ~10% of all diabetes. Making the diagnosis of T1D is critical, given the therapeutic requirement of exogenous administration of insulin. In more specialized settings, hyperglycemia might be detected from an inherited or *de novo* loss of function in a single gene (e.g., monogenic diabetes, comprising 2-3% of all diabetes diagnosed in children or young adults). Diabetes can also appear after pancreatitis or organ transplantation, during pregnancy, or as a result of cystic fibrosis. The remaining 85-90% of individuals with diabetes, however, are likely diagnosed as having type 2 diabetes (T2D), which will have manifest through defects in one or (more often) multiple pathways (e.g., beta cell insufficiency, fat accumulation or miscompartmentalization, inflammation, incretin resistance, dysfunction of insulin signaling).

Our modern capacity to comprehensively interrogate diverse axes of biology has facilitated the approach of studying an individual to infer general principles, from which a discrete treatment plan is selected. These axes include developmental/metabolic context, genomic variation, chromatin signals that mark genes as active or repressed in tissues, expressed

transcripts, biomarkers of disease and increased knowledge of lifestyle/environmental risk factors. Parallel advances in computational power and analytic methods required to appropriately interrogate 'big data' are driving insights that may radically transform the practice of medicine. Yet, at this time, the individual physician often lacks time and training to incorporate this into medical decision making. Thus, the translation of the rapidly accumulating new knowledge into practice requires careful evaluation and translational strategies involving specialist training, education and policy considerations.

The failure to adequately understand the diverse molecular and environmental processes that underlie diabetes and our inability to identify the pathophysiological mechanisms that trigger diabetes in individual patients, limit our ability to prevent and treat the disease. Public health strategies have struggled to slow the epidemic, even in countries with the greatest financial and scientific resources. Pharmacologic therapies, comprising 12 different drug classes currently approved by the Food and Drug Administration (FDA) ([www.fda.gov/media/91130/download](http://www.fda.gov/media/91130/download)), may, at best, control glycemia and modify disease course, but not provide a cure or result in the remission of disease. Moreover, these agents are sometimes prescribed based on non-medical considerations (cost, side effects, patient preference, or comorbidities) which may overlook the biological mechanism. Thus, more people are developing diabetes worldwide and progressing to complications, incurring a significant health care burden and cost.

There are, however, several reasons for hope. First, diabetes caused by single gene defects can be characterized and targeted therapies are particularly effective (1; 2). Second, islet autoantibody biomarkers and genomic risk have clarified autoimmune diabetes from other forms of the disease (3; 4), thereby facilitating immune-intervention trials, pre-onset monitoring to reduce risk of severe complications, and aid in detection of environmental triggers (5). Third, multiple biomarkers and genetic variants have been shown to alter risk of T2D, revealing previously unsuspected biological pathways and providing new targets. Fourth, T2D has been shown to be a complex combination of multiple conditions and processes, defined by process-specific subgroups in which individuals with extreme burdens of risk in particular pathways reside and for whom a specific therapeutic approach may be optimal (6). Finally, the tools, resources and data now exist to determine the biological and lifestyle/environmental predictors of drug response, as measured by a variety of clinical outcomes (7).

**What is the *Precision Medicine in Diabetes Initiative (PMDI)*?**

The *idea* of precision diabetes medicine is gaining momentum, based upon the promise of reducing the enormous and growing burden of diabetes worldwide. To address this, the PMDI was launched in 2018 by the American Diabetes Association (ADA), in partnership with the European Association for the Study of Diabetes (EASD). The PMDI has partnered subsequently with other organizations (the USA National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK)).

The mandate of the PMDI is to establish consensus on the viability and potential implementation of precision medicine for the diagnosis, prognosis, prevention and treatment of diabetes, through expert consultation, stakeholder engagement and systematic evaluation of available evidence. This mandate is pursued in order to realize a future of longer, healthier lives for people with diabetes.

The PMDI is focused on assessing evidence, promoting research, providing education, and developing guidelines for the application of precision medicine in diabetes. The 2019 ADA Scientific Sessions (June 2019) sponsored a research symposium focused on precision medicine, followed by a PMDI Stakeholder Meeting (October 2019) that was attended by experts in areas germane to precision diabetes medicine from around the world. Future PMDI symposia will extend the themes of precision diabetes medicine during the 2020 ADA and EASD Scientific Sessions. In the coming years, educational approaches to translate the science into practice will be the target of a series of postgraduate education symposia. A global clinical research network focused on precision diabetes medicine is also being planned, along with other education and dissemination activities (see Figure 1 for overview of key objectives).

The purpose of the work underlying the ADA/EASD Precision Medicine in Diabetes consensus reports, of which this is the first, is to define relevant terminology (see Text Box 1) and overview the current status of diagnostics and therapeutics (prevention and treatment) in diabetes, including key areas of opportunity and where further inquiry is needed (see Text Boxes 2-4). Particular focus is placed on elucidating the etiological heterogeneity of diabetes, which involves a combination of approaches including contemporaneous measures of risk factors, biomarkers and genomics, as well as lifestyle and pharmacologic interventions. Monogenic diabetes is one of few areas where precision diabetes medicine has been proven feasible and is practiced (overviewed in detail in the Diabetes Care Expert Forum (ref)). This first consensus report does not seek to address extensively the role of precision medicine in the complications of diabetes and is a topic for future evaluation. In addition, we do not discuss diabetes digital device technology, as this is addressed in a joint ADA/EASD consensus report (8; 9). A second PMDI consensus report will be published documenting the

findings of a systematic evidence review, focusing on precision diagnostics and precision therapeutics (prevention and treatment).

An *Executive Oversight Committee*, comprised of representatives from the founding organizations, ADA (LP) and EASD (JJN), and the two co-chairs of the initiative (PWF and SSR), provide PMDI governance. The Executive Oversight Committee is responsible for ensuring the PMDI activities are executed. Leadership and direction of the PMDI are provided by members of the *PMDI Steering Committee*, currently comprised of academic leaders in precision diabetes medicine from the United States (WKC, JCF, JMN) and Europe (ATH, MIM, ERP), a representative from NIDDK (CGL), and the Executive Oversight Committee members (LP, JJN, PWF, SSR). The Steering Committee is responsible for providing guidance for PMDI activities and engages in developing precision diabetes medicine education, drafting consensus statements, and building interest/working groups to achieve its mission. The Executive Oversight Committee and the Steering Committee work closely together under the banner of the *PMDI Taskforce*. Membership of the Steering Committee will expand to include experts from around the world and across multiple areas of expertise germane to the topic of precision diabetes medicine.

Work for this consensus report began at the October 2019 Stakeholder Meeting in Madrid. The meeting included presentations and roundtable discussions. At the conclusion of the meeting, a writing group meeting attended by the PMDI Taskforce and stakeholders was held to determine what should be addressed in the consensus report. Following the meeting, consensus was reached by the PMDI Taskforce through bimonthly calls and electronic communication. Relevant experts outside of the Taskforce were asked to contribute sections as needed. The consensus report was then peer-reviewed by experts in the field and by the clinical committees of the participating organizations. The report was then submitted to *Diabetes Care*, *Diabetologia*, and *The Journal of Clinical Endocrinology & Metabolism* for simultaneous publication.

### **Precision Diabetes Medicine: What It Is and What It Is Not** (see Text box 1)

Precision diabetes medicine refers to an approach to optimize the diagnosis, prediction, prevention or treatment by integrating multi-dimensional data, accounting for individual differences. The major distinction from standard medical approaches is the use of complex data to characterize the individual's health status, predisposition, prognosis, and likely treatment response. These data may stem from traditional sources such as clinical records, as well as from emergent sources of 'big data' such as individual medical records from very large cohorts of patients, geo-mobility patterns obtained from devices, behavioral monitors



(e.g., actigraphy for exercise and sleep assessments), ingestible, subcutaneous or wearable sensors (e.g., for blood glucose monitoring), and genomic and other 'omics data. Integration of patient preferences, patient-centered outcomes, cost-effectiveness, and shared decision-making will guide how precision diabetes medicine is formulated and applied.

There are several terms sometimes used interchangeably with precision medicine, including *personalized medicine*, *individualized medicine*, and *stratified medicine*. The 2020 ADA Standards of Medical Care in Diabetes (ADA SMCD) places considerable emphasis on the *personalization* of diabetes medicine, highlighting that “*clinicians care for patients and not populations*” [S2] (10). This reflects the realization of individual differences with respect to symptomatology, presentation, behaviors, preferences, social circumstances, response to treatment, comorbidities, or clinical course. For precision diabetes medicine to be effective, it must be tailored to the individual. Thus, the ADA SMCD instructs the clinician to adapt guidelines to each patient’s characteristics, circumstance, and preferences, including the patient’s food security, housing, and financial stability. In the context of the PMDI, this is not considered to be *precision* medicine; rather, this final step in the process of translating knowledge into practice is *personalized* (or *individualized*) medicine. In contrast, precision (or stratified) medicine emphasizes tailoring diagnostics or therapeutics (prevention or treatment) to *subgroups* of populations sharing similar characteristics, thereby minimizing error and risk while maximizing efficacy. Included within precision diabetes medicine is the monitoring of disease progression using advanced technologies or how patient features affect the reliability of assays. The application of precision diabetes medicine may substantially reduce errors in the diagnostic (Figure 2), therapeutic (Figure 3) and prognostic (Figure 4) processes. For example, the interrogation of large sets of longitudinal clinical data could identify disease subtypes and match the patient to others with a similar disease profile; through knowledge of treatment efficacy and outcomes, more precise prognosis and optimization of therapies for this patient by concordance to similar subgroups would emerge (see Text box 3 and figure 3).

### **Precision Diagnostics** (see Text Box 2)

#### *What are the Requirements for Precision Diagnosis?*

Precision diagnostics employs methods to sub-classify patients to enable the successful application of precision medicine approaches (Figure 2). This will facilitate matching precise prevention strategies and treatments to individuals either at risk of or diagnosed with diabetes. Ideally, a precision diagnostic test should be: (i) robust (high test-retest reliability within and between laboratories); (ii) able to define a discrete subgroup giving insights into

disease etiology, prognosis, and treatment response; (iii) widely available; (iv) easily performed with accepted norms for interpretation; and (v) inexpensive (or at least cost-effective).

Precision diagnosis can be conceptualized as a pathway, rather than a single step, that moves through stages. The diagnostic stages include assessing the:

- Expected prevalence based on epidemiology, including age, or age at diagnosis of diabetes, sex and ancestry,
- Probable clinical diagnosis using clinical features and other data, and
- Modification by diagnostic tests that are interpreted in the light of prevalence and diagnosis

A diagnosis in precision medicine is a probability-based decision, typically made at a point in the natural history of a disease, reflecting neither an absolute truth nor a permanent state. Presenting the degree of uncertainty in a manner that is intuitive to the patient and practitioner is critical if the precision diagnosis is to be effective.

#### *Precision Diagnosis in Clinical Practice*

Data and outcomes from the widespread use of glycosylated hemoglobin, rather than blood glucose levels, for diagnosis has led to a precision approach for the diagnosis of diabetes. The level of glycosylated hemoglobin will depend on factors that impact hemoglobin and red cell stability as well as average glucose values (10). Genetic testing can reveal unsuspected variants that alter HbA1c. In African Americans, for example, heterozygosity for the HbS variant may lower HbA1c by ~0.3% ((11), and one or two copies of the minor allele at the X-linked glucose-6-phosphate dehydrogenase G202A variant (found in ~11% of African Americans) lowers HbA1c by ~0.7% (12). Thus, knowledge of the patient's ancestry and specific genetic information can guide interpretation of assay results and diabetes management

DIAGNOSING T1D vs T2D. Currently, the most common precision diagnosis that is made in clinical diabetes medicine is the classification of T1D versus T2D, the two most prevalent sub-categories with different etiologies and different treatment requirements. Part of the diagnostic dilemma is that neither T1D nor T2D are monolithic entities and robust "gold standards" are not universally agreed. Diagnostic issues arise when expected clinical features are discordant from established norms (e.g., people diagnosed with diabetes who are young and obese, or old and slim, or are a rare subtype in that clinical setting) (13). Islet

autoantibody positivity varies by clinical setting (e.g., in people without diabetes, patients diagnosed with probable T1D as children, and patients with clinical features of T2D), resulting in an altered prior probability of T1D that reflects the different prevalence in these diverse settings. The best diagnosis depends on integrating all diagnostic modalities, as demonstrated in predicting long term C-peptide negativity in patients diagnosed with diabetes between 20 and 40 years of age, where an integrated model outperformed clinical features, circulating antibodies or genetics used in isolation (3). The misdiagnosis of T1D and T2D in middle-aged and elderly adults (13; 14) suggest that precise diagnostic approaches are needed, especially as failure to recognize insulin-deficient states can be fatal.

**DIAGNOSING MONOGENIC DIABETES.** An Expert Diabetes Forum report (ref) has concluded recently that a monogenic diabetes diagnosis is closest to meeting all criteria for a perfect diagnostic test as it defines a discrete subgroup giving insights into etiology, prognosis, and treatment response (1; 2). Perhaps the best example of precision diabetes medicine is the excellent and long-lasting glycemic response to oral sulfonylureas in insulin-dependent infants with neonatal diabetes when diagnosed to be due to abnormalities in the beta cell potassium channel (15-17). In MODY, it is established that *GCK* patients do not require (18), or respond to, oral medication (19). Other MODY diagnoses (*HNF1A*, *HNF4A* and *ABCC8*) are acutely sensitive to the glucose-lowering effects of sulfonylureas (20-22); however, unless the diagnosis is precise, these therapeutic benefits are lost. With the clear benefits of precision diagnosis of monogenic diabetes, it is important to reduce diagnostic barriers to its implementation. For example, the cost of performing molecular genetic testing is high and universal testing is not cost-effective. It is thus necessary to limit testing to those most likely to have a monogenic diagnosis. Moreover, identification protocols require pre-screening based on clinical features (e.g., family history, age at onset, phenotype including syndromic features) and non-genetic testing (islet autoantibodies and C-peptide).

One approach for implementing precision medicine in the case of monogenic diabetes is:

- Test all patients diagnosed with diabetes in the first 6 months of age, because >80% have a monogenic cause of neonatal diabetes
- Use a MODY calculator to identify those whose clinical features suggest a high likelihood of MODY ([www.diabetesgenes.org/mody-probability-calculator/](http://www.diabetesgenes.org/mody-probability-calculator/)) (23)
- Test pediatric diabetes cases when at least three islet autoantibodies are antibody negative (24)

The effective use of these pre-genetic selection criteria should greatly improve the likelihood of correctly diagnosing monogenic diabetes and not have the burden of costly genetic screens. Although diagnostic molecular genetic testing utilizes robust analysis of germline DNA, which is virtually unchanged throughout life, there are still issues with its implementation. One issue is through errors of interpretation of the genetic information, leading to inaccurate identification of causal mutations in both clinical practice and in the published research literature (25). Curation of pathogenic variants for monogenic diabetes is critical and is currently being addressed by international consortia. Technological advances have resulted in testing multiple causes of monogenic diabetes in a single next-generation sequencing test. This approach is generally advantageous as it does mean syndromic monogenic diabetes is diagnosed genetically when the patient presents with isolated diabetes. This will allow other features to be examined and treated appropriately before clinical presentation. Examples of this are neonatal diabetes (2) *HNF1B* (RCAD) (26), *WFS1* (Wolfram syndrome) (27) and mitochondrial diabetes (28). For these patients, the genetic diagnosis of diabetes will have implications far beyond the prognosis and care of diabetes, as the patient with certain types of monogenic diabetes will also be at high risk of developmental delay, neurological disease, developmental kidney disease, liver failure, deafness and cardiomyopathy.

DIAGNOSING LATENT AUTOIMMUNE DIABETES IN ADULTS (LADA). LADA is not currently recognized by the ADA as a formal subtype of diabetes. Nevertheless, LADA reveals some of the difficulties in diabetes subtyping. It was shown that the presence of GAD autoantibodies in patients with T2D was associated with progression to early insulin therapy (29); yet, controversy remains whether LADA is a discrete subtype, a milder form of T1D, or a mixture of T1D and T2D (sometimes termed “*type 3 diabetes*”, where some patients with T1D also develop T2D). The uncertainty is increased by variation in the diagnostic criteria, with initial treatment based upon physician preference as well as the patient’s disease (30). In addition, there is variation in the level of GAD autoantibodies required for positivity that alters the diagnosis (31).

SUBCATEGORIES OF COMMON FORMS OF DIABETES. The subcategorization of T1D or T2D may not always be the optimal approach for precision diabetes diagnosis or therapy. Nevertheless, the ability to delineate T1D or T2D using non-traditional data and approaches may lead to improvements in its prevention or treatment, including diabetes subclassifications beyond T1D or T2D.

