

## **A global overview of precision medicine in type 2 diabetes**

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## **Abstract**

The detailed characterization of human biology and behaviors is now possible at scale owing to innovations in biomarker, bioimaging, and wearable technologies; 'big data' from electronic medical records, health insurance databases and other platforms is also becoming increasingly accessible, and computational power and bioinformatics methods are evolving rapidly. Collectively, these advances are creating unprecedented opportunities to better understanding diabetes and many other complex traits. Identifying hidden structures within these complex datasets and linking these structures to outcome data may yield unique insights into the risk factors and natural history of diabetes, which may in turn help optimize the prevention and management of the disease. This emerging area is broadly termed 'precision medicine'. In this perspective, we overview the evidence and barriers to the development and implementation of precision medicine in type 2 diabetes. We also discuss recently presented paradigms through which complex data might enhance our understanding of diabetes and ultimately our ability to tackle the disease more effectively than ever before.

The etiology, clinical presentation and consequences of type 2 diabetes can vary greatly from one patient to the next, complicating the prevention and management of the disease. The cardinal feature of type 2 diabetes is chronically elevated blood glucose concentrations; however, to categorize it as “type 2 diabetes” the clinician must exclude autoimmunity, pregnancy, pancreatic disease or injury, and rare syndromic or genetic forms of diabetes. In addition to assessing the signs and symptoms of diabetes, the clinician uses high-level data about the patient such as their age, family history, ethnicity, mental health, medications, biochemical profile, lifestyle, and body weight to understand the nature of the disease and in turn to help optimize treatment. The fact that type 2 diabetes is diagnosed on the basis of exclusion speaks to the lack of mechanistic understanding we have of the disease and the absence of assays that detect the underlying defect(s) rather than its biochemical consequence (elevated glucose).

In Western health care systems, diabetes treatment follows an algorithmic sequence that starts with lifestyle modification + metformin (absent contraindications), and later may progress to other drugs and/or insulin, meanwhile monitoring tolerability and glycemic goals to determine if the next step in the sequence should be taken. Lifestyle modification alone is usually unsuccessful and even with combined drug therapy about one third of diabetes patients in the US eventually require endogenous insulin(1).

The emergence of type 2 diabetes as one of the major causes of morbidity and premature mortality is closely linked to widespread adoption of obesogenic (Westernized) lifestyles. This relationship is likely to be causal, as aggressively intervening on lifestyle factors that promote and/or help maintain weight loss delays the onset of diabetes in high-risk adults(2-5), and about half of patients undergoing medium-term hypocaloric diet interventions leading to major weight loss ( $\geq 15$  kg) achieve medication-free diabetes remission within a year(6); diabetes remission is also common in patients who experience major weight loss with bariatric surgery(7). The population-scale decline in rates of obesity, diabetes and cardiovascular disease during economic crises that have forced entire populations to increase physical activity levels and reduce caloric intake reinforces the role of negative energy-balance in diabetes prevention(8).

The proven benefits of lifestyle modification in diabetes prevention and the effectiveness of several diabetes drugs are counterbalanced by the continuing emergence of type 2 diabetes as one of the most prevalent and burdensome diseases globally(9). In the US for example, diabetes was the seventh leading cause of death in 2010, accounting for at least 10%-15% of deaths in people aged  $\geq 20$ -years, with adult deaths rates  $\sim 50\%$  higher in people with

diabetes than in those without(1). The economic burden of diabetes is also formidable, with diabetes costing the US economy about US\$245 billion in 2012, with the average annual medical costs per diabetes patient more than double those for people without the disease(1).

The rising prevalence of diabetes on a population-scale and the insufficiency of established therapeutic options justifies the search for orthogonal diabetes prevention and treatment strategies to complement existing approaches. Ideally, these new approaches would be better tailored to the individual for enhanced tolerability and effectiveness.

This drive to develop precision medicine for diabetes is predicated on the major technological advances seen in recent years that include high-resolution omic assays, wearable devices that monitor behaviors and exposures, and digital imaging technologies. The intelligent integration of the data these technologies yield can provide detailed digital impressions of a person's physical condition, their past exposure and ongoing susceptibility to certain risk factors, and how they might respond to specific antidiabetic therapies, as well as help track disease progression. All of this has the potential to substantially improve the prediction, prevention and treatment of type 2 diabetes, and there are, as discussed later, many major initiatives underway with this objective; however, as also discussed, there is much to resolve before precision diabetes medicine becomes common practice.

### **How precision diabetes medicine might work**

The foundation of precision medicine in type 2 diabetes, like all other complex diseases, is population genetics, the catalyst for which was the sequencing of the human genome, a US\$3 billion initiative that completed its work in 2003(10). The availability of human genome sequences provided a framework that facilitated the design of massively-parallel, chip-based genotyping arrays. These technologies have since been used to characterize common genomic variation in millions of people worldwide, which in turn has helped identify hundreds of variants associated with type 2 diabetes and related traits through genome-wide association studies (GWAS)(11). The development of biotechnologies designed for high-resolution characterization of other types of biological variants (transcripts, proteins, epigenetic marks, metabolites, microbiota, etc) has followed, further expanding our ability to map the paths that link a person's biological idiosyncrasies to disease susceptibility. Although this work has primarily involved hypothesis-free association studies in large cohort collections, and thus the results are highly descriptive and of minimal relevance to the individual patient, it has provided substrate for functional studies, revealing novel aspects of disease biology and therapeutic targets that may seed individualized therapies.

It is generally accepted that precision medicine, informed by diverse sources of “big data”, will improve prevention and treatment of common, multifactorial diseases, such as type 2 diabetes but there are few examples to date. The common variants shown by GWAS to be associated with type 2 diabetes have at best modest effect sizes, and the consensus view has historically been that, even in combination, their predictive value is limited, particularly when compared with the performance of classical risk factors such as age, BMI and glucose(12). In the past year, however, there has been a reinvigoration of interest in the translational potential offered by genetic risk scores(13). Recent expanded GWAS datasets have yielded loci that explain a sizable proportion (50%) of diabetes heritability and highlight that there are millions of people (in the UK or US) who, on the basis of genetic evidence alone, have very high (~50%) lifetime risks of type 2 diabetes(14). This raises the prospect that the roll-out of medical genotyping and sequencing will provide clinically actionable information on diabetes-risk, particularly if genetic information is combined with other relevant clinical or exposure data.

So far however, the clinical application of genetics in diabetes remains limited to rare, monogenic subtypes. Models for the personalization of type 2 diabetes care (especially in relation to exploiting the marked clinical heterogeneity within type 2 diabetes) have often extrapolated from this experience to invoke quasi-Mendelian scenarios characterized by distinctive subtypes of type 2 diabetes, each of which has the potential to be mapped to a specific remedial therapy or intervention. In reality, effective strategies in this area must address the multifactorial etiology of type 2 diabetes and a continuous spectrum of predisposition mediated, in most individuals, through joint effects across multiple pathways.

One recently described conceptualization of the pathophysiological architecture of type 2 diabetes predisposition (termed the “palette model”) focuses attention instead on the intermediary processes contributing to type 2 diabetes risk(15). The most obvious of these include obesity, fat distribution, islet development and function, and insulin sensitivity, but other, as yet poorly-characterized contributors are likely. Each of these processes is itself under multifactorial (genetic and non-genetic) control and individual “loadings” across them combinatorially influence both diabetes-risk and the phenotype of any diabetes that results. Several recent studies\_(16-19) have added empirical support for this approach, demonstrating, for example, differential relationships between process-specific risk scores and the risk of complications such as DKD and CAD.