*Subcategories in T1D*

The age at which the initial islet autoantibody appears and the type of autoantibody (e.g., which of the four primary antibodies among ICA512, Ins, GAD, ZnT8) may be important in defining etiological subtypes of T1D (32). Data supporting this potential subcategory are based upon those diagnosed in the first 10 years of life and in predominantly white European populations. The relevance to other ethnic groups and those diagnosed later in life is uncertain.

The majority of the genetic risk of T1D is now known, and the sensitivity and specificity of T1D genetic risk scores (T1D-GRS) both exceed 80% (5; 33-35); however, a high T1D-GRS will have low positive predictive value in populations with typically low prevalence. The greatest utility of a T1D-GRS may require integration with clinical features and islet autoantibodies (3; 4). There is variation in the genetic susceptibility with age at diagnosis but, at present, genetics is not suggested as an approach to defining subtypes of T1D.

There is strong evidence for enrichment of immune cell types that are associated with genetic risk of T1D, particularly T cells (CD4+ and CD8+) and B cells (CD19+). However, at present, there is no immune-based test sufficiently reproducible and robust that it can be used diagnostically for T1D.

Persistent, endogenous beta cell function in T1D is associated with greater potential for improved glycemic control and reduced complications (36). A stimulated C-peptide measurement represents a candidate for defining subcategories of T1D with different treatment aims. C-peptide levels exponentially fall in the honeymoon period after T1D diagnosis (37) but have been shown to be stable 7 years after diagnosis (38). Persistent C-peptide is associated with a later age of diagnosis, although there are few data to predict those likely to maintain high levels of C-peptide.

### *Subcategories in T2D*

Family history in T2D, as a surrogate for precise genetic evaluation, fails to meet many of the criteria of a robust test as any assessment changes over time and depends on the relatives selected for reporting the “family”. The value of a family history may be greatest in monogenic diabetes, in which a pedigree will often demonstrate a pattern of inheritance consistent with a single gene disorder and a consistent phenotype.

T2D treatment response and disease progression can be predicted from continuous clinical features with specific models. These models appear to perform better than dividing into cluster based subgroups (7). An advantage of using clinical features is that they are widely

available and easily obtained (e.g., sex, BMI, HbA<sub>1c</sub>); however, a limitation is that clinical features may vary over time and with the natural history of the disease. Incorporation of longitudinal change with treatment response could be a strength as the model's prediction would change in concert with changes in the patient's phenotype.

Recent research has attempted to define subcategories of T2D (and T1D) based on cluster analysis at diagnosis to provide insights into likely progression, risk of complications, and treatment response (39; 40). Barriers facing this and other approaches include collection of data that are not routinely obtained (e.g., a fasting C-peptide at the time of diagnosis with assay variability (41)) and the change in biomarkers over time that are dependent on disease course or its treatment. Genetic data has been used to define T2D subcategories by clustering genetic variants that associate with physiologic traits and which are correlated with clinical outcomes (6). At this time, the available genetic data for T2D and the clustering does not have sufficient predictive accuracy to replace existing delineative approaches. None of the methods described above are established for subclassification of T2D in clinical practice; nevertheless, it is true that in a minority of patients, their specific type of diabetes may be adequately characterized using genetic clustering (42; 43).

### **Precision Therapeutics** (see Figure 3)

Careful diagnosis is necessary for successful precision therapy, whether for prevention or treatment. This is true where subgroup(s) of the population must be defined to determine which targeted interventions will be applied, as well as for determination of treatment outcome. In monogenic diabetes, there are no currently known options for prevention. In T1D, precision prevention involves mainly the optimization of monitoring methods (see Text Box 3), thereby facilitating early detection, prevention of onset complications, and optimizing treatment. In contrast, T2D has many avenues for prevention; thus, the possibilities for precision approaches, possibly through tailoring of lifestyle (e.g., diet), are broad in T2D.

#### *Precision Prevention in Diabetes (see Text Box 3)*

**PRECISION PREVENTION IN T1D:** T1D is characterized by damage, impairment, and eventual destruction of the insulin-producing pancreatic beta cells, thought to be the result of an autoimmune process. T1D progression has been grouped into discrete "stages" (44). Stage 1 is defined by the presence of  $\geq 2$  islet autoantibodies, with normal blood glucose. Stage 2 is defined by the presence of  $\geq 2$  islet autoantibodies with elevation of blood glucose, signaling the functional impairment of the beta cells. Stage 3 is characterized by symptoms of dysglycemia, such as polyuria or diabetic ketoacidosis, although not all symptoms need be

present. A clinical diagnosis of T1D typically is not given until Stage 3. T1D is nearly inevitable once  $\geq 2$  islet autoantibodies appear, particularly in those of younger age, with a lifetime diabetes risk approaching 100% (45; 46). Approximately one half of the risk of T1D is due to genetic factors, with over 30% of the genetic risk attributable to genes of the human leukocyte antigen (*HLA*) complex but also including more than 50 non-*HLA* loci (35). Unknown environmental factors are thought to trigger the autoimmune process that results in initial beta cell damage and progression toward symptomatic T1D (47).

Primary prevention trials in genetically-susceptible individuals who have not yet developed autoantibodies (i.e., pre-Stage 1) and secondary prevention trials in children with Stages 1 and 2 have been conducted (48) using dietary interventions and immune-targeting approaches. Dietary manipulation studies have been largely unsuccessful in reducing islet autoimmunity (49-51) or T1D (52). Previous intervention studies among individuals at Stage 1 or Stage 2 have been unable to slow, halt, or reverse the destruction of insulin-producing beta cells. Of nine completed secondary prevention trials (53-60), only one (using an anti-CD3 antibody) has shown a slight delay in progression to T1D (61).

Most prevention trials in T1D have not been effective, partially because the individual's unique T1D genetic risk profile and their unique response to the preventive agent (immune therapy or dietary intervention) have not been considered. For example, the inflammatory response to infection with enteroviruses implicated in the onset of T1D has been shown to be genetically mediated (62) and diet has had different effects on development of autoimmunity and progression to T1D (63) dependent upon genetic risk. Several studies have suggested that susceptibility to islet autoimmunity and progression to T1D may be related to the ability to adequately use vitamin D, as higher cord blood 25(OH)D was associated with a decreased risk of T1D, but only in children who were homozygous for a vitamin D receptor gene (*VDR*) variant (64). Risk of islet autoimmunity was observed with reduced dietary intake of the omega-3 fatty acid, alpha-linolenic acid, but only in those with a specific genotype in the fatty acid desaturase gene (*FADS*) cluster (65). Thus, without considering the unique genetic profiles of children, dietary supplementation may not be successful, arguing for an appropriately validated precision approach.

**PRECISION PREVENTION IN T2D:** The emergence of T2D as a global public health crisis during recent decades has motivated numerous large randomized controlled trials assessing the efficacy of pharmacologic or lifestyle interventions for prevention. An emphasis has been placed on intervening in people with "prediabetes," defined as a person with levels of fasting blood glucose, 2-hr blood glucose, or HbA1c that are chronically elevated but below the diagnostic thresholds for diabetes. Although prediabetes is a major risk factor for T2D and

other diseases (66), intervening in everyone with prediabetes may not be cost-effective (67). Aggressive precision prevention in those with relevant risk factors is discussed in the current ADA SMCD (68). Youth with prediabetes should be the focus of preventive interventions, especially those who are overweight or obese, and with one or more additional risk factors (e.g., maternal history or exposure to gestational diabetes mellitus (GDM), a positive family history of diabetes in first- or second-degree relatives, signs of insulin resistance, or of specific high-risk ancestry).

Multiple interventions in T2D have been evaluated for risk reduction and prevention, both in the short- and the long-term. A recent systematic review (69) reported that after active interventions lasting from 6 months to >6 years, lifestyle relative risk reduction (39%) was similar to that from use of drugs (36%); however, only lifestyle interventions had a sustained reduction in risk once the intervention period ended. The post-intervention follow-up (~7 years) demonstrated a lifestyle risk reduction of 28% compared to a non-significant reduction (5%) from drug interventions.

Most lifestyle intervention programs use standardized approaches designed to change diet and exercise habits for reducing body weight. The Diabetes Prevention Program (DPP) evaluated the efficacy of lifestyle intervention and metformin therapy, compared with standard of care and placebo, for delay or prevention of diabetes in those with impaired glucose regulation at baseline. Although reductions in diabetes risk from lifestyle (58% reduction) and metformin (31% reduction) compared with the control intervention were impressive (70), there was considerable variation across the study population (71), with many participants developing T2D during the active intervention period (the first 2.8 years of the trial). Thus, the DPP lifestyle intervention did not truly "prevent" diabetes. Indeed, in the decade after randomization, during which participants were offered lifestyle reinforcement semi-annually, the average duration before disease onset was ~3 years (72). Those participants in the DPP who progressed most rapidly were those who lost the *least* weight in the early stages of the intervention (73), with genetic variants representing significant predictors of peak weight loss and weight loss maintenance (74). Results from the DPP and other large prevention trials suggest a "one-size-fits-all" lifestyle intervention strategy will not be efficacious for all, particularly if it cannot be sustained, strengthening the case for precision lifestyle interventions in T2D prevention.

Although precision diabetes medicine is much more than genetics, the majority of relevant research has focused on evaluating the role of genetic variants in precision prevention. Large epidemiological studies (75) and intervention trials (76; 77) strongly suggest that standard approaches for lifestyle modification are equally efficacious in preventing diabetes regardless



of the underlying genetic risk. This contrasts the extensive epidemiological evidence suggesting that the relationship of lifestyle with obesity is conditional on genetic risk (78-81); however, with few exceptions (e.g., (74)), analyses in large randomized controlled trials have failed to show that these same genetic variants modify weight loss in response to lifestyle intervention (82). It is also important to recognize that knowledge of increased genetic risk for diabetes may not motivate improvements in lifestyle behaviors. Indeed, knowledge of increased genetic risk for diabetes may decrease motivation to modify behavior in genetic fatalists (83).

Diet recommendations optimized to the individual have been shown to reduce postprandial glycemic excursions to a greater extent than standard approaches in healthy individuals (84). Meal compositions that induce the most favorable glycemic profiles have been guided by models derived from an individual's biological data (e.g., microbiome, genome, and metabolome) lifestyle factors (e.g., sleep and exercise) and postprandial glycemia following the consumption of a series of standardized meals. Although these studies indicate that personalized diet plans may help minimize postprandial glycemic excursions, no studies have reported the long-term impact on glycemic control of adhering to personalized diets.

Of the 12 approved classes of diabetes drugs ([www.fda.gov/media/91130/download](http://www.fda.gov/media/91130/download)), many having been assessed for efficacy in prevention. Overall, drugs that enhance insulin action have proven more effective in diabetes prevention than those that increase insulin secretion. Some of the variability in the diabetes-reducing effect of metformin in the DPP has been associated with variation in the *SLC47A1* gene that encodes the multidrug and toxin extrusion 1 transporter protein (85). In the DPP Outcomes Study, the effects of lifestyle, metformin and placebo interventions were assessed in weight reduction during the 6–15 years that followed the end of the randomized intervention phase (86). As a percentage of baseline weight, those assigned to metformin maintained an average 6.2% weight loss, compared to the lifestyle intervention group which maintained a 3.7% weight loss, and the placebo group that maintained a 2.8% weight loss. In the subgroup of DPP participants who, at one-year post-randomization, lost <5% baseline weight (poor responders), body weight during the following 14 years remained essentially unchanged, whether receiving metformin or placebo interventions. In contrast, those participants in the lifestyle intervention group who lost <5% baseline weight gained and sustained ~2 kg excess body weight in the years that followed. This findings reveal a subgroup of DPP participants in whom lifestyle intervention led to weight gain, which presents a potential avenue for stratified intervention, where individuals who are unlikely to respond well to lifestyle modification might be better served by other therapeutic approaches.

### *Precision treatment in diabetes (see Text Box 4)*

Once diabetes develops, there are a number of therapeutic steps clinically indicated to improve disease management. These steps include:

- Glucose monitoring
- Patient education and lifestyle intervention (87)
- Surgery
- Drug treatments to lower HbA1c
- Drug treatments to lower cardiovascular risk (e.g., statins, anti-hypertensives)
- Drug treatments targeted at specific complications (e.g., ACEi/ARB and SGLT2i for proteinuric kidney disease, fibrates for retinopathy, and atypical analgesics for painful neuropathy)

For each of these treatments, there will be patients who respond well and those who respond less well, in addition to those who have adverse outcomes from the therapy. Thus, precision treatment can be considered as using patient characteristics to guide the choice of an efficacious therapy to achieve the desired therapeutic goal or outcome, while reducing unnecessary side effects (figure 3). Given the broad scope of precision treatment, pharmacological therapy in T2D has the best evidence-base for precision therapeutics at present.

### *Subcategories and Drug Outcomes*

Traditionally, trials of therapeutic intervention do not recognize variation in etiologic processes that lead to development of T2D. The MasterMind consortium recently re-analyzed data from the ADOPT and RECORD studies in order to highlight how clinical phenotype can be used to help guide treatment intervention. On average, men who were non-obese had greater HbA1c reduction over 5 years with sulfonylureas than they did with thiazolidinediones; however, women with obesity had sustained HbA1c-lowering over the 5 years compared to sulfonylureas (88). When considering the clinical and physiological parameters used to subgroup individuals with diabetes (39), the insulin-resistant cluster defined in ADOPT and RECORD responded better to thiazolidinediones while the older patient cluster responded better to sulfonylureas (88). This increasingly granular view of T2D will lead to increasing precision therapeutic paradigms requiring evaluation and potential implementation.

The most current examples of precision therapeutics can be seen in monogenic diabetes, for which single gene mutations are causal for the development of diabetes and for which targeted treatments can, in effect, bypass the etiological defect (e.g., sulfonylurea sensitivity in *HNF1A* MODY (20) and insulin independence with high-dose sulfonylureas in neonatal diabetes due to  $K_{ATP}$  channel defects (16)). Genetic variation not only can capture etiological variation (i.e., genetic variants associated with diabetes risk) but also variation in drug pharmacokinetics (absorption, distribution, metabolism, excretion – ADME) and in drug action (pharmacodynamics). As T2D is a common complex disease characterized by thousands of etiological gene variants, it remains uncertain that individual variants will be identified that are highly predictive of drug outcomes in T2D. In contrast, there are examples of small-to-modest magnitude effects of genetic variants in HbA1c response to diabetes treatments (e.g., 0.5% difference in HbA1c reduction with metformin based upon *SLC2A2* rs8192675 genotype (89)), with the largest effects seen affecting variation in ADME genes (e.g., *CYP2C9* genotype and sulfonylurea response (90); *CYP2C8* and *SLCO1B1* genotypes and rosiglitazone response (91)). These data highlight the potential of genetic information to be incorporated into clinical decision support tools to guide a precision therapeutics approach.

The diabetes phenotype is markedly different across ethnic groups; thus, it is likely that drug outcomes will differ between populations. The current and growing burden of diabetes is growing rapidly in all populations, particularly South and East Asians, yet, these populations are under-represented in clinical and drug outcome trials. A lack of systematic reviews and meta-analyses from these high-prevalence regions still points to differences in drug response. For example, the DPP4i response is greater in Asians than Whites (92), a result supported by a subgroup analysis of TECOS showing a greater HbA1c reduction to sitagliptin in East Asians compared to Whites (93). Glycemic response to metformin has also been reported to differ by ethnic group, with African American individuals having greater response than European Americans (PMID: 24921653).

### **Precision Approaches in Diabetes Pregnancy**

In women, being affected by gestational diabetes mellitus (GDM) is a major risk factor for T2D. The risk of developing T2D in women with prior GDM approaches 70% after the index pregnancy (94), climbing to 84% developing T2D in women of East Indian ancestry (95). Currently, genetic studies of GDM have identified those variants known to increase risk of T2D (96); however, other variants have been shown to influence glycemic traits specifically in pregnancy (97). Furthermore, like T2D, GDM is a heterogeneous condition linked to primary defects in either insulin secretion or sensitivity (98; 99). Attempts to develop models to

predict pregnancy complications (100) or subsequent T2D (101) in GDM using clinical characteristics, biomarkers, and/or genetic variants have yet to be adopted, even though both lifestyle interventions and metformin use have demonstrated benefits in reducing the risk of T2D in women with prior GDM (102).