The palette model captures the range of diabetes subtypes (from monogenic via hybrid forms (e.g. LADA), through to the clinical heterogeneity evident within type 2 diabetes) as a

continuum consistent with the genetic architecture of diabetes and “real-world” clinical observation(20, 21). The model suggests that for many people with type 2 diabetes, their condition is the consequence not of a major defect in a single process, but in the confluence of suboptimal performance across several processes contributing in parallel. This is what one would predict given evidence that type 2 diabetes risk can be subtly modulated by common variants acting through any one of several distinct mechanisms (energy balance, adipocyte differentiation, incretin signaling, insulin secretion, etc.), and by the wide-range of therapeutic interventions that have the proven capacity to ameliorate, to some degree at least, the diabetic state (e.g. insulin sensitizers, beta-cell secretagogues, calorie restriction, exercise, metabolic surgery).

This model provides a framework for understanding the mechanistic basis of heterogeneity and its clinical consequences. It also allows for the existence of cases at the extremes of the distribution for whom a targeted intervention might be particularly effective. Genetic risk scores that capture each of these processes may help to tease apart heterogeneity in phenotype, progression, and therapeutic response. They may allow identification, within the overall population, of subsets of selected individuals in whom the profile of genetic predisposition is dominated by defects in a single pathway, facilitating personalized, mechanism-specific interventions.

Nevertheless, for multifactorial diseases like type 2 diabetes, where individual predisposition is influenced as much by non-genetic as genetic factors, there is an absolute limit to the clinical precision that genetics alone can provide. For precision medicine to flourish, this genetic information will need to be integrated with relevant measures of those aspects of the external and internal environment (the latter term, for example, encompassing the gut microbiome) that also influence type 2 diabetes predisposition, phenotype and progression. This information would ideally be supported by pertinent biomarker and clinical readouts, generating integrated profiles that may provide the predictive accuracy needed for clinical utility.

Along these lines, Ahlqvist et al used data from 8,980 Swedish patients with newly diagnosed diabetes (of any type) and applied machine learning algorithms to derive a data-driven approach to classifying diabetes subtypes(20). The authors proposed five subtypes determined by variations across six variables (glutamate decarboxylase antibodies, age at diagnosis, BMI, HbA1c, and homoeostatic model assessment 2 estimates of  $\beta$ -cell function and insulin resistance). The relationship of subtype and incident events (use of antidiabetic medication, achieving treatment goals, and diabetic complications) were assessed and

replicated in independent cohorts. Each cluster was characterized by certain phenotypic features assessed soon after diagnosis. These include early-onset *severe autoimmune diabetes* (SAID) (6.7% of patients), *severe insulin-deficient diabetes* (SIDD) (17.5% of patients), *severe insulin-resistance diabetes* (SIRD) (15.3% of patients), mild obesity-related diabetes (MOD) (21.6% of patients) and *mild age-related diabetes* (MARD) (39.1% of patients). Rates of diabetic renal disease and coronary disease were highest in SIRD, although rates of retinopathy were lowest for this group (retinopathies were more frequent in SIDD). SIRD also progressed most rapidly to oral diabetes medications (other than metformin) and was the slowest to reach the HbA1c treatment goal <6.9% [52 mmol/mol]). Both SAID and SIDD progressed to sustained insulin use considerably more quickly than the remaining clusters. By contrast, MARD and MOD were characterized by reasonably favorable profiles.

This initial step demonstrated that one can derive clusters from existing big data that make eminent physiological sense. One limitation of this approach though, in contrast with a genetically driven strategy, resides in the use of phenotypic criteria for clustering that are ascertained at disease onset and are not necessarily generalizable to the many people one would want to stratify (with normoglycemia or with advanced diabetes). One should also remain cognizant that a clinician may not be able to unequivocally place an individual patient into a given cluster; thus, the implementation and clinical utility of this approach remains to be demonstrated.