The target for all patients with T1D or T2D in pregnancy is to achieve as near normal glucose as possible, particularly around conception (to reduce developmental anomalies) and in the third trimester (to reduce the risk of macrosomia; (103). In pregnancy, the only clear exception so far is for mothers with MODY2 (mutations in the *GCK* gene) as fetal growth is determined predominantly by fetal genotype (104). In mothers whose fetus inherits the mother's *GCK* mutation, fetal growth is normal despite the maternal hyperglycaemia and treatment of the maternal hyperglycaemia is not recommended (104; 105). Establishing whether the fetus is likely to be affected is determined usually by ultrasound scan. In the future, the use of non-invasive cell-free DNA methods in maternal blood will likely establish fetal risk (106). In GDM, whether maternal hyperglycaemia is closely monitored and treated in the third trimester is based on the degree of hyperglycaemia as shown by an oral glucose tolerance test at 24-28 weeks gestation (10) In the future, this decision could be modified by non-glycaemic factors that impact fetal growth.

### **Patient-first, Mental Health, and Quality of Life Outcomes** (see Text Box 5)

Precision diabetes medicine holds the promise of reducing uncertainty by providing therapies that are more effective, less burdensome and with fewer adverse outcomes, which ultimately improve quality of life and reduce premature death. Of high relevance in this context is mental health (e.g., risk of distress and depression), yet little has been done to investigate how precision medicine might play a useful role.

Depression and anxiety are twice as common in people with diabetes compared to the general population, occurring in up to 20% of adult patients (107). Distress occurs in ~30% of people with diabetes (110), as a separate and related psychological symptom, reflecting the emotional and psychological burden that comes with diabetes and its complications, the life adjustments it requires, and anxiety about hypoglycemia or the impact on the fetus for gestational diabetes. Distress has been reported as more common in patients in secondary, rather than primary care, as well as in non-European ancestry populations. Depression is more common in lower- and middle-income countries, the location for ~75% of people with T2D (108). Both depression and distress in diabetes are more common in those who progress from oral agents to insulin therapy (109). The onset of complications with the

initiation of a more complex pattern of treatment is associated with increased rates of depression (109).

There are key points in the life-course of the person with diabetes when both rational and irrational fears are often elevated, typically coinciding with “events”, including:

- Increased medication dose
- Transition to insulin or other injectables or devices
- Emergence of complications or worsening of complications
- Following a severe hypoglycemic event
- Change in diabetes provider

In many cases, patient self-evaluations may be distorted at these times because the patient attributes blame for the disease to his/her self, the future feels uncertain and distress peaks. In the setting of precision diabetes medicine, providers should assess symptoms of diabetes distress, depression, anxiety, disordered eating, and cognitive capacities using appropriate standardized and validated tools at the initial visit, at periodic intervals, and when there is a change in disease, treatment, or life circumstance (110), information that, when combined with other data, are likely to improve the precision of clinical decision making.

Psychological counseling can help patients understand and manage their emotional reactions to major events by developing a more optimistic outlook and a more realistic, modulated and adaptive emotional reactions (111). Precision medicine may be used in the future to help predict the frequency and extent of emotional crises. As a result, precision diabetes medicine may lessen the patient burden, objectivize their disease, and provide targets for behavioral and point-of-care interventions at critical moments in the clinical care cycle. Effective and tailored education and professional counselling will be necessary to mitigate the risk that a clearer prognosis may raise anxiety about the future for some patients.

### **Equity in Precision Diabetes Medicine**

The experience with monogenic diabetes has shown that there is a large degree of regional, national, and international variation in how, and how often, these cases are diagnosed (1; 112; 113). This variation is, in part, due to differences in access to general medical care and treatments, access to relevant healthcare professionals with the necessary education, training, and experience, and access to laboratories with the necessary experience, assays and standards (114). A precision approach to diabetes care will require that the relevant

laboratory methods and assays are carefully standardized and comparable. Standardized assays include:

- T1D-associated autoantibodies
- C-peptide
- Clinical genetic/genomic assays
- Decision-support interpretation

A challenge is that the frequency of various diabetes phenotypes and risk genotypes may vary by regions of the world and between ethnicities within a region. For example, T2D often manifests very differently in Native Americans than in people of European ancestry, with Native Americans tending to develop diabetes at a much younger age and experience loss of beta cell function earlier in the life-course of the disease (115). Recent insights following the ADA Precision Diabetes Medicine meeting in Madrid (October 2019) confirm that case-based interactive learning is an excellent way to support this type of postgraduate education for clinicians at all levels of training.

### **The Road to Implementation**

Advances in science allow for generation of large-scale biologic and physiologic data that can be harnessed for precision diagnostic (Figure 2), therapeutic (Figure 3) and prognostic (Figure 4) purposes. Strategies to integrate and analyze such data should provide increased understanding of the pathophysiology of diabetes and its apparent heterogeneity. Programs are needed to train, foster and retain individuals with biologic and data science expertise who will contribute to precision diabetes medicine efforts. Furthermore, clinicians, scientists, and regulators must collaborate to develop standards and safeguards for protecting the accumulated 'precise' data, which in some instances may lead to unintended and sensitive revelations, on individuals in a secure manner across populations and across countries.

Inclusion of understudied populations are needed within the cohorts studied in precision diabetes medicine research for development of precision diagnostics and therapeutics. There are known regional and country-specific dietary habits and food sources. While a Mediterranean diet rich in olive oil and nuts has shown to be efficacious in preventing diabetes (116; 117), it is not safe to assume that incorporating this diet will be as efficacious or well-adopted in other countries. While lifestyle modification is efficacious for preventing diabetes, it is difficult to sustain, and harnessing the expertise of behavioral and social scientists to study how individuals from different backgrounds and communities can best sustain lifestyle change behaviors is needed.

Diagnosis of diabetes may vary in different populations based on subtype frequency or genetic differences. Diagnostic studies should be conducted in different populations to obtain necessary data to tailor screening criteria based upon the prevalence of diabetes subtypes. In addition, a series of personal and societal barriers exist in the implementation of precision prevention across geographic regions and countries.

The communication strategy used by the interventionalist and the patient's perception of risk may be important factors contributing to the successful implementation of precision diabetes medicine. While there are clear possibilities for the use of genetics in the precision prevention of T2D, focusing on other non-genetic biomarkers will enhance precision prevention strategies. A series of challenges will exist in T1D, particularly as there is currently no intervention in the disease process, while there is an accepted treatment (i.e., insulin). Yet, appropriate lifestyle change (e.g., diet, exercise) to reduce the risk of complications remains difficult to achieve.

Precision prevention may aid the adoption of behavioral modification through individual goal-based behavioral change, a process that is currently both labor-intensive and costly. The Food4Me Study, a European initiative focused on personalized nutrition, suggests that including genetic feedback into online nutritional guidance may improve dietary habits more than conventional diet advice (118). Despite wide-spread dissemination of more pragmatic programs and payor coverage, evaluation of uptake and engagement in various programs and tailoring of them, requires routine and rigorous administration.

Precision diabetes medicine will require careful evaluation. Leveraging large-scale, real-world evidence and federated clinical trial data using unbiased approaches may facilitate the identification of relevant subgroups or unique characteristics with differential prognosis or therapeutic response. Real-world evidence may also provide the benefit of including patient subgroups that have been excluded from trials to better understand efficacy and risk for these patients. Cost-effectiveness studies of importance to payors to support screening practices or therapies for subgroups may require simulations under different assumptions and regional conditions. Discussions with various regulatory agencies will be needed to determine the level of evidence needed for regulatory approval and adoption of precision diagnostics and therapeutics.

Diagnoses and therapeutic devices that incorporate multilevel data that may be analysed using artificial intelligence methods (e.g., machine learning) will require strategies to ensure that algorithms are robust and reproducible, requiring consensus for regulatory bodies to deem a surrogate outcome as "acceptable". Similar discussions are needed to determine

acceptable outcomes of relevance to patients (i.e., 'patient-reported outcomes'). There are a growing number of biobanks linked with clinical information in health care systems, as well as efforts to combine these biobanks. The amount and diversity of data required for understanding and predicting individual patients' risks and therapeutic responses is likely to overwhelm the general provider caring for a patient with diabetes unless the data is carefully articulated. Thus, development of tools and strategies to synthesize such data and to facilitate shared decision making will be needed to translate evidence for precision diabetes medicine into individualized diabetes care, accounting for patient preferences and behaviors, health literacy and socioeconomic considerations. Pragmatic studies of decision support systems utilizing rich information in these health care systems, particularly those with biobank linked electronic health care records, are needed to guide implementation of precision diabetes medicine into clinical practice and to generate the much needed cost-efficacy data for broader adoption.

There is an enormous amount of work needed to move the field of precision diabetes medicine forward. The critical partnerships must be established between the scientific community, patients, health care systems, providers, payors, industry and regulatory bodies involved in the development, evaluation, approval, adoption and implementation of precision diagnostics, monitoring and therapeutics that are deemed acceptable for safe, efficacious and cost-effective use in precision diabetes care.

### **Building Partnerships**

If precision medicine is the future of diabetes care, it will represent a clear progression from current and established clinical practice, owing mainly to the possibilities to characterize the patient, the disease and the disease processes in greater detail and with higher certainty. Making the most of the opportunities offered by precision diabetes medicine will require many different stakeholders to form highly effective partnerships. Without networks of partnerships that span academic, corporate, payors, regulators, and medical and public interest groups with shared understanding and vision (Figure 5), precision diabetes medicine is destined to fail.

#### *People with Diabetes*

People with diabetes are the most important stakeholders. In Western countries, between 1:10 and 1:20 people suffer from diabetes, while in other parts of the world, diabetes is more prevalent (1:3 in some middle-eastern populations (119), and 1:2 in some Native American tribes (115)). The precision approach to diabetes will require effective patient-facing, bi-



directional communication strategies that explain what precision medicine is and how it works. Engagement with local patient groups and patient organizations through in-person and online forums will be essential. Although patient education will be important, it will be equally important to learn from patients, so that precision diabetes medicine is not only tailored to a patient's biology, but also to the socioeconomic and psychosocial characteristics that impact therapeutic interventions across the lifespan and across societies. People with diabetes should be invited to contribute to postgraduate educational programs for clinicians and to have a central role in discussions with politicians, regulators, and payors.

### *Regulatory Agencies*

The transition from current diabetes clinical practice to a precision medicine approach will have important implications for the development, prescription, and regulation of diagnostics and therapeutics. Current evidence evaluation processes are becoming impracticable. As a result, regulators are using alternatives, including simulation models, to inform efficacy and safety without incurring the cost and complexity of long-term outcomes trials ([www.fda.gov/science-research/about-science-research-fda/how-simulation-can-transform-regulatory-pathways](http://www.fda.gov/science-research/about-science-research-fda/how-simulation-can-transform-regulatory-pathways)). The cost-effectiveness of new drugs developed in the age of precision diabetes medicine is uncertain, as the efficacy of those drugs may increase but in smaller target groups. Recognizing these challenges, the FDA and the European Medicines Agency (EMA) have initiated discussions relating to standards for evidence and the design of future clinical trials for precision diabetes medicine (120). Involvement of regulators at the earliest stages of the precision diabetes medicine workflow will be critical to the successful implementation of the precision approach.

### *Payors*

Payment for medical care related to diabetes varies greatly, including between regions within countries. Often, costs for diabetes are hidden in other areas of medical care, largely from the complexity of treatment and those costs associated with complications of diabetes. Fragmentation of sites of delivery for diabetes care and its costs directly impact payment policies. Costs need to be directly addressed and involve payors, even if the current cost-effectiveness of precision diabetes care is largely undetermined. Nevertheless, for precision approaches to prevention, diagnosis and treatment of diabetes to be acceptable in most clinical settings requires that they are cost-effective. There is evidence in the case of monogenic diabetes that this is true (121). The delay, or prevention, of complications (the major contributor to diabetes costs) through precision diabetes medicine may be the strongest driver for adoption.

## *Industry*

Diabetes technology, including the development of wearable devices for glucose monitoring and for regulating insulin infusions (i.e., the artificial pancreas), has developed rapidly and is an example of widespread personalized diabetes medicine. In current clinical practice, however, technology and pharmaceutical implementation remains at a pre-precision level, as guidelines remain fairly generic. Industry and other major stakeholders are focused on developing precision diabetes medicine approaches. The European Federation of Pharmaceutical Industries and Associations (EFPIA) Diabetes Platform, in which six leading pharmaceutical companies are developing shared policy goals focused on improving diabetes clinical outcomes, has initiated multiple projects with strong precision diabetes medicine agendas. These projects reside under the banner of the Innovative Medicines Initiative (IMI), a joint undertaking between public and private sector scientists organized by the European Commission. Many other public-private partnerships focused on precision diabetes medicine are underway (122).

## *Government and Foundation Funders*

Support for diabetes research funding has struggled as its priority has fallen amongst the general public and some political decision makers. Despite the enormous burden on individuals and society at large, diabetes has struggled for political attention in western countries, where cancer and cardiovascular disease rank consistently higher than diabetes on the public agenda. An important contributor to this lack of world-wide political engagement includes differences in research support, economies and priorities of governments, and internal societal factors and needs. Insufficient resources for research are a concern, given the public health impact and the influence of diabetes complications on health care cost. For precision diabetes medicine to meaningfully improve the lives of patients, it will be necessary to build highly-effective networks of key stakeholders, such that common agendas are agreed and funding for research and implementation is made available. This in turn requires that the evidence justifying a precision diabetes medicine approach is clearly articulated to all major decision makers, including funders.

## *Clinicians and Professional Organizations*

Medical care for the person with diabetes involves a wide-spectrum of health care providers, from tertiary and secondary specialists, general internists, primary care doctors, nurses, dietitians, podiatrists, pharmacists, and other paramedical professionals. Several organizations are engaged in the PMDI (ADA, EASD, NIDDK) and representatives of

professional bodies in Asia, Africa and elsewhere are being engaged by the PMDI to ensure global impact. As outlined earlier in this report, collaborative opportunities are being enhanced through the development of new postgraduate educational modules, inclusion of precision medicine symposia at sponsored scientific meetings and conferences, and the development of a global research network on precision diabetes medicine. Tailoring these modules and educational content to different professional and cultural settings is ideally suited to these partner organizations.

### *General Public*

The enormous burden that diabetes places on many health care systems is usually shouldered by the general public, owing to the high costs of treating the disease and loss of public revenue through decreased productivity. As some subtypes of diabetes can, in principle, be prevented, intervention prior to disease onset has great appeal. As the prevalence of diabetes is rising rapidly, the current public health strategies appear to be failing. The effective implementation of precision prevention will require that the general public has the willingness to embrace the approach and that those in greatest need can access precision prevention programs. In comparison to other medical conditions, diabetes is often perceived by the public as less serious and sympathetic than cancer and cardiovascular disease (123), as well as being more stigmatized with obesity. Diabetes messaging for the general public can be modeled on precision oncology, for which public advocacy and engagement have been successful. In order to reach those who most need of precision diabetes medicine, advocates will need to effectively utilize social media as well as traditional media to communicate its strengths and weaknesses and its risks and benefits.

### **Summary and Future Perspectives**

Precision diabetes medicine has already found a firm foothold in the diagnosis and treatment of monogenic diabetes, while the application of precision medicine to other types of diabetes is at this time aspirational rather than standard of care. Nevertheless, there are clear avenues along which precision medicine may enhance diabetes diagnosis and therapy. Future precision diabetes medicine approaches are likely to include diagnostic algorithms for defining diabetes subtypes; such algorithms should have most of the characteristics of an ideal test and necessary decision support infrastructure if they are to be widely adopted. Based upon limited ideal tests and uncertainty in etiology, more research is needed in T1D and T2D in order to define subtypes and decide the best interventional and therapeutic approaches. The ability to integrate the diagnosis of monogenic diabetes into routine clinical care is one example where diagnostics are essential and meet many of the characteristics of

the ideal test. Once defined as monogenic diabetes, there is a clear pathway for clinical course and treatment, even though considerable work remains on diagnostics. Other areas of precision diabetes medicine will need to develop therapeutics and prognosis predication in parallel with diagnostic approaches, coupled with evidence of clinical utility and a demonstrable benefit in the diagnosis and treatment of the patient. Current diagnostic strategies are suboptimal for defining even the major diabetes categories.

Despite an excellent diagnostic paradigm, there are no known avenues for prevention in monogenic diabetes. Similarly, there are no known ways to prevent T1D, although careful monitoring in high-risk individuals prevents complications at onset. Thus, precision prevention in T1D is likely to involve stratification of at-risk populations within which innovative monitoring technologies will be applied. In T2D, lifestyle factors play a dominant role, yet standardized preventive interventions have relatively low efficacy. Although both lifestyle and pharmaceutical interventions can delay onset of diabetes in people at high-risk (e.g., those with obesity and impaired glucose tolerance), completely preventing diabetes has proven challenging. Nevertheless, because lifestyle is paramount and there are such variable responses to lifestyle interventions, opportunities for precision prevention of T2D are perhaps most apparent, with some studies showing that tailoring diet to an individual's biological characteristics can help minimize postprandial glucose excursions (84). The scope and potential for precision treatment in diabetes is vast, yet deep understanding is lacking. For drug outcomes, there is a pressing need to move beyond early glycemic response and examine variation in response in terms of cardiovascular outcomes, mortality and other patient-centered outcomes, especially for the newer agents such as SGLT2i and GLP-1RA. It will be imperative to determine when and how the application of therapeutics in precision diabetes medicine improves outcomes in a cost-effective fashion.

There are many important stakeholders whose engagement will be necessary for the implementation of precision diabetes medicine to succeed (Figure 5). Progress in translating advances in biology and technology will be governed by the identification, accurate measurement and scalable deployment of agents for diagnosis and therapy, so broad stakeholder engagement is essential. It is crucial that precision approaches are available to the full diversity of human populations and societal contexts, such that precision diabetes medicine does not widen health disparity but achieves the greatest benefits to all individuals and society as a whole. Highly functional partnerships with patient representatives and public organizations will be required to reap the benefits of precision diabetes medicine.

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## **Potential conflicts of interest**

WKC is on the scientific advisory board of the Regeneron Genetics Center. JCF has received a speaking honorarium from Novo Nordisk and consulting fees from Janssen Pharmaceuticals. MMcC has in the past 3 years served on advisory panels for Pfizer, NovoNordisk and Zoe Global Ltd, has received honoraria from Merck, Pfizer, Novo Nordisk and Eli Lilly, and research funding from Abbvie, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk A/S, Pfizer, Roche, Sanofi Aventis, Servier, and Takeda. As of June 2019, MMcC is an employee of Genentech, and a holder of Roche stock. ERP has received research funding from Boehringer Ingelheim, Eli Lilly, Janssen, Novo Nordisk A/S, Sanofi Aventis and Servier and honoraria from Eli Lilly. LP has received research funding from Janssen and Provention Bio. PWF has received research funding from Boehringer Ingelheim, Eli Lilly, Janssen, Novo Nordisk A/S, Sanofi Aventis and Servier, received consulting fees from Eli Lilly, Novo Nordisk and Zoe Global Ltd and has stock options in Zoe Global Ltd.

## Text boxes

### Text box 1: DEFINITIONS.

- Definition. **Precision diagnosis** involves refining the characterization of the diabetes diagnosis for therapeutic optimization or to improve prognostic clarity using information about a person's unique biology, environment and/or context.
  - *Precision diagnostics* may involve subclassifying the diagnosis into subtypes, such as is the case in MODY, or utilizing probabilistic algorithms that help refine a diagnosis without categorization.
  - Careful diagnosis is often necessary for successful precision therapy, whether for prevention or treatment. This is true where subgroup(s) of the population must be defined, within which targeted interventions will be applied and also where one seeks to determine whether progression toward disease has been abated.
  - *Precision diagnosis* can be conceptualized as a pathway, rather than a single step, that moves through stages. The diagnostic stages include i) an evaluation of prevalence based on epidemiology, including age, or age at diagnosis of diabetes, sex and ancestry; ii) probability based on clinical features; and iii) diagnostic tests that are interpreted in the light of i) and ii). A diagnosis in precision medicine is a probability-based decision, typically made at a specific point in the natural history of a disease, and neither an absolute truth nor a permanent state.
- 
- Definition. **Precision therapeutics** involves tailoring medical approaches using information about a person's unique biology, environment and/or context for the purposes of preventing or treating disease (see *precision prevention* and *precision treatment*).
- 
- Definition. **Precision prevention** includes using information about a person's unique biology, environment and/or context to determine their likely responses to health interventions and risk factors and/or to monitor progression toward disease.
  - *Precision prevention* should optimize the prescription of health enhancing interventions and/or minimize exposure to specific risk factors for that individual. Precision prevention may also involve monitoring of health markers or behaviors in people at high risk of disease, to facilitate targeted prophylactic interventions.

<ul style="list-style-type: none"> <li>○ Definition. <b>Precision treatment</b> involves using information about a person's unique biology, environment and/or context to guide the choice of an efficacious therapy to achieve the desired therapeutic goal or outcome, while reducing unnecessary side effects.</li> <li>○ Today, the objective of precision therapy is to maximize the probability that the best treatment of all those available is selected for a given patient. It is possible that in the future, precision diabetes medicines will be designed according to the biological features of specific patient subgroups, rather than for the patient population as a whole.</li> </ul>
<ul style="list-style-type: none"> <li>○ Definition. <b>Precision prognostics</b> focuses on improving the precision and accuracy with which a patient's disease-related outcomes are predicted using information about their unique biology, environment and/or context.</li> <li>○ The focus of <i>precision prognostics</i> includes predicting the risk and severity of diabetes complications, patient-centered outcomes, and/or early mortality</li> </ul>
<ul style="list-style-type: none"> <li>○ Definition. <b>Precision monitoring</b> may include the detailed assessment of biological markers (e.g., continuous glucose monitoring), behaviours (e.g., physical activity), diet, sleep, and psychophysiological stress.</li> <li>○ <i>Precision monitoring</i> can be achieved using digital apps, cutaneous or subcutaneous sensors, ingestible sensors, blood assays etc.</li> <li>○ The intelligent processing, integration and interpretation of the data obtained through <i>precision monitoring</i> are key determinants of success</li> <li>○ Precision monitoring may be valuable for precision prevention (e.g., in T1D), precision diagnostics (e.g., where diagnoses are based on time-varying characteristics) and precision prognostics (e.g., where disease trajectories are informative of the development of key outcomes).</li> </ul>

**Text box 2: PRECISION DIAGNOSTICS: BACKGROUND, BARRIERS TO IMPLEMENTATION AND RESEARCH GAPS**

<ul style="list-style-type: none"> <li>○ Type 1 Diabetes. Best diagnostic results depend on integrating all diagnostic modalities, not by relying on prior prevalence, clinical features, or test results in isolation. The age at which the initial islet autoantibody appears and the type of autoantibody (e.g., which of the four primary antibodies among ICA512, Ins, GAD, ZnT8) may be important in defining etiological subtypes of T1D. The majority of the genetic risk of T1D is now known, and the sensitivity and specificity of a T1D polygenic score (T1D-PS) exceed 80%. Despite this, a high T1D-PS will have low positive predictive value in patient populations where the overall prevalence of</li> </ul>
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T1D is low, such as those aged >50 years when diabetes is diagnosed. It will likely prove most useful when the T1D-PS is combined with clinical features and islet autoantibodies. At present, there is no immune-based test sufficiently reproducible and robust that it can be used diagnostically

- Type 2 Diabetes. Categories based on cluster analysis at diagnosis can provide insights into likely progression, risk of complications, and treatment response, which offer an exciting approach to subclassification of T2D. At this time, the available genetic data for T2D does not have sufficient predictive accuracy to replace existing delineative approaches. Although the subcategorization of T2D using genetic data is informative of the etiological processes that underlie the disease, the methods described so far (77; 78) are not intended to be used to subclassify a T2D diagnosis nor are the existing genetic data sufficient for this purpose for the majority of patients with T2D. Treatment response and progression can be predicted from clinical features (36). An advantage of using clinical features for diagnosis of T2D is that they are widely available and easily obtained (e.g., sex, BMI, HbA<sub>1c</sub>); however, a potential limitation is that they may be time varying.

- Barriers to implementation. One of several important translational barriers facing the proposed clustering approach for T1D and T2D is that a fasting C-peptide is required at the time of diagnosis, which is not routinely performed in clinical practice and the reliability of C-peptide assays vary considerably between labs (35). Another limitation is that the biomarkers used to define these clusters change in time depending on the disease course or its treatment, such that this approach can only be applied to newly diagnosed cases, but not to individuals years before disease onset or the many millions of people with long-standing diabetes worldwide. Moreover, because the current approaches for clustering in T2D require continuously distributed data to be categorized, which typically results in loss of power, these methods do not yield good predictive accuracy, a major expectation in precision medicine, but this may change as the approach is refined

- Research gaps. Based upon limited ideal tests and uncertainty in etiology, more research is needed in T1D and T2D in order to define subtypes and decide the best interventional and therapeutic approaches.



**Text box 3: PRECISION PREVENTION: BACKGROUND, BARRIERS TO IMPLEMENTATION AND RESEARCH GAPS**

- Type 1 Diabetes. In T1D, precision prevention mainly involves the optimization of monitoring methods, thereby facilitating early detection and treatment. The reasons most prevention trials in T1D have not been effective may include failure to consider the individual's unique T1D risk profile (e.g., genetic susceptibility) and their unique response to the preventive agent (immune therapy or dietary intervention). Without considering the unique genetic profiles of children, interventions aimed at preventing type 1 diabetes (e.g., dietary intervention or immunotherapy) may be unlikely to succeed. Thus, precision prevention in T1D is likely to involve stratification of at-risk populations and innovative monitoring technologies.
- Type 2 Diabetes. T2D has many avenues for prevention and thus the possibilities for precision approaches, possibly through tailoring of diet, are broad. To date, prevention of type 2 diabetes has focused on people with prediabetes. To be cost-effective, it is likely necessary to stratify the prediabetic population such that only in those with other relevant risk factors be the focus of preventative interventions. Relevant risk factors may include lifestyle, socioeconomic status, family history, ethnicity and/or certain biomarker profiles, including genetics).
- Barriers to implementation. The effective implementation of precision prevention will require that appropriate technologies are available, the general public has the willingness to embrace the approach, and that those in greatest need can access precision prevention programs. A communication plan used by the interventionalist and the patient's perception of risk should be a focus of precision prevention strategies.
- Research gaps. There are critical areas of research required for implementation of precision prevention in diabetes, including determining for whom online care is more effective than in-person care, the types of staff delivering the lifestyle modification programs, the impact of group and/or individual interaction, and the frequency of such sessions. There is also uncertainty about how best to provide and sustain lifestyle modification. Additionally, emphasis should be placed on identifying profiles that indicate likely response to specific lifestyle interventions (focusing on specific diets, exercise programs and other behavioural factors) and sensitivity to risk factors (such as sleep disturbance, stress,

depression, poor diet, sedentary behaviors, smoking, certain drugs and obesity).

**Text box 4: PRECISION MEDICINE APPROACHES TO TREAT DIABETES:  
BACKGROUND, BARRIERS TO IMPLEMENTATION AND RESEARCH GAPS**

- Type 1 diabetes. In T1D, the only existing therapy is insulin. Developments in long-acting and glucose sensitive insulins are improving the health and wellbeing of people with T1D, as are technological advances in the artificial pancreas.
  - Type 2 diabetes. It has long been recognized that T2D is heterogeneous in its etiology, clinical presentation and pathogenesis. Yet, traditionally, trials of therapeutic intervention do not recognize this variation.
  - With increasing efforts to map patients with T2D in etiological space using clinical and molecular phenotype, physiology and genetics it is likely that this increasingly granular view of T2D will lead to increasing precision therapeutic paradigms requiring evaluation and potential implementation. Genetic variation not only can capture etiological variation (i.e., genetic variants associated with diabetes risk) but also variation in drug pharmacokinetics (absorption, distribution, metabolism, excretion – ADME) and in drug action (pharmacodynamics).
  - In contrast, ‘true’ T2D is a common complex disease characterized by thousands of etiological variants, each contributing to a small extent to diabetes risk. Thus, it remains uncertain that genetic variants will be identified that are highly predictive of drug outcomes in T2D, even if process-specific polygenic risk scores are derived (where all variants on an etiological pathway are combined to increase power).
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- Barriers to implementation. The current and growing burden of diabetes is not from western white populations but from other ethnic groups, in particular South and East Asians. Yet, these populations are under-represented in clinical trials and, in particular, in attempts to understand variation in drug outcomes.
  - Because the diabetes phenotype can vary markedly by ethnic group, it is likely that complications and drug outcomes will differ between populations.
  - Many of the approaches gaining traction in precision medicine generate massive datasets that are burdensome to store and require powerful computational servers for analysis.

- Undertaking appropriately designed clinical trials for precision treatments that meet the current expectations of regulatory authorities may be challenging, given the many subgroups within which treatments will need to be evaluated. Innovative clinical trials will likely be needed and real-world evidence will likely need to be part of the evaluation process.
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- Research gaps. For drug outcomes, there is a pressing need to move beyond early glycemic response and examine variation in response in terms of cardiovascular outcomes and mortality, especially of the newer agents such as SGLT2i and GLP-1RA, with focus on specific patient subgroups. Identifying predictive markers (especially genetic markers) of serious adverse events in patients treated with these drugs presents an additional area urgently in need of greater attention.
  - Need for better understanding of the pathophysiology of diabetes to inform on new therapeutic targets
  - Need to study broader populations/ethnic groups
  - Need for understanding outcomes of highest relevance to patients
  - Need for decision support tools to implement precision diabetes medicine in clinical practice
  - Need to demonstrate that approaches are cost-effective

**Text box 5: PRECISION MEDICINE APPROACHES TO LESSEN TREATMENT BURDEN AND IMPROVE QUALITY OF LIFE.**

- Diagnosis. A more specific diagnosis has the potential to reduce uncertainty and manage future expectations about disease course. This is clearly the case for some monogenic forms of diabetes, where diagnosis is nearly certain, given its strong genetic indication, and the specific treatment is coupled to the subcategory (genetic subtype) of disease. Emerging knowledge regarding subtypes of T2D has the potential to classify individuals with diabetes with risk for progression to complications.
- 
- Misdiagnosis. Inaccurate classification of the type of diabetes, either from lack of precision or inadequate clinical attention to detail at the time of presentation, can have long-lasting, adverse effects on mental health and quality of life. In the pediatric and younger adult population, the risk of misclassification is increasing as both “true” T1D and “true” T2D classifications are confused through the growing obesity epidemic in youth (T2D) and older onset ages (T1D). In addition, monogenic variants of

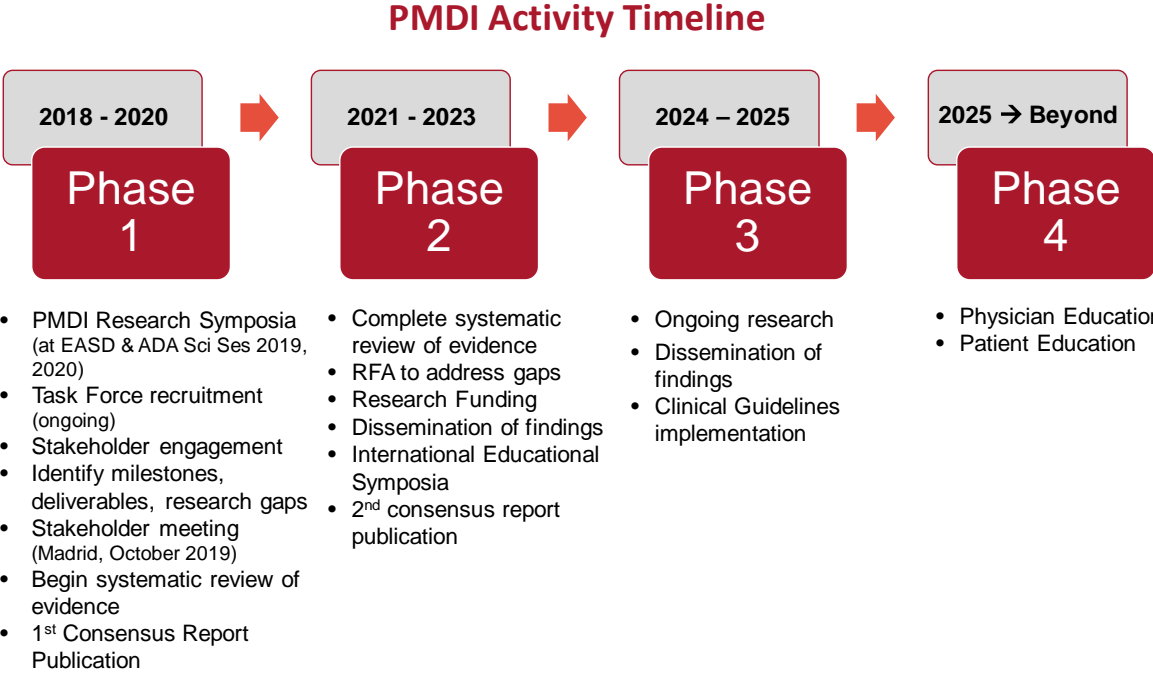
diabetes can be misdiagnosed as either T1D or T2D. A precision approach to diagnosis with appropriate standardized laboratory support and increased research to obtain novel biomarkers of disease has the potential to solve this problem.

- Complications. Worry about complications is an issue for all people with diabetes. Currently, having diabetes (either T1D or T2D) is given a label of being unequivocally at risk of reduced lifespan, amputation, kidney failure, and blindness. A more precise diagnosis, prognosis, and strategy to predict and prevent complications has the potential to greatly reduce disease burden, distress, and improve quality of life. Nevertheless, there is also a risk that more precise prognostification may cause distress if the options for successful intervention are limited or incompatible with the patient's needs or desires.