It will be essential to understand how the relationships between these genetic and physiological approaches to stratification might be combined and in doing so, how much value is added from a clinical perspective. A crucial missing piece is evidence that by clustering patients in this way, disease course, diabetes complications or treatment response can be predicted with sufficient accuracy to be of clinical value. This determination requires the explicit assessment of predictive accuracy and reclassification. Similarly, it is not known whether treatment that is guided by cluster identity will be more or less effective than current approaches, for which intervention studies will be needed. Moreover, because clustering techniques typically require the dichotomization of continuous exposure variables, which usually results in loss of power, the predictive accuracy of algorithms that do not require this type of data transformation is likely to be superior.

Family history of diabetes is a strong predictor of disease and is frequently included in diabetes prediction algorithms. For information on family history to enhance the predictive ability of the phenotypic clusters proposed by Ahlqvist et al. would require that some clusters

be more driven by familial factors than others. This may well be true and future studies exploring the genetic basis of these clusters may help test this hypothesis. However, family history is the consequence of both genetic and environmental influences (including developmental exposures), and understanding why family history affects disease progression differentially across clusters, if indeed it does, would likely be intensely scrutinized owing to the etiological insights this might reveal.

## **Overview of major precision medicine initiatives**

After the first draft sequence of the human genome was published in 2001(10), methods and technologies were rapidly developed that enabled large-scale quantification of human genetic variation, and subsequently too, variation across other biological strata. As investigators began using these technologies, global research consortia grew through which novel biomarkers for type 2 diabetes were discovered. The rapid growth of large datasets and *ad hoc* collaborative networks, as well as clear evidence that this new approach to biomarker discovery worked, laid the foundations for large precision medicine initiatives. Although some initiatives have built new cohorts from scratch, most have leveraged existing data and biomaterials already stored in biobanks (see Table 1 and Fig 1).

In 2008, a joint undertaking between the European Commission, European academic institutions and the European Federation of Pharmaceutical Industries and Associations (EFPIA) was launched. This 5.6 billion EUR program, called the *Innovative Medicines Initiative* (IMI), comprises ~100 projects focused on the major diseases affecting European citizens. Of these, several focus on precision medicine in type 2 diabetes: SUMMIT (diabetes complications), DIRECT (drug response and glycemic deterioration before and after the onset of type 2 diabetes)(22), RHAPSODY (glycemic deterioration before and after the onset of type 2 diabetes), BEATDKD (diabetic kidney disease). A common objective is the discovery and validation of biomarkers that facilitate the stratification of patient populations into subgroups that might be treated more effectively than without biomarker stratification. In some instances, the focus is also on diagnostic reclassification. Unlike most other precision medicine initiatives, those within the IMI focus on the integration of multiple biomarkers, such as genotypes, transcripts, proteins, metabolites and metagenomics sequences.

The *UK Biobank* cohort (est. 2005) includes around 500,000 adults, the vast majority of whom have provided non-fasting blood samples, self-report data on lifestyle, health and well-being, and have been genotyped using genome-wide arrays. In sub-cohorts, more



detailed phenotyping has been undertaken, such as MRI scans, physical activity monitoring, and metabolomics. Research conducted using UK Biobank data, for example, has shown that genetic variants associated with obesity are likely to influence susceptibility to a range of modifiable lifestyle exposures(23-26), which may have relevance to diabetes. Nevertheless, the very small magnitude of these effects and susceptibility to confounding(25) precludes the immediate translation of these findings into clinical practice. Alternatively, as UK Biobank accrues incident events of diabetes complications, the database is likely to become a powerful resource through which the prognostic value of stratifying populations into subgroups or determining how environmental risk factors differentially affect disease susceptibility by subgroup can be assessed.

Plans to implement precision medicine into US medical practice accelerated in 2015 with the announcement of the *Precision Medicine Initiative* (PMI), for which US\$215 million was initially budgeted by the federal government(27, 28). In the short term, the PMI is focused on cancer, whereas in the longer-term all areas of health and health-care will be studied, with specific emphasis placed on the discovery of predictive biomarkers for type 2 diabetes(28). A major feature of the PMI is a one-million-person cohort and research program called *All of Us*. The cohort, supported by a US\$55 million budget, is built around nation-wide recruitment sites under the banner of the *PMI Cohort Program*. Managed-access for accredited researchers to biobanked data and samples is intended to facilitate several major goals, including those related to gene-environment interactions, pharmacogenomics, risk stratification, mobile health technologies, health empowerment, and innovative clinical trials (<https://allofus.nih.gov>).

Several other major US initiatives predate the PMI and have diabetes and its risk factors at their core. These include the *Million Veteran Project* (MVP) and the *Accelerating Medicines Partnership in Type 2 Diabetes* (AMP T2D). The MVP uses genomics and other health data obtained through electronic medical records and follow-up surveys in about 600,000 military veterans aged 50 to 69-years(29). The AMP T2D seeks to gather genomic and meta-genomic data and create an analytical engine that can be used to mine the genetic basis to diabetes and related traits, while safeguarding the confidentiality of the results. Data access is a central pillar of AMP T2D, and through the *T2D Knowledge Portal* ([www.type2diabetesgenetics.org](http://www.type2diabetesgenetics.org)), the consortium has assembled genetic and phenotypic data from type 2 diabetic cases and controls from multiple populations, creating a central repository for such data ([www.type2diabetesgenetics.org/informational/about](http://www.type2diabetesgenetics.org/informational/about)). These ability of these initiatives to contribute to precision diabetes medicine is likely to be enhanced by

their partnerships with industry, which are necessary to translate research into FDA-approved therapeutics.

The Nordic countries have a long history of biobanking and registry-based research and have contributed substantially to discoveries in diabetes genetics over the past decade. In 2015, the *Nordic Precision Medicine Initiative* was formed to bring together genetic and other biomedical data from >1 million Nordic citizens(30). Several national precision and genomic medicine projects are underway: in Estonia, for example, the Estonian Genome Center at the University of Tartu (EGCUT) is curating a population-based biobank suitable for precision medicine research in diabetes and other complex diseases. The aim is to promote and advance the development of genetic research and the implementation of genomic data into clinical practice to improve public health. The Estonian Government recently launched the *Estonian Precision Medicine Pilot Project* (2015-2018), which seeks to implement personalized medicine on a national scale. Accordingly, the government has provided US\$5.9 million to support genotyping in 100,000 Estonians. In Finland, the *FinnGen* project was launched in 2017 with the objective to link genomic data with digital health care data for 500,000 Finnish citizens (10% of the country's population) through a public-private partnership. In Sweden, GAPS (the Genomic Aggregation Project in Sweden) has assimilated >160,000 genotyped samples with corresponding phenotype data covering a wide-range of diseases, including diabetes(31) and GMS (Genomic Medicine Sweden) is spearheading clinical genomics on a national scale. In Iceland, the company deCode genetics has established a genetic and phenotype database that encompasses the entire population (n=334,000), which fuels genetics research and drug target validation for a wide-range of diseases, including diabetes.

Several other countries have launched large-scale programs of research on genomic and precision medicine, many with clear paths to clinical application although often only in relation to rare pediatric diseases. In Saudi Arabia, the very high prevalence of type 2 diabetes (~20%) led the Saudi government and King Abdulaziz City for Science and Technology to initiate the Saudi Human Genome Project, which seeks to sequence the genomes of 100,000 Saudi citizens in order to identify the genetic basis of monogenic and complex diseases like type 2 diabetes. In China, which has become a formidable force in decoding genomes(32), the government in 2016 announced a bold initiative to become a global superpower in precision medicine, with a US\$9-billion, 15-year precision medicine initiative(33). The Chinese PMI has three core objectives, focused on recruiting: i) millions of participants from the seven main regions of China to form a nationally-representative cohort; ii) eight disease-specific cohorts (cardiovascular, cerebrovascular, respiratory, metabolic,

neurological, psychosomatic, immune system disorders, and seven common malignant tumors) totaling 700,000 participants; iii) a clinical cohort (N=50,000 patients with 50 rare diseases)(34).