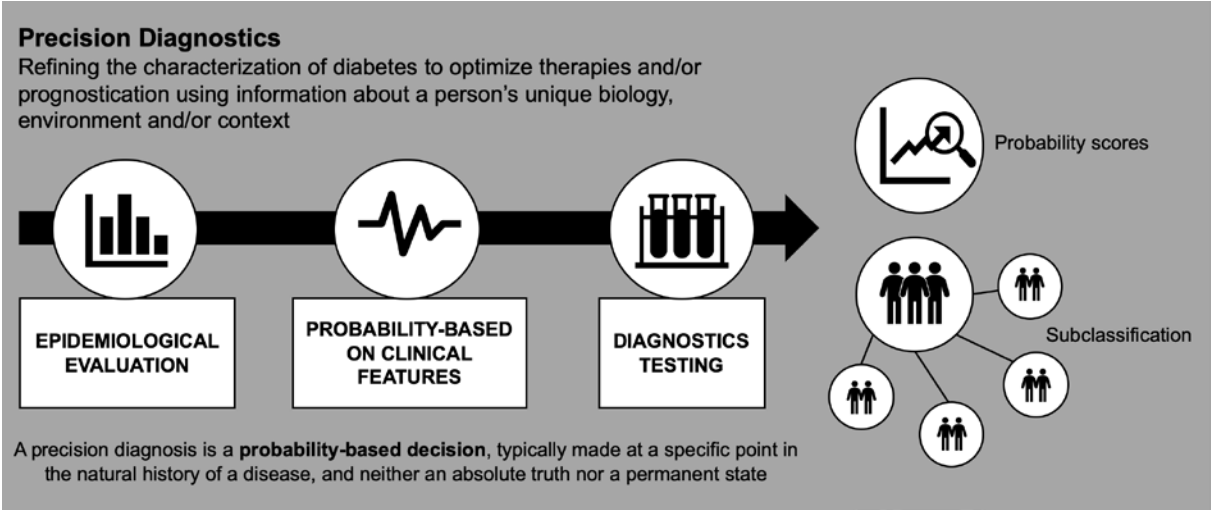
- Stigmatization. A major burden for people with diabetes is that the disease is often considered the fault of the patient. This is particularly true for T2D, as it is often labelled as 'just' a lifestyle disease. Clinical care of those with diabetes often results in a singular approach to treatment, regardless of their specific needs, life situation, and other conditions. A clinical process that makes diagnosis more precise and includes the patient-oriented evaluation and response to needs has the potential to lessen stigma and reduce associated distress.

**Figures**

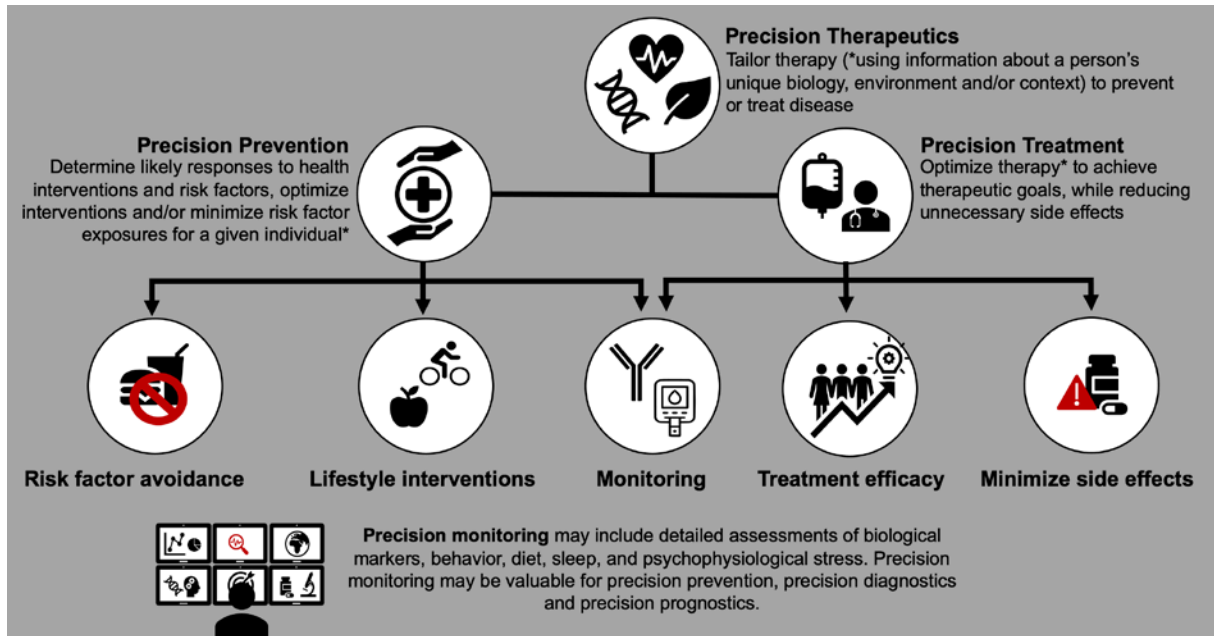
**Figure 1 . Precision Medicine in Diabetes Initiative (PMDI) Activities**



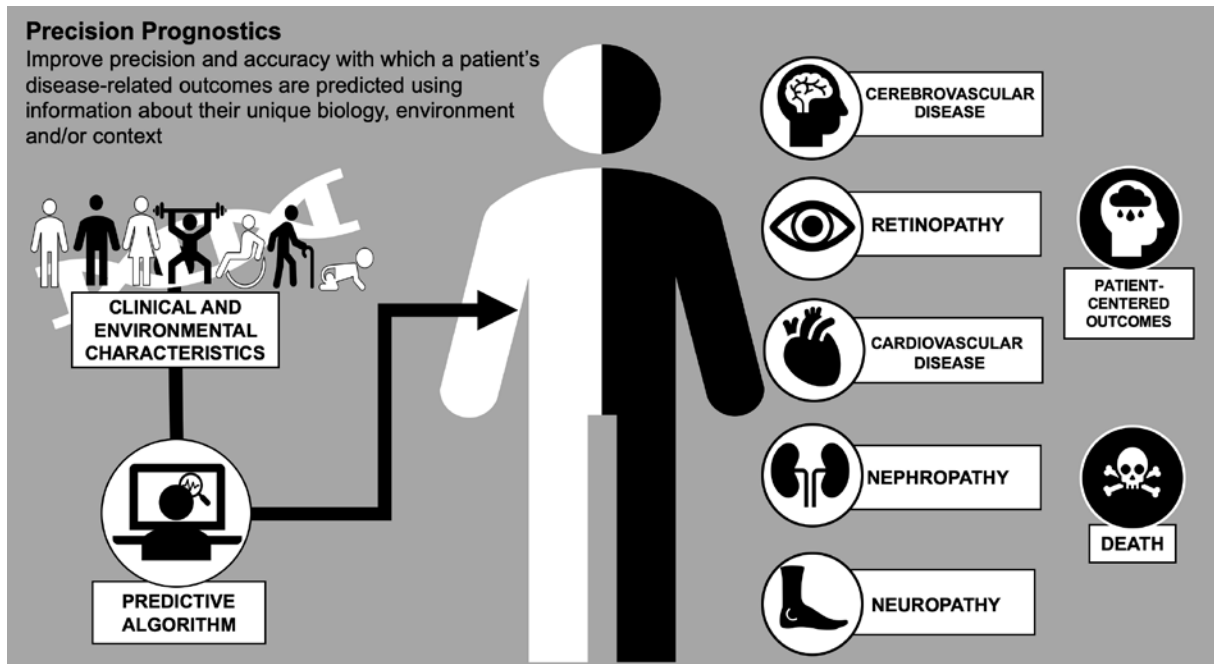
**Figure 2 – Precision Diagnostics**



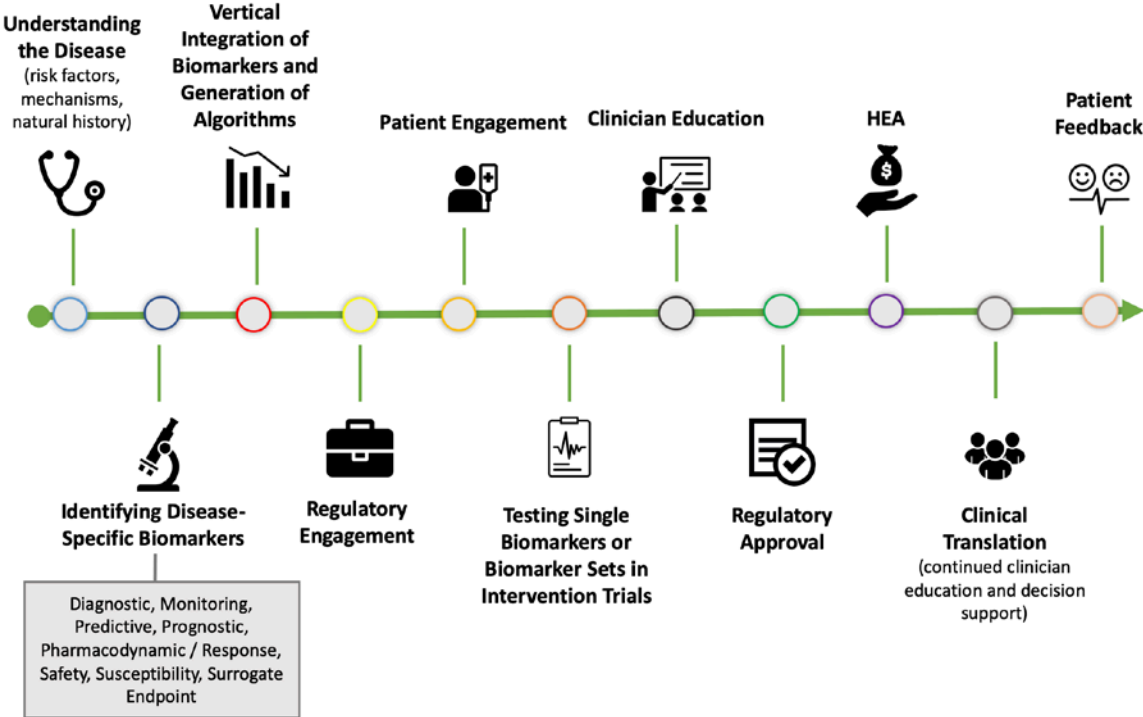
**Figure 3 – Precision Therapeutics**



**Figure 4 – Precision Prognostics**



**Figure 5 – The Path to Precision Diabetes Medicine** (From: Fitipaldi et al. *Diabetes*, 2018)



## References

1. Hattersley AT, Patel KA. Precision diabetes: learning from monogenic diabetes. *Diabetologia* 2017;60:769-777
2. De Franco E, Flanagan SE, Houghton JA, Lango Allen H, Mackay DJ, Temple IK, Ellard S, Hattersley AT. The effect of early, comprehensive genomic testing on clinical care in neonatal diabetes: an international cohort study. *Lancet* 2015;386:957-963
3. Oram RA, Patel K, Hill A, Shields B, McDonald TJ, Jones A, Hattersley AT, Weedon MN. A Type 1 Diabetes Genetic Risk Score Can Aid Discrimination Between Type 1 and Type 2 Diabetes in Young Adults. *Diabetes Care* 2016;39:337-344
4. Grubb AL, McDonald TJ, Rutters F, Donnelly LA, Hattersley AT, Oram RA, Palmer CNA, van der Heijden AA, Carr F, Elders PJM, Weedon MN, Sliker RC, Hart LM, Pearson ER, Shields BM, Jones AG. A Type 1 Diabetes Genetic Risk Score Can Identify Patients With GAD65 Autoantibody-Positive Type 2 Diabetes Who Rapidly Progress to Insulin Therapy. *Diabetes Care* 2019;42:208-214
5. Sharp SA, Rich SS, Wood AR, Jones SE, Beaumont RN, Harrison JW, Schneider DA, Locke JM, Tyrrell J, Weedon MN, Hagopian WA, Oram RA. Development and Standardization of an Improved Type 1 Diabetes Genetic Risk Score for Use in Newborn Screening and Incident Diagnosis. *Diabetes Care* 2019;42:200-207
6. Udler MS, McCarthy MI, Florez JC, Mahajan A. Genetic Risk Scores for Diabetes Diagnosis and Precision Medicine. *Endocr Rev* 2019;40:1500-1520
7. Dennis JM, Shields BM, Henley WE, Jones AG, Hattersley AT. Disease progression and treatment response in data-driven subgroups of type 2 diabetes compared with models based on simple clinical features: an analysis using clinical trial data. *Lancet Diabetes Endocrinol* 2019;7:442-451
8. Fleming GA, Petrie JR, Bergenstal RM, Holl RW, Peters AL, Heinemann L. Diabetes Digital App Technology: Benefits, Challenges, and Recommendations. A Consensus Report by the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) Diabetes Technology Working Group. *Diabetes Care* 2020;43:250-260
9. Fleming GA, Petrie JR, Bergenstal RM, Holl RW, Peters AL, Heinemann L. Diabetes digital app technology: benefits, challenges, and recommendations. A consensus report by the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) Diabetes Technology Working Group. *Diabetologia* 2020;63:229-241
10. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. *Diabetes Care* 2020;43:S14-s31
11. Lacy ME, Wellenius GA, Sumner AE, Correa A, Carnethon MR, Liem RI, Wilson JG, Sacks DB, Jacobs DR, Jr., Carson AP, Luo X, Gjelsvik A, Reiner AP, Naik RP, Liu S, Musani SK, Eaton CB, Wu WC. Association of Sickle Cell Trait With Hemoglobin A1c in African Americans. *Jama* 2017;317:507-515
12. Wheeler E, Leong A, Liu CT, Hivert MF, Strawbridge RJ, Podmore C, Li M, Yao J, Sim X, Hong J, Chu AY, Zhang W, Wang X, Chen P, Maruthur NM, Porneala BC, Sharp SJ, Jia Y, Kabagambe EK, Chang LC, Chen WM, Elks CE, Evans DS, Fan Q, Giulianini F, Go MJ, Hottenga JJ, Hu Y, Jackson AU, Kanoni S, Kim YJ, Kleber ME, Ladenvall C, Lecoecur C, Lim SH, Lu Y, Mahajan A, Marzi C, Nalls MA, Navarro P, Nolte IM, Rose LM, Rybin DV, Sanna S, Shi Y, Stram DO, Takeuchi F, Tan SP, van der Most PJ, Van Vliet-Ostaptchouk JV,



Wong A, Yengo L, Zhao W, Goel A, Martinez Larrad MT, Radke D, Salo P, Tanaka T, van Iperen EPA, Abecasis G, Afaq S, Alizadeh BZ, Bertoni AG, Bonnefond A, Bottcher Y, Bottinger EP, Campbell H, Carlson OD, Chen CH, Cho YS, Garvey WT, Gieger C, Goodarzi MO, Grallert H, Hamsten A, Hartman CA, Herder C, Hsiung CA, Huang J, Igase M, Isono M, Katsuya T, Khor CC, Kiess W, Kohara K, Kovacs P, Lee J, Lee WJ, Lehne B, Li H, Liu J, Lobbens S, Luan J, Lyssenko V, Meitinger T, Miki T, Miljkovic I, Moon S, Mulas A, Muller G, Muller-Nurasyid M, Nagaraja R, Nauck M, Pankow JS, Polasek O, Prokopenko I, Ramos PS, Rasmussen-Torvik L, Rathmann W, Rich SS, Robertson NR, Roden M, Roussel R, Rudan I, Scott RA, Scott WR, Sennblad B, Siscovick DS, Strauch K, Sun L, Swertz M, Tajuddin SM, Taylor KD, Teo YY, Tham YC, Tonjes A, Wareham NJ, Willemsen G, Wilsgaard T, Hingorani AD, Egan J, Ferrucci L, Hovingh GK, Jula A, Kivimaki M, Kumari M, Njolstad I, Palmer CNA, Serrano Rios M, Stumvoll M, Watkins H, Aung T, Bluher M, Boehnke M, Boomsma DI, Bornstein SR, Chambers JC, Chasman DI, Chen YI, Chen YT, Cheng CY, Cucca F, de Geus EJC, Deloukas P, Evans MK, Fornage M, Friedlander Y, Froguel P, Groop L, Gross MD, Harris TB, Hayward C, Heng CK, Ingelsson E, Kato N, Kim BJ, Koh WP, Kooner JS, Korner A, Kuh D, Kuusisto J, Laakso M, Lin X, Liu Y, Loos RJJ, Magnusson PKE, Marz W, McCarthy MI, Oldehinkel AJ, Ong KK, Pedersen NL, Pereira MA, Peters A, Ridker PM, Sabanayagam C, Sale M, Saleheen D, Saltevo J, Schwarz PE, Sheu WHH, Snieder H, Spector TD, Tabara Y, Tuomilehto J, van Dam RM, Wilson JG, Wilson JF, Wolffenbuttel BHR, Wong TY, Wu JY, Yuan JM, Zonderman AB, Soranzo N, Guo X, Roberts DJ, Florez JC, Sladek R, Dupuis J, Morris AP, Tai ES, Selvin E, Rotter JJ, Langenberg C, Barroso I, Meigs JB. Impact of common genetic determinants of Hemoglobin A1c on type 2 diabetes risk and diagnosis in ancestrally diverse populations: A transethnic genome-wide meta-analysis. *PLoS Med* 2017;14:e1002383

13. Thomas NJ, Jones SE, Weedon MN, Shields BM, Oram RA, Hattersley AT. Frequency and phenotype of type 1 diabetes in the first six decades of life: a cross-sectional, genetically stratified survival analysis from UK Biobank. *Lancet Diabetes Endocrinol* 2018;6:122-129

14. Thomas NJ, Lynam AL, Hill AV, Weedon MN, Shields BM, Oram RA, McDonald TJ, Hattersley AT, Jones AG. Type 1 diabetes defined by severe insulin deficiency occurs after 30 years of age and is commonly treated as type 2 diabetes. *Diabetologia* 2019;62:1167-1172

15. Gloyn AL, Pearson ER, Antcliff JF, Proks P, Bruining GJ, Slingerland AS, Howard N, Srinivasan S, Silva JM, Molnes J, Edghill EL, Frayling TM, Temple IK, Mackay D, Shield JP, Sumnik Z, van Rhijn A, Wales JK, Clark P, Gorman S, Aisenberg J, Ellard S, Njolstad PR, Ashcroft FM, Hattersley AT. Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. *N Engl J Med* 2004;350:1838-1849

16. Pearson ER, Flechtner I, Njolstad PR, Malecki MT, Flanagan SE, Larkin B, Ashcroft FM, Klimes I, Codner E, Iotova V, Slingerland AS, Shield J, Robert JJ, Holst JJ, Clark PM, Ellard S, Sovik O, Polak M, Hattersley AT. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. *N Engl J Med* 2006;355:467-477

17. Babenko AP, Polak M, Cave H, Busiah K, Czernichow P, Scharfmann R, Bryan J, Aguilar-Bryan L, Vaxillaire M, Froguel P. Activating mutations in the ABCC8 gene in neonatal diabetes mellitus. *N Engl J Med* 2006;355:456-466

18. Steele AM, Shields BM, Wensley KJ, Colclough K, Ellard S, Hattersley AT. Prevalence of vascular complications among patients with glucokinase mutations and prolonged, mild hyperglycemia. *Jama* 2014;311:279-286

19. Stride A, Shields B, Gill-Carey O, Chakera AJ, Colclough K, Ellard S, Hattersley AT. Cross-sectional and longitudinal studies suggest pharmacological treatment used in patients with glucokinase mutations does not alter glycaemia. *Diabetologia* 2014;57:54-56
  20. Pearson ER, Starkey BJ, Powell RJ, Gribble FM, Clark PM, Hattersley AT. Genetic cause of hyperglycaemia and response to treatment in diabetes. *Lancet* 2003;362:1275-1281
  21. Pearson ER, Pruhova S, Tack CJ, Johansen A, Castleden HA, Lumb PJ, Wierzbicki AS, Clark PM, Lebl J, Pedersen O, Ellard S, Hansen T, Hattersley AT. Molecular genetics and phenotypic characteristics of MODY caused by hepatocyte nuclear factor 4alpha mutations in a large European collection. *Diabetologia* 2005;48:878-885
  22. Bowman P, Flanagan SE, Edghill EL, Damhuis A, Shepherd MH, Paisey R, Hattersley AT, Ellard S. Heterozygous ABCC8 mutations are a cause of MODY. *Diabetologia* 2012;55:123-127
  23. Shields BM, McDonald TJ, Ellard S, Campbell MJ, Hyde C, Hattersley AT. The development and validation of a clinical prediction model to determine the probability of MODY in patients with young-onset diabetes. *Diabetologia* 2012;55:1265-1272
  24. Carlsson A, Shepherd M, Ellard S, Weedon M, Lernmark A, Forsander G, Colclough K, Brahimi Q, Valtonen-Andre C, Ivarsson SA, Elding Larsson H, Samuelsson U, Ortvist E, Groop L, Ludvigsson J, Marcus C, Hattersley AT. Absence of Islet Autoantibodies and Modestly Raised Glucose Values at Diabetes Diagnosis Should Lead to Testing for MODY: Lessons From a 5-Year Pediatric Swedish National Cohort Study. *Diabetes Care* 2020;43:82-89
  25. Ellard S, Colclough K, Patel KA, Hattersley AT. Prediction algorithms: pitfalls in interpreting genetic variants of autosomal dominant monogenic diabetes. *J Clin Invest* 2020;130:14-16
  26. Clissold RL, Hamilton AJ, Hattersley AT, Ellard S, Bingham C. HNF1B-associated renal and extra-renal disease-an expanding clinical spectrum. *Nat Rev Nephrol* 2015;11:102-112
  27. Tranebjaerg L, Barrett T, Rendtorff ND. WFS1-Related Disorders. In *GeneReviews((R))* Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, Eds. Seattle (WA), University of Washington, Seattle
- University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved., 1993
28. Murphy R, Turnbull DM, Walker M, Hattersley AT. Clinical features, diagnosis and management of maternally inherited diabetes and deafness (MIDD) associated with the 3243A>G mitochondrial point mutation. *Diabet Med* 2008;25:383-399
  29. Tuomi T, Groop LC, Zimmet PZ, Rowley MJ, Knowles W, Mackay IR. Antibodies to glutamic acid decarboxylase reveal latent autoimmune diabetes mellitus in adults with a non-insulin-dependent onset of disease. *Diabetes* 1993;42:359-362
  30. Brophy S, Yderstraede K, Mauricio D, Hunter S, Hawa M, Pozzilli P, Schernthaner G, Schloot N, Buzzetti R, Davies H, Leslie D, Williams R. Time to insulin initiation cannot be used in defining latent autoimmune diabetes in adults. *Diabetes Care* 2008;31:439-441
  31. Hawa MI, Kolb H, Schloot N, Beyan H, Paschou SA, Buzzetti R, Mauricio D, De Leiva A, Yderstraede K, Beck-Neilsen H, Tuomilehto J, Sarti C, Thivolet C, Hadden D, Hunter S, Schernthaner G, Scherbaum WA, Williams R, Brophy S, Pozzilli P, Leslie RD. Adult-onset autoimmune diabetes in Europe is prevalent with a broad clinical phenotype: Action LADA 7. *Diabetes Care* 2013;36:908-913

32. Battaglia M, Ahmed S, Anderson MS, Atkinson MA, Becker D, Bingley PJ, Bosi E, Brusko TM, DiMeglio LA, Evans-Molina C, Gitelman SE, Greenbaum CJ, Gottlieb PA, Herold KC, Hessner MJ, Knip M, Jacobsen L, Krischer JP, Long SA, Lundgren M, McKinney EF, Morgan NG, Oram RA, Pastinen T, Peters MC, Petrelli A, Qian X, Redondo MJ, Roep BO, Schatz D, Skibinski D, Peakman M. Introducing the Endotype Concept to Address the Challenge of Disease Heterogeneity in Type 1 Diabetes. *Diabetes Care* 2020;43:5-12
33. Onengut-Gumuscu S, Chen WM, Robertson CC, Bonnie JK, Farber E, Zhu Z, Oksenberg JR, Brant SR, Bridges SL, Jr., Edberg JC, Kimberly RP, Gregersen PK, Rewers MJ, Steck AK, Black MH, Dabelea D, Pihoker C, Atkinson MA, Wagenknecht LE, Divers J, Bell RA, Erlich HA, Concannon P, Rich SS. Type 1 Diabetes Risk in African-Ancestry Participants and Utility of an Ancestry-Specific Genetic Risk Score. *Diabetes Care* 2019;42:406-415
34. Rich SS. Genetics and its potential to improve type 1 diabetes care. *Curr Opin Endocrinol Diabetes Obes* 2017;24:279-284
35. Onengut-Gumuscu S, Chen WM, Burren O, Cooper NJ, Quinlan AR, Mychaleckyj JC, Farber E, Bonnie JK, Szpak M, Schofield E, Achuthan P, Guo H, Fortune MD, Stevens H, Walker NM, Ward LD, Kundaje A, Kellis M, Daly MJ, Barrett JC, Cooper JD, Deloukas P, Todd JA, Wallace C, Concannon P, Rich SS. Fine mapping of type 1 diabetes susceptibility loci and evidence for colocalization of causal variants with lymphoid gene enhancers. *Nat Genet* 2015;47:381-386
36. Rickels MR, Evans-Molina C, Bahnson HT, Ylescupidez A, Nadeau KJ, Hao W, Clements MA, Sherr JL, Pratley RE, Hannon TS, Shah VN, Miller KM, Greenbaum CJ. High residual C-peptide likely contributes to glycemic control in type 1 diabetes. *J Clin Invest* 2020;
37. Hao W, Gitelman S, DiMeglio LA, Boulware D, Greenbaum CJ. Fall in C-Peptide During First 4 Years From Diagnosis of Type 1 Diabetes: Variable Relation to Age, HbA1c, and Insulin Dose. *Diabetes Care* 2016;39:1664-1670
38. Shields BM, McDonald TJ, Oram R, Hill A, Hudson M, Leete P, Pearson ER, Richardson SJ, Morgan NG, Hattersley AT. C-Peptide Decline in Type 1 Diabetes Has Two Phases: An Initial Exponential Fall and a Subsequent Stable Phase. *Diabetes Care* 2018;41:1486-1492
39. Ahlqvist E, Storm P, Karajamaki A, Martinell M, Dorkhan M, Carlsson A, Vikman P, Prasad RB, Aly DM, Almgren P, Wessman Y, Shaat N, Spegel P, Mulder H, Lindholm E, Melander O, Hansson O, Malmqvist U, Lernmark A, Lahti K, Forsen T, Tuomi T, Rosengren AH, Groop L. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *Lancet Diabetes Endocrinol* 2018;6:361-369
40. Zaharia OP, Strassburger K, Strom A, Bonhof GJ, Karusheva Y, Antoniou S, Bodis K, Markgraf DF, Burkart V, Mussig K, Hwang JH, Asplund O, Groop L, Ahlqvist E, Seissler J, Nawroth P, Kopf S, Schmid SM, Stumvoll M, Pfeiffer AFH, Kabisch S, Tselmin S, Haring HU, Ziegler D, Kuss O, Szendroedi J, Roden M. Risk of diabetes-associated diseases in subgroups of patients with recent-onset diabetes: a 5-year follow-up study. *Lancet Diabetes Endocrinol* 2019;7:684-694
41. Little RR, Rohlfing CL, Tennill AL, Madsen RW, Polonsky KS, Myers GL, Greenbaum CJ, Palmer JP, Rogatsky E, Stein DT. Standardization of C-peptide measurements. *Clin Chem* 2008;54:1023-1026
42. Udler MS, Kim J, von Grotthuss M, Bonas-Guarch S, Cole JB, Chiou J, Boehnke M, Laakso M, Atzmon G, Glaser B, Mercader JM, Gaulton K, Flannick J, Getz G, Florez JC.

Type 2 diabetes genetic loci informed by multi-trait associations point to disease mechanisms and subtypes: A soft clustering analysis. *PLoS Med* 2018;15:e1002654

43. Mahajan A, Wessel J, Willems SM, Zhao W, Robertson NR, Chu AY, Gan W, Kitajima H, Taliun D, Rayner NW, Guo X, Lu Y, Li M, Jensen RA, Hu Y, Huo S, Lohman KK, Zhang W, Cook JP, Prins BP, Flannick J, Grarup N, Trubetskoy VV, Kravic J, Kim YJ, Rybin DV, Yaghootkar H, Muller-Nurasyid M, Meidtner K, Li-Gao R, Varga TV, Marten J, Li J, Smith AV, An P, Ligthart S, Gustafsson S, Malerba G, Demirkan A, Tajes JF, Steinthorsdottir V, Wuttke M, Lecoeur C, Preuss M, Bielak LF, Graff M, Highland HM, Justice AE, Liu DJ, Marouli E, Peloso GM, Warren HR, Afaq S, Afzal S, Ahlqvist E, Almgren P, Amin N, Bang LB, Bertoni AG, Bombieri C, Bork-Jensen J, Brandslund I, Brody JA, Burt NP, Canouil M, Chen YI, Cho YS, Christensen C, Eastwood SV, Eckardt KU, Fischer K, Gambaro G, Giedraitis V, Grove ML, de Haan HG, Hackinger S, Hai Y, Han S, Tybjaerg-Hansen A, Hivert MF, Isomaa B, Jager S, Jorgensen ME, Jorgensen T, Karajamaki A, Kim BJ, Kim SS, Koistinen HA, Kovacs P, Kriebel J, Kronenberg F, Lall K, Lange LA, Lee JJ, Lehne B, Li H, Lin KH, Linneberg A, Liu CT, Liu J, Loh M, Magi R, Mamakou V, McKean-Cowdin R, Nadkarni G, Neville M, Nielsen SF, Ntalla I, Peyser PA, Rathmann W, Rice K, Rich SS, Rode L, Rolandsson O, Schonherr S, Selvin E, Small KS, Stancakova A, Surendran P, Taylor KD, Teslovich TM, Thorand B, Thorleifsson G, Tin A, Tonjes A, Varbo A, Witte DR, Wood AR, Yajnik P, Yao J, Yengo L, Young R, Amouyel P, Boeing H, Boerwinkle E, Bottinger EP, Chowdhury R, Collins FS, Dedoussis G, Dehghan A, Deloukas P, Ferrario MM, Ferrieres J, Florez JC, Frossard P, Gudnason V, Harris TB, Heckbert SR, Howson JMM, Ingelsson M, Kathiresan S, Kee F, Kuusisto J, Langenberg C, Launer LJ, Lindgren CM, Mannisto S, Meitinger T, Melander O, Mohlke KL, Moitry M, Morris AD, Murray AD, de Mutsert R, Orho-Melander M, Owen KR, Perola M, Peters A, Province MA, Rasheed A, Ridker PM, Rivadineira F, Rosendaal FR, Rosengren AH, Salomaa V, Sheu WH, Sladek R, Smith BH, Strauch K, Uitterlinden AG, Varma R, Willer CJ, Bluher M, Butterworth AS, Chambers JC, Chasman DI, Danesh J, van Duijn C, Dupuis J, Franco OH, Franks PW, Froguel P, Grallert H, Groop L, Han BG, Hansen T, Hattersley AT, Hayward C, Ingelsson E, Kardia SLR, Karpe F, Kooner JS, Kottgen A, Kuulasmaa K, Laakso M, Lin X, Lind L, Liu Y, Loos RJF, Marchini J, Metspalu A, Mook-Kanamori D, Nordestgaard BG, Palmer CNA, Pankow JS, Pedersen O, Psaty BM, Rauramaa R, Sattar N, Schulze MB, Soranzo N, Spector TD, Stefansson K, Stumvoll M, Thorsteinsdottir U, Tuomi T, Tuomilehto J, Wareham NJ, Wilson JG, Zeggini E, Scott RA, Barroso I, Frayling TM, Goodarzi MO, Meigs JB, Boehnke M, Saleheen D, Morris AP, Rotter JI, McCarthy MI. Refining the accuracy of validated target identification through coding variant fine-mapping in type 2 diabetes. *Nat Genet* 2018;50:559-571

44. Insel RA, Dunne JL, Atkinson MA, Chiang JL, Dabelea D, Gottlieb PA, Greenbaum CJ, Herold KC, Krischer JP, Lernmark A, Ratner RE, Rewers MJ, Schatz DA, Skyler JS, Sosenko JM, Ziegler AG. Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. *Diabetes Care* 2015;38:1964-1974

45. Krischer JP. The use of intermediate endpoints in the design of type 1 diabetes prevention trials. *Diabetologia* 2013;56:1919-1924

46. Ziegler AG, Rewers M, Simell O, Simell T, Lempainen J, Steck A, Winkler C, Ilonen J, Veijola R, Knip M, Bonifacio E, Eisenbarth GS. Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. *Jama* 2013;309:2473-2479

47. Rewers M SL, Norris JM. Risk factors for type 1 diabetes. In *Diabetes in America, 3 ed* Cowie CC CS, Menke A, Cissell MA, Eberhardt MS, Meigs JB, Gregg EW, Knowler WC,