## Clinical translation

The practice of precision diabetes medicine is currently confined to rare monogenic forms of the disease. Nevertheless, individual variants present only in specific population isolates have been discovered that may have clinical value in the prevention or treatment of type 2 diabetes. These include a *TBC1D4* nonsense variant (p.Arg684ter) of relatively high prevalence in Greenlandic Inuit (MAF 17%) and other circumpolar Inuit populations that predisposes a substantially increased risk of diabetes (odds ratio >10 in those homozygous for the variant)(35). The mechanism of action involves the muscle-selective loss of the long *TBC1D4* isoform and diminished GLUT4-mediated cellular glucose uptake in response to insulin. A thymine for cytosine substitution that causes a premature stop at codon 363 of *TBC1D4* has also been discovered in people with acanthosis nigricans; the mutation causes post-prandial hyperinsulinemia as a possible consequence of a specific muscle and adipose tissue insulin resistance (36).

In Latinos, a low frequency (MAF = 2.1% in people with type 2 diabetes) missense variant (p.E508K) at *HNF1A* conveys a type 2 diabetes odds ratio >5(37). *HNF1A* also harbors mutations that cause rare monogenic diabetes that can be successfully treated with sulfonylureas (discussed later), suggesting this is true for the non-trivial number of Latino individuals with type 2 diabetes who carry p.E508K. Despite the relatively large effects these variants convey, whether they will prove useful in the context of precision medicine is unknown, as no formal assessment of clinical utility or cost-effectiveness has been reported.

Metformin was discovered in the 1960s and is currently the frontline drug for early-stage diabetes treatment, although its mechanisms of action remain unclear(38). There is genetic evidence for metformin intolerance(39), although this has not been widely replicated. By contrast, variants at *ATM*(40) and *SLC2A2* (encoding GLUT2)(41) have been associated at a genome-wide level of statistical significance with metformin response. Whilst the effects conveyed by these variants are too small to guide patient-level treatment decisions, these findings may prove valuable in determining metformin's mechanisms of action.

Many major precision medicine statements, including the Executive Summary of the US Precision Medicine Initiative(28) and a National Research Council report focused on

precision medicine and new disease taxonomies(42), make clear that research and practice in precision medicine should consider the major impact of lifestyle in disease etiology, prevention and treatment. The incorporation of lifestyle into precision diabetes medicine is adequately justified by its proven benefits in diabetes prevention and treatment. Yet, there is good evidence that people benefit to varying degrees from diet and exercise and that personal biology underlies this(43). Thus, if precision medicine programs are to adequately consider the impact of lifestyle and other environmental exposures, it seems logical that emphasis should be placed on improving the precision of this type of antidiabetic therapy too, and not only drugs.

One compelling example of how glycemic response to food can be predicted using an individual's biomarkers comes from a study of 800 young adults whose gut metagenomic sequences were ascertained and diet and blood glucose variation (from continuous glucose monitors) were monitored for a week(44). Each participant received one standardized meal (50g carbohydrate) daily. The authors observed that although participants elicited different postprandial glycemic responses, the responses to the same food were consistent within individuals. Using machine learning algorithms, these data were used to predict each participant's postprandial glycemic response to a given food. They subsequently administered tailored diet interventions to modulate glucose levels, providing proof-of-concept that personalized diets can reduce blood glucose variability. Notwithstanding the importance of this work from a basic science perspective, to determine its value for precision medicine requires knowing if minimizing variations in glucose in healthy adults is clinically relevant and whether the approach to predicting glycemic response to food also works in people with diabetes. To date, neither of these important questions is addressed in the published literature.