- Barrett-Connor E, Becker DJ, Brancati FL, Boyko EJ, Herman WH, Howard BV, Narayan KMV, Rewers M, Fradkin JE, , Ed., National Institutes of Health, 2017
48. Skyler JS KJ, Becker D, Rewers M. Prevention of type 1 diabetes In *Diabetes in America*, 3<sup>rd</sup> ed Cowie CC CS, Menke A, Cissell MA, Eberhardt MS, Meigs JB, Gregg EW, Knowler WC, Barrett-Connor E, Becker DJ, Brancati FL, Boyko EJ, Herman WH, Howard BV, Narayan KMV, Rewers M, Fradkin JE, Ed., National Institutes of Health, 2017
49. Knip M, Akerblom HK, Becker D, Dosch HM, Dupre J, Fraser W, Howard N, Ilonen J, Krischer JP, Kordonouri O, Lawson ML, Palmer JP, Savilahti E, Vaarala O, Virtanen SM. Hydrolyzed infant formula and early beta-cell autoimmunity: a randomized clinical trial. *Jama* 2014;311:2279-2287
50. Vaarala O, Ilonen J, Ruohtula T, Pesola J, Virtanen SM, Harkonen T, Koski M, Kallioinen H, Tossavainen O, Poussa T, Jarvenpaa AL, Komulainen J, Lounamaa R, Akerblom HK, Knip M. Removal of Bovine Insulin From Cow's Milk Formula and Early Initiation of Beta-Cell Autoimmunity in the FINDIA Pilot Study. *Arch Pediatr Adolesc Med* 2012;166:608-614
51. Hummel S, Pfluger M, Hummel M, Bonifacio E, Ziegler AG. Primary dietary intervention study to reduce the risk of islet autoimmunity in children at increased risk for type 1 diabetes: the BABYDIET study. *Diabetes Care* 2011;34:1301-1305
52. Knip M, Akerblom HK, Al Taji E, Becker D, Bruining J, Castano L, Danne T, de Beaufort C, Dosch HM, Dupre J, Fraser WD, Howard N, Ilonen J, Konrad D, Kordonouri O, Krischer JP, Lawson ML, Ludvigsson J, Madacsy L, Mahon JL, Ormison A, Palmer JP, Pozzilli P, Savilahti E, Serrano-Rios M, Songini M, Taback S, Vaarala O, White NH, Virtanen SM, Wasikowa R. Effect of Hydrolyzed Infant Formula vs Conventional Formula on Risk of Type 1 Diabetes: The TRIGR Randomized Clinical Trial. *Jama* 2018;319:38-48
53. Nanto-Salonen K, Kupila A, Simell S, Siljander H, Salonsaari T, Hekkala A, Korhonen S, Erkkola R, Sipila JI, Haavisto L, Siltala M, Tuominen J, Hakalax J, Hyoty H, Ilonen J, Veijola R, Simell T, Knip M, Simell O. Nasal insulin to prevent type 1 diabetes in children with HLA genotypes and autoantibodies conferring increased risk of disease: a double-blind, randomised controlled trial. *Lancet* 2008;372:1746-1755
54. Krischer JP, Schatz DA, Bundy B, Skyler JS, Greenbaum CJ. Effect of Oral Insulin on Prevention of Diabetes in Relatives of Patients With Type 1 Diabetes: A Randomized Clinical Trial. *Jama* 2017;318:1891-1902
55. Elding Larsson H, Lundgren M, Jonsdottir B, Cuthbertson D, Krischer J. Safety and efficacy of autoantigen-specific therapy with 2 doses of alum-formulated glutamate decarboxylase in children with multiple islet autoantibodies and risk for type 1 diabetes: A randomized clinical trial. *Pediatr Diabetes* 2018;19:410-419
56. Lampeter EF, Klinghammer A, Scherbaum WA, Heinze E, Haastert B, Giani G, Kolb H. The Deutsche Nicotinamide Intervention Study: an attempt to prevent type 1 diabetes. DENIS Group. *Diabetes* 1998;47:980-984
57. Gale EA, Bingley PJ, Emmett CL, Collier T. European Nicotinamide Diabetes Intervention Trial (ENDIT): a randomised controlled trial of intervention before the onset of type 1 diabetes. *Lancet* 2004;363:925-931
58. Effects of insulin in relatives of patients with type 1 diabetes mellitus. *N Engl J Med* 2002;346:1685-1691

59. Vehik K, Cuthbertson D, Ruhlig H, Schatz DA, Peakman M, Krischer JP. Long-term outcome of individuals treated with oral insulin: diabetes prevention trial-type 1 (DPT-1) oral insulin trial. *Diabetes Care* 2011;34:1585-1590
60. Vandemeulebroucke E, Gorus FK, Decochez K, Weets I, Keymeulen B, De Block C, Tits J, Pipeleers DG, Mathieu C. Insulin treatment in IA-2A-positive relatives of type 1 diabetic patients. *Diabetes Metab* 2009;35:319-327
61. Herold KC, Bundy BN, Long SA, Bluestone JA, DiMeglio LA, Dufort MJ, Gitelman SE, Gottlieb PA, Krischer JP, Linsley PS, Marks JB, Moore W, Moran A, Rodriguez H, Russell WE, Schatz D, Skyler JS, Tsalikian E, Wherrett DK, Ziegler AG, Greenbaum CJ. An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes. *N Engl J Med* 2019;381:603-613
62. Hober D, Alidjinou EK. Enteroviral pathogenesis of type 1 diabetes: queries and answers. *Curr Opin Infect Dis* 2013;26:263-269
63. Hakola L, Takkinen HM, Niinisto S, Ahonen S, Nevalainen J, Veijola R, Ilonen J, Toppari J, Knip M, Virtanen SM. Infant Feeding in Relation to the Risk of Advanced Islet Autoimmunity and Type 1 Diabetes in Children With Increased Genetic Susceptibility: A Cohort Study. *Am J Epidemiol* 2018;187:34-44
64. Tapia G, Marild K, Dahl SR, Lund-Blix NA, Viken MK, Lie BA, Njolstad PR, Joner G, Skrivarhaug T, Cohen AS, Stordal K, Stene LC. Maternal and Newborn Vitamin D-Binding Protein, Vitamin D Levels, Vitamin D Receptor Genotype, and Childhood Type 1 Diabetes. *Diabetes Care* 2019;42:553-559
65. Norris JM, Kroehl M, Fingerlin TE, Frederiksen BN, Seifert J, Wong R, Clare-Salzler M, Rewers M. Erythrocyte membrane docosapentaenoic acid levels are associated with islet autoimmunity: the Diabetes Autoimmunity Study in the Young. *Diabetologia* 2014;57:295-304
66. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med* 2001;161:397-405
67. Within-trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes. *Diabetes Care* 2003;26:2518-2523
68. 12. Older Adults: Standards of Medical Care in Diabetes-2020. *Diabetes Care* 2020;43:S152-s162
69. Haw JS, Galaviz KI, Straus AN, Kowalski AJ, Magee MJ, Weber MB, Wei J, Narayan KMV, Ali MK. Long-term Sustainability of Diabetes Prevention Approaches: A Systematic Review and Meta-analysis of Randomized Clinical Trials. *JAMA Intern Med* 2017;177:1808-1817
70. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393-403
71. Crandall J, Schade D, Ma Y, Fujimoto WY, Barrett-Connor E, Fowler S, Dagogo-Jack S, Andres R. The influence of age on the effects of lifestyle modification and metformin in prevention of diabetes. *J Gerontol A Biol Sci Med Sci* 2006;61:1075-1081
72. Knowler WC, Fowler SE, Hamman RF, Christophi CA, Hoffman HJ, Brenneman AT, Brown-Friday JO, Goldberg R, Venditti E, Nathan DM. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet* 2009;374:1677-1686

73. Delahanty LM, Pan Q, Jablonski KA, Aroda VR, Watson KE, Bray GA, Kahn SE, Florez JC, Perreault L, Franks PW. Effects of weight loss, weight cycling, and weight loss maintenance on diabetes incidence and change in cardiometabolic traits in the Diabetes Prevention Program. *Diabetes Care* 2014;37:2738-2745
74. Papandonatos GD, Pan Q, Pajewski NM, Delahanty LM, Peter I, Erar B, Ahmad S, Harden M, Chen L, Fontanillas P, Wagenknecht LE, Kahn SE, Wing RR, Jablonski KA, Huggins GS, Knowler WC, Florez JC, McCaffery JM, Franks PW. Genetic Predisposition to Weight Loss and Regain With Lifestyle Intervention: Analyses From the Diabetes Prevention Program and the Look AHEAD Randomized Controlled Trials. *Diabetes* 2015;64:4312-4321
75. Langenberg C, Sharp SJ, Franks PW, Scott RA, Deloukas P, Forouhi NG, Froguel P, Groop LC, Hansen T, Palla L, Pedersen O, Schulze MB, Tormo MJ, Wheeler E, Agnoli C, Arriola L, Barricarte A, Boeing H, Clarke GM, Clavel-Chapelon F, Duell EJ, Fagherazzi G, Kaaks R, Kerrison ND, Key TJ, Khaw KT, Kroger J, Lajous M, Morris AP, Navarro C, Nilsson PM, Overvad K, Palli D, Panico S, Quiros JR, Rolandsson O, Sacerdote C, Sanchez MJ, Slimani N, Spijkerman AM, Tumino R, van der AD, van der Schouw YT, Barroso I, McCarthy MI, Riboli E, Wareham NJ. Gene-lifestyle interaction and type 2 diabetes: the EPIC interact case-cohort study. *PLoS Med* 2014;11:e1001647
76. Hivert MF, Christophi CA, Franks PW, Jablonski KA, Ehrmann DA, Kahn SE, Horton ES, Pollin TI, Mather KJ, Perreault L, Barrett-Connor E, Knowler WC, Florez JC. Lifestyle and Metformin Ameliorate Insulin Sensitivity Independently of the Genetic Burden of Established Insulin Resistance Variants in Diabetes Prevention Program Participants. *Diabetes* 2016;65:520-526
77. Hivert MF, Jablonski KA, Perreault L, Saxena R, McAteer JB, Franks PW, Hamman RF, Kahn SE, Haffner S, Meigs JB, Altshuler D, Knowler WC, Florez JC. Updated genetic score based on 34 confirmed type 2 diabetes Loci is associated with diabetes incidence and regression to normoglycemia in the diabetes prevention program. *Diabetes* 2011;60:1340-1348
78. Kilpelainen TO, Qi L, Brage S, Sharp SJ, Sonestedt E, Demerath E, Ahmad T, Mora S, Kaakinen M, Sandholt CH, Holzapfel C, Autenrieth CS, Hypponen E, Cauchi S, He M, Kutalik Z, Kumari M, Stancakova A, Meidtner K, Balkau B, Tan JT, Mangino M, Timpson NJ, Song Y, Zillikens MC, Jablonski KA, Garcia ME, Johansson S, Bragg-Gresham JL, Wu Y, van Vliet-Ostaptchouk JV, Onland-Moret NC, Zimmermann E, Rivera NV, Tanaka T, Stringham HM, Silbernagel G, Kanoni S, Feitosa MF, Snitker S, Ruiz JR, Metter J, Larrad MT, Atalay M, Hakanen M, Amin N, Cavalcanti-Proenca C, Grontved A, Hallmans G, Jansson JO, Kuusisto J, Kahonen M, Lutsey PL, Nolan JJ, Palla L, Pedersen O, Perusse L, Renstrom F, Scott RA, Shungin D, Sovio U, Tammelin TH, Ronnema T, Lakka TA, Uusitupa M, Rios MS, Ferrucci L, Bouchard C, Meirhaeghe A, Fu M, Walker M, Borecki IB, Dedoussis GV, Fritsche A, Ohlsson C, Boehnke M, Bandinelli S, van Duijn CM, Ebrahim S, Lawlor DA, Gudnason V, Harris TB, Sorensen TI, Mohlke KL, Hofman A, Uitterlinden AG, Tuomilehto J, Lehtimaki T, Raitakari O, Isomaa B, Njolstad PR, Florez JC, Liu S, Ness A, Spector TD, Tai ES, Froguel P, Boeing H, Laakso M, Marmot M, Bergmann S, Power C, Khaw KT, Chasman D, Ridker P, Hansen T, Monda KL, Illig T, Jarvelin MR, Wareham NJ, Hu FB, Groop LC, Orho-Melander M, Ekelund U, Franks PW, Loos RJ. Physical activity attenuates the influence of FTO variants on obesity risk: a meta-analysis of 218,166 adults and 19,268 children. *PLoS Med* 2011;8:e1001116
79. Shungin D, Deng WQ, Varga TV, Luan J, Mihailov E, Metspalu A, Morris AP, Forouhi NG, Lindgren C, Magnusson PKE, Pedersen NL, Hallmans G, Chu AY, Justice AE, Graff M, Winkler TW, Rose LM, Langenberg C, Cupples LA, Ridker PM, Wareham NJ, Ong KK,

Loos RJF, Chasman DI, Ingelsson E, Kilpelainen TO, Scott RA, Magi R, Pare G, Franks PW. Ranking and characterization of established BMI and lipid associated loci as candidates for gene-environment interactions. *PLoS Genet* 2017;13:e1006812

80. Graff M, Scott RA, Justice AE, Young KL, Feitosa MF, Barata L, Winkler TW, Chu AY, Mahajan A, Hadley D, Xue L, Workalemahu T, Heard-Costa NL, den Hoed M, Ahluwalia TS, Qi Q, Ngwa JS, Renstrom F, Quaye L, Eicher JD, Hayes JE, Cornelis M, Kutalik Z, Lim E, Luan J, Huffman JE, Zhang W, Zhao W, Griffin PJ, Haller T, Ahmad S, Marques-Vidal PM, Bien S, Yengo L, Teumer A, Smith AV, Kumari M, Harder MN, Justesen JM, Kleber ME, Hollensted M, Lohman K, Rivera NV, Whitfield JB, Zhao JH, Stringham HM, Lyytikainen LP, Huppertz C, Willemsen G, Peyrot WJ, Wu Y, Kristiansson K, Demirkan A, Fornage M, Hassinen M, Bielak LF, Cadby G, Tanaka T, Magi R, van der Most PJ, Jackson AU, Bragg-Gresham JL, Vitart V, Marten J, Navarro P, Bellis C, Pasko D, Johansson A, Snitker S, Cheng YC, Eriksson J, Lim U, Aadahl M, Adair LS, Amin N, Balkau B, Auvinen J, Beilby J, Bergman RN, Bergmann S, Bertoni AG, Blangero J, Bonnefond A, Bonnycastle LL, Borja JB, Brage S, Busonero F, Buyske S, Campbell H, Chines PS, Collins FS, Corre T, Smith GD, Delgado GE, Dueker N, Dorr M, Ebeling T, Eiriksdottir G, Esko T, Faul JD, Fu M, Faerch K, Gieger C, Glaser S, Gong J, Gordon-Larsen P, Grallert H, Grammer TB, Grarup N, van Grootheest G, Harald K, Hastie ND, Havulinna AS, Hernandez D, Hindorf L, Hocking LJ, Holmens OL, Holzappel C, Hottenga JJ, Huang J, Huang T, Hui J, Huth C, Hutri-Kahonen N, James AL, Jansson JO, Jhun MA, Juonala M, Kinnunen L, Koistinen HA, Kolcic I, Komulainen P, Kuusisto J, Kvaloy K, Kahonen M, Lakka TA, Launer LJ, Lehne B, Lindgren CM, Lorentzon M, Luben R, Marre M, Milanesechi Y, Monda KL, Montgomery GW, De Moor MHM, Mulas A, Muller-Nurasyid M, Musk AW, Mannikko R, Mannisto S, Narisu N, Nauck M, Nettleton JA, Nolte IM, Oldehinkel AJ, Olden M, Ong KK, Padmanabhan S, Paternoster L, Perez J, Perola M, Peters A, Peters U, Peyser PA, Prokopenko I, Puolijoki H, Raitakari OT, Rankinen T, Rasmussen-Torvik LJ, Rawal R, Ridker PM, Rose LM, Rudan I, Sarti C, Sarzynski MA, Savonen K, Scott WR, Sanna S, Shuldiner AR, Sidney S, Silbernagel G, Smith BH, Smith JA, Snieder H, Stancakova A, Sternfeld B, Swift AJ, Tammelin T, Tan ST, Thorand B, Thuillier D, Vandenput L, Vestergaard H, van Vliet-Ostaptchouk JV, Vohl MC, Volker U, Waeber G, Walker M, Wild S, Wong A, Wright AF, Zillikens MC, Zubair N, Haiman CA, Lemarchand L, Gyllensten U, Ohlsson C, Hofman A, Rivadeneira F, Uitterlinden AG, Perusse L, Wilson JF, Hayward C, Polasek O, Cucca F, Hveem K, Hartman CA, Tonjes A, Bandinelli S, Palmer LJ, Kardina SLR, Rauramaa R, Sorensen TIA, Tuomilehto J, Salomaa V, Penninx B, de Geus EJC, Boomsma DI, Lehtimaki T, Mangino M, Laakso M, Bouchard C, Martin NG, Kuh D, Liu Y, Linneberg A, Marz W, Strauch K, Kivimaki M, Harris TB, Gudnason V, Volzke H, Qi L, Jarvelin MR, Chambers JC, Kooner JS, Froguel P, Kooperberg C, Vollenweider P, Hallmans G, Hansen T, Pedersen O, Metspalu A, Wareham NJ, Langenberg C, Weir DR, Porteous DJ, Boerwinkle E, Chasman DI, Abecasis GR, Barroso I, McCarthy MI, Frayling TM, O'Connell JR, van Duijn CM, Boehnke M, Heid IM, Mohlke KL, Strachan DP, Fox CS, Liu CT, Hirschhorn JN, Klein RJ, Johnson AD, Borecki IB, Franks PW, North KE, Cupples LA, Loos RJF, Kilpelainen TO. Genome-wide physical activity interactions in adiposity - A meta-analysis of 200,452 adults. *PLoS Genet* 2017;13:e1006528

81. Tyrrell J, Wood AR, Ames RM, Yaghoobkar H, Beaumont RN, Jones SE, Tuke MA, Ruth KS, Freathy RM, Davey Smith G, Joost S, Guessous I, Murray A, Strachan DP, Kutalik Z, Weedon MN, Frayling TM. Gene-obesogenic environment interactions in the UK Biobank study. *Int J Epidemiol* 2017;46:559-575

82. Livingstone KM, Celis-Morales C, Papandonatos GD, Erar B, Florez JC, Jablonski KA, Razquin C, Marti A, Heianza Y, Huang T, Sacks FM, Svendstrup M, Sui X, Church TS,



- Jaaskelainen T, Lindstrom J, Tuomilehto J, Uusitupa M, Rankinen T, Saris WH, Hansen T, Pedersen O, Astrup A, Sorensen TI, Qi L, Bray GA, Martinez-Gonzalez MA, Martinez JA, Franks PW, McCaffery JM, Lara J, Mathers JC. FTO genotype and weight loss: systematic review and meta-analysis of 9563 individual participant data from eight randomised controlled trials. *Bmj* 2016;354:i4707
83. Godino JG, van Sluijs EM, Marteau TM, Sutton S, Sharp SJ, Griffin SJ. Lifestyle Advice Combined with Personalized Estimates of Genetic or Phenotypic Risk of Type 2 Diabetes, and Objectively Measured Physical Activity: A Randomized Controlled Trial. *PLoS Med* 2016;13:e1002185
84. Zeevi D, Korem T, Zmora N, Israeli D, Rothschild D, Weinberger A, Ben-Yacov O, Lador D, Avnit-Sagi T, Lotan-Pompan M, Suez J, Mahdi JA, Matot E, Malka G, Kosower N, Rein M, Zilberman-Schapira G, Dohnalova L, Pevsner-Fischer M, Bikovsky R, Halpern Z, Elinav E, Segal E. Personalized Nutrition by Prediction of Glycemic Responses. *Cell* 2015;163:1079-1094
85. Jablonski KA, McAteer JB, de Bakker PI, Franks PW, Pollin TI, Hanson RL, Saxena R, Fowler S, Shuldiner AR, Knowler WC, Altshuler D, Florez JC. Common variants in 40 genes assessed for diabetes incidence and response to metformin and lifestyle intervention in the diabetes prevention program. *Diabetes* 2010;59:2672-2681
86. Apolzan JW, Venditti EM, Edelstein SL, Knowler WC, Dabelea D, Boyko EJ, Pi-Sunyer X, Kalyani RR, Franks PW, Srikanthan P, Gadde KM. Long-Term Weight Loss With Metformin or Lifestyle Intervention in the Diabetes Prevention Program Outcomes Study. *Ann Intern Med* 2019;170:682-690
87. Lean ME, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, Peters C, Zhyzhneuskaya S, Al-Mrabeh A, Hollingsworth KG, Rodrigues AM, Rehackova L, Adamson AJ, Sniehotta FF, Mathers JC, Ross HM, McIlvenna Y, Stefanetti R, Trenell M, Welsh P, Kean S, Ford I, McConnachie A, Sattar N, Taylor R. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet* 2018;391:541-551
88. Dennis JM, Shields BM, Jones AG, Pearson ER, Hattersley AT, Henley WE. Evaluating associations between the benefits and risks of drug therapy in type 2 diabetes: a joint modeling approach. *Clin Epidemiol* 2018;10:1869-1877
89. Zhou K, Yee SW, Seiser EL, van Leeuwen N, Tavendale R, Bennett AJ, Groves CJ, Coleman RL, van der Heijden AA, Beulens JW, de Keyser CE, Zaharenko L, Rotroff DM, Out M, Jablonski KA, Chen L, Javorsky M, Zidzik J, Levin AM, Williams LK, Dujic T, Semiz S, Kubo M, Chien HC, Maeda S, Witte JS, Wu L, Tkac I, Kooy A, van Schaik RHN, Stehouwer CDA, Logie L, Sutherland C, Klovins J, Pirags V, Hofman A, Stricker BH, Motsinger-Reif AA, Wagner MJ, Innocenti F, t Hart LM, Holman RR, McCarthy MI, Hedderon MM, Palmer CNA, Florez JC, Giacomini KM, Pearson ER. Variation in the glucose transporter gene SLC2A2 is associated with glycemic response to metformin. *Nat Genet* 2016;48:1055-1059
90. Zhou K, Donnelly L, Burch L, Tavendale R, Doney AS, Leese G, Hattersley AT, McCarthy MI, Morris AD, Lang CC, Palmer CN, Pearson ER. Loss-of-function CYP2C9 variants improve therapeutic response to sulfonylureas in type 2 diabetes: a Go-DARTS study. *Clin Pharmacol Ther* 2010;87:52-56

91. Dawed AY, Donnelly L, Tavendale R, Carr F, Leese G, Palmer CN, Pearson ER, Zhou K. CYP2C8 and SLCO1B1 Variants and Therapeutic Response to Thiazolidinediones in Patients With Type 2 Diabetes. *Diabetes Care* 2016;39:1902-1908
92. Kim YG, Hahn S, Oh TJ, Kwak SH, Park KS, Cho YM. Differences in the glucose-lowering efficacy of dipeptidyl peptidase-4 inhibitors between Asians and non-Asians: a systematic review and meta-analysis. *Diabetologia* 2013;56:696-708
93. Davis TME, Mulder H, Lokhnygina Y, Aschner P, Chuang LM, Raffo Grado CA, Standl E, Peterson ED, Holman RR. Effect of race on the glycaemic response to sitagliptin: Insights from the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS). *Diabetes Obes Metab* 2018;20:1427-1434
94. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. *Diabetes Care* 2002;25:1862-1868
95. Das Gupta R, Gupta S, Das A, Biswas T, Haider MR, Sarker M. Ethnic predisposition of diabetes mellitus in the patients with previous history of gestational diabetes mellitus: a review. *Expert Rev Endocrinol Metab* 2018;13:149-158
96. Lowe WL, Jr., Scholtens DM, Sandler V, Hayes MG. Genetics of Gestational Diabetes Mellitus and Maternal Metabolism. *Curr Diab Rep* 2016;16:15
97. Hayes MG, Urbanek M, Hivert MF, Armstrong LL, Morrison J, Guo C, Lowe LP, Scheftner DA, Pluzhnikov A, Levine DM, McHugh CP, Ackerman CM, Bouchard L, Brisson D, Layden BT, Mirel D, Doheny KF, Leya MV, Lown-Hecht RN, Dyer AR, Metzger BE, Reddy TE, Cox NJ, Lowe WL, Jr. Identification of HKDC1 and BACE2 as genes influencing glycemic traits during pregnancy through genome-wide association studies. *Diabetes* 2013;62:3282-3291
98. Powe CE, Allard C, Battista MC, Doyon M, Bouchard L, Ecker JL, Perron P, Florez JC, Thadhani R, Hivert MF. Heterogeneous Contribution of Insulin Sensitivity and Secretion Defects to Gestational Diabetes Mellitus. *Diabetes Care* 2016;39:1052-1055
99. Benhalima K, Van Crombrugge P, Moyson C, Verhaeghe J, Vandeginste S, Verlaenen H, Vercammen C, Maes T, Dufraimont E, De Block C, Jacquemyn Y, Mekahli F, De Clippel K, Van Den Bruel A, Loccafier A, Laenen A, Minschart C, Devlieger R, Mathieu C. Characteristics and pregnancy outcomes across gestational diabetes mellitus subtypes based on insulin resistance. *Diabetologia* 2019;62:2118-2128
100. Cooray SD, Boyle JA, Soldatos G, Wijeyaratne LA, Teede HJ. Prognostic prediction models for pregnancy complications in women with gestational diabetes: a protocol for systematic review, critical appraisal and meta-analysis. *Syst Rev* 2019;8:270
101. Tobias DK. Prediction and Prevention of Type 2 Diabetes in Women with a History of GDM. *Curr Diab Rep* 2018;18:78
102. Aroda VR, Christophi CA, Edelstein SL, Zhang P, Herman WH, Barrett-Connor E, Delahanty LM, Montez MG, Ackermann RT, Zhuo X, Knowler WC, Ratner RE. The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without gestational diabetes: the Diabetes Prevention Program outcomes study 10-year follow-up. *J Clin Endocrinol Metab* 2015;100:1646-1653
103. 14. Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes-2020. *Diabetes Care* 2020;43:S183-s192

104. Spyer G, Macleod KM, Shepherd M, Ellard S, Hattersley AT. Pregnancy outcome in patients with raised blood glucose due to a heterozygous glucokinase gene mutation. *Diabet Med* 2009;26:14-18
105. Sanyoura M, Letourneau L, Knight Johnson AE, Del Gaudio D, Greeley SAW, Philipson LH, Naylor RN. GCK-MODY in the US Monogenic Diabetes Registry: Description of 27 unpublished variants. *Diabetes Res Clin Pract* 2019;151:231-236
106. De Franco E, Caswell R, Houghton JA, Iotova V, Hattersley AT, Ellard S. Analysis of cell-free fetal DNA for non-invasive prenatal diagnosis in a family with neonatal diabetes. *Diabet Med* 2017;34:582-585
107. Petrak F, Baumeister H, Skinner TC, Brown A, Holt RIG. Depression and diabetes: treatment and health-care delivery. *Lancet Diabetes Endocrinol* 2015;3:472-485
108. Snoek FJ, Bremmer MA, Hermanns N. Constructs of depression and distress in diabetes: time for an appraisal. *Lancet Diabetes Endocrinol* 2015;3:450-460
109. Moulton CD, Pickup JC, Ismail K. The link between depression and diabetes: the search for shared mechanisms. *Lancet Diabetes Endocrinol* 2015;3:461-471
110. 5. Facilitating Behavior Change and Well-being to Improve Health Outcomes: Standards of Medical Care in Diabetes-2020. *Diabetes Care* 2020;43:S48-s65
111. Avissar N, Farkash Y, Shaklai M. Erythrocyte enzymes in polycythemia vera: a comparison to erythrocyte enzyme activities of patients with iron deficiency anemia. *Acta Haematol* 1986;76:37-43
112. Shields BM, Hicks S, Shepherd MH, Colclough K, Hattersley AT, Ellard S. Maturity-onset diabetes of the young (MODY): how many cases are we missing? *Diabetologia* 2010;53:2504-2508
113. Shepherd M, Colclough K, Ellard S, Hattersley AT. Ten years of the national genetic diabetes nurse network: a model for the translation of genetic information into clinical care. *Clin Med (Lond)* 2014;14:117-121
114. Owen KR. Monogenic diabetes in adults: what are the new developments? *Curr Opin Genet Dev* 2018;50:103-110
115. Poudel A, Zhou JY, Story D, Li L. Diabetes and Associated Cardiovascular Complications in American Indians/Alaskan Natives: A Review of Risks and Prevention Strategies. *J Diabetes Res* 2018;2018:2742565
116. Salas-Salvado J, Bullo M, Babio N, Martinez-Gonzalez MA, Ibarrola-Jurado N, Basora J, Estruch R, Covas MI, Corella D, Aros F, Ruiz-Gutierrez V, Ros E. Reduction in the incidence of type 2 diabetes with the Mediterranean diet: results of the PREDIMED-Reus nutrition intervention randomized trial. *Diabetes Care* 2011;34:14-19
117. Salas-Salvado J, Bullo M, Babio N, Martinez-Gonzalez MA, Ibarrola-Jurado N, Basora J, Estruch R, Covas MI, Corella D, Aros F, Ruiz-Gutierrez V, Ros E. Erratum. Reduction in the Incidence of Type 2 Diabetes With the Mediterranean Diet: Results of the PREDIMED-Reus nutrition intervention randomized trial. *Diabetes Care* 2011;34:14-19. *Diabetes Care* 2018;41:2259-2260
118. Celis-Morales C, Livingstone KM, Marsaux CF, Macready AL, Fallaize R, O'Donovan CB, Woolhead C, Forster H, Walsh MC, Navas-Carretero S, San-Cristobal R, Tsirigoti L, Lambrinou CP, Mavrogianni C, Moschonis G, Kolossa S, Hallmann J, Godlewska M, Surwillo A, Traczyk I, Drevon CA, Bouwman J, van Ommen B, Grimaldi K, Parnell LD,

- Matthews JN, Manios Y, Daniel H, Martinez JA, Lovegrove JA, Gibney ER, Brennan L, Saris WH, Gibney M, Mathers JC. Effect of personalized nutrition on health-related behaviour change: evidence from the Food4Me European randomized controlled trial. *Int J Epidemiol* 2017;46:578-588
119. Al Busaidi N, Shanmugam P, Manoharan D. Diabetes in the Middle East: Government Health Care Policies and Strategies that Address the Growing Diabetes Prevalence in the Middle East. *Curr Diab Rep* 2019;19:8
120. Meyer RJ. Precision Medicine, Diabetes, and the U.S. Food and Drug Administration. *Diabetes Care* 2016;39:1874-1878
121. Naylor R. Economics of Genetic Testing for Diabetes. *Curr Diab Rep* 2019;19:23
122. Fitipaldi H, McCarthy MI, Florez JC, Franks PW. A Global Overview of Precision Medicine in Type 2 Diabetes. *Diabetes* 2018;67:1911-1922
123. Wang C, O'Neill SM, Rothrock N, Gramling R, Sen A, Acheson LS, Rubinstein WS, Nease DE, Jr., Ruffin MT. Comparison of risk perceptions and beliefs across common chronic diseases. *Prev Med* 2009;48:197-202
124. Mahajan A, Taliun D, Thurner M, Robertson NR, Torres JM, Rayner NW, Payne AJ, Steinthorsdottir V, Scott RA, Grarup N, Cook JP, Schmidt EM, Wuttke M, Sarnowski C, Magi R, Nano J, Gieger C, Trompet S, Lecoeur C, Preuss MH, Prins BP, Guo X, Bielak LF, Below JE, Bowden DW, Chambers JC, Kim YJ, Ng MCY, Petty LE, Sim X, Zhang W, Bennett AJ, Bork-Jensen J, Brummett CM, Canouil M, Ec Kardt KU, Fischer K, Kardia SLR, Kronenberg F, Lall K, Liu CT, Locke AE, Luan J, Ntalla I, Nylander V, Schonherr S, Schurmann C, Yengo L, Bottinger EP, Brandslund I, Christensen C, Dedoussis G, Florez JC, Ford I, Franco OH, Frayling TM, Giedraitis V, Hackinger S, Hattersley AT, Herder C, Ikram MA, Ingelsson M, Jorgensen ME, Jorgensen T, Kriebel J, Kuusisto J, Ligthart S, Lindgren CM, Linneberg A, Lyssenko V, Mamakou V, Meitinger T, Mohlke KL, Morris AD, Nadkarni G, Pankow JS, Peters A, Sattar N, Stancakova A, Strauch K, Taylor KD, Thorand B, Thorleifsson G, Thorsteinsdottir U, Tuomilehto J, Witte DR, Dupuis J, Peyser PA, Zeggini E, Loos RJF, Froguel P, Ingelsson E, Lind L, Groop L, Laakso M, Collins FS, Jukema JW, Palmer CNA, Grallert H, Metspalu A, Dehghan A, Kottgen A, Abecasis GR, Meigs JB, Rotter JI, Marchini J, Pedersen O, Hansen T, Langenberg C, Wareham NJ, Stefansson K, Gloyn AL, Morris AP, Boehnke M, McCarthy MI. Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. *Nat Genet* 2018;50:1505-1513
125. O'Brien RL, Brinster RL, Storb U. Somatic hypermutation of an immunoglobulin transgene in kappa transgenic mice. *Nature* 1987;326:405-409