Despite lifestyle's proven efficacy in diabetes prevention, the resources available for research on lifestyle medicine are massively outweighed by investments in pharmacotherapy. In 2013, for example, ~US\$35 billion was spent by pharmaceutical companies on research and development(45). Although there are no comparable statistics for research in lifestyle medicine, funding is likely to be orders of magnitude less as most of this comes from the public purse. The marketing of foods and beverages on the other hand is a huge industry whose messages often counter public health efforts to promote healthy lifestyle. On an international scale, hundreds of billions of USD are spent on food marketing annually; one of the biggest spenders is Unilever, which spent ~US\$8 billion on brand and marketing investments in 2017 alone(46). Marketing junk foods and beverages is handsomely resourced, competing with public health initiatives. The major food companies

in the UK, for example, have invested roughly US\$200 million each year in junk food advertising, which contrasts the US\$7.2 million spent on *Change4Life*, the UK government's flagship healthy eating campaign(47).

Notwithstanding the relative dearth of funding for lifestyle medicine, some key initiatives exist. One of the largest of these is the National Institutes of Health's Common Fund initiative on the *Molecular Transducers of Physical Activity* (<http://commonfund.nih.gov/MolecularTransducers>), which seeks to determine “*optimal physical activity recommendations for people at various stages of life*” and develop “*precisely targeted [exercise] regimens for individuals with particular health needs*”. Elsewhere, the *Food4Me* study, a research program funded by the European Union, explored the role of genetics in the personalization of diet; data from the study suggest that personalized diet interventions supported by genetic data improve consumption of healthy foods(48) and help sustain healthy food choices(49). Interestingly, most loci selected for this intervention (variants at *MTHFR*, *FTO*, *TCF7L2*, *APOE* and *FADS1*) lack evidence of individual-level clinical relevance(50), suggesting that the success of the Food4Me intervention was not dependent on the quality of the genetic information.

Although most if not all precision medicine initiatives are predicated on the assumption that their findings will help improve public health, the emphasis of these initiatives is almost always on the generation of new knowledge. MVP, for example, seeks “*to improve understanding of how health is affected by genetic characteristics, behaviors, and environmental factors*”(29). Whilst this objective will undoubtedly be achieved, how this information will eventually be used to optimize prevention and treatment of diabetes and other diseases is unclear. Indeed, few precision medicine initiatives focused on complex diseases provide a clear plan for clinical translation (see **Fig. 2**).

## **Potential bottlenecks on the path to precision medicine**

### *Cost-effectiveness*

The global precision medicine market was valued at US\$43.6 billion in 2016, and is predicted to triple in value within the next decade(51). The economic dynamics associated with precision medicine differ from those of conventional medicines, as the nature of the approach means that precision medicines are likely to be approved for use only in specific subpopulations, limiting the number of patients eligible for treatment with a given drug. By

contrast, the effectiveness of precision medicines should be higher for patients within these subpopulations than for conventional medicines, and side-effects may be fewer and less severe. Owing to the smaller market share for a given precision medicine, competition to produce cheaper drugs between manufacturers may be less than for conventional drugs, and the drive to develop off-patent biosimilars (i.e., drugs with active properties identical or similar to a previously licensed drugs) is likely to differ compared with conventional medicines, depending on the extent to which first-in-class drugs are undercut by cheaper alternatives. Collectively, these factors will impact the cost-effectiveness of precision medicines in type 2 diabetes(52).

Thus far, very few cost-effectiveness analyses in precision diabetes medicine have been published, despite longstanding recognition that cost-effectiveness is a key requirement for clinical translation(53). The rare examples of such studies have focused exclusively on rare monogenic forms of diabetes: neonatal diabetes(54) and maturity onset diabetes of the young (MODY)(55, 56).

Neonatal diabetes is diagnosed in infancy and affects about 1:400,000 live births and roughly half (~1:252 000 in people aged <20-years) develop permanent neonatal diabetes (PND)(54). Of the latter group, up to 70% are estimated to carry mutations in the genes encoding the ATP-sensitive potassium channel (*KCNJ11* and *ABCC8*). These mutations block the closing of the K(ATP) channels, which prevents beta cell depolarization and corresponding insulin secretion(57). However, treatment with sulfonylureas rectifies this defect in ~90% of cases, allowing the discontinuation of exogenous insulin(58). The earliest cost-effect analysis in precision medicine focused on sulfonylurea therapy in PND(54). The authors estimated that genetic testing in PND would convey significant quality-of-life benefits at 10-years (0.32 QALYs; US\$12,528 saved), increasing to 0.70 at 30-years (US\$30,437 saved).

A range of single gene defects cause MODY, each of which are used to diagnose one of five forms of the disease. In MODY1 and MODY3, insulin secretion is impaired. The disease occurs early in life and is often misdiagnosed as type 1 diabetes, and exogenous insulin therapy is thus prescribed. However, treatment with sulfonylureas enables secretion of endogenously produced insulin. Switching from insulin to sulfonylureas is preferable for a number of reasons, including those related to safety and burden. MODY2 is caused by mutations in *GCK*, which lead to chronically elevated, but non-progressive blood glucose concentrations that do not typically require treatment; thus, diagnosing MODY2 also conveys reduced costs and burdens associated with unnecessary treatment. The first cost-

effectiveness analyses focused on MODY1-3 in US adults (25-40 years) with diagnosed type 2 diabetes(56) based many of its assumptions on the findings of the UK Prospective Diabetes Study(59). It also assumed a 2% frequency of MODY amongst people with diabetes and set genetic screening costs at US\$2,580. Under these assumptions, genetic screening for MODY would not be cost-effective. The second study focused only on MODY1 screening and found that genetic screening was not cost-effective given the diabetes population frequency of MODY1 mutations are unlikely to exceed 2%. Substantial reductions in genetic sequencing costs may, however, render screening cost-effective(55).

### *Regulatory consensus*

More than half of the most clinically impactful drugs developed recently were discovered through academia-led research(60), emphasizing the huge value of public-private partnerships. Many of the large precision diabetes medicine consortia involve both academia and industry within which unsurprising emphasis is placed on the discovery and validation of biomarkers that expedite drug development. This expectation is backed-up by the proven ability of genetics to fast-track drug development by pinpointing high-value drug targets, helping halve drug failures and markedly reducing their costs(61). In drug-repositioning, genetics has also proven its worth, by revealing previously unknown conditions that a drug can be used to treat and by helping predict drug side-effects.

To obtain FDA (or EMA) approval for biomarkers in medical products and devices involves a comprehensive qualification process (see: <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm535395.htm>), within which exists the requirement for a statement termed a *context of use* (COU). The COU statement requires a clear and detailed description of the intended role of the biomarker in drug development, as well as risks and benefits. The Foundation of the NIH (FNIH) recently published the *Framework for Defining Evidentiary Criteria for Biomarker Qualification*(62), which provides an expanded outline of the biomarker classifications defined by the FDA.

The process of biomarker qualification in drug development requires stringent adherence to the relevant regulatory agencies' approvals processes. In some studies that seek to discover biomarkers for diabetes drug development, the process is well-rehearsed and aligning biomarker discovery and validation strategies with regulatory expectations is relatively straightforward; however, it does require that precision medicine consortia are well-versed in these processes. Biomarker discovery in prediabetes is more challenging though, as prediabetes is not a distinct disease state and although some people with prediabetes

develop diabetes and its complications, a large proportion remain healthy for many years(63). Nevertheless, a subgroup of those with prediabetes will progress to diabetes and identifying these people before beta-cell function is substantially diminished would open the door for several powerful therapeutics that are ineffective once endogenous insulin production has faded. However, because neither the FDA nor EMA currently recognizes an intermediate endpoint for disease progression in prediabetes drug trials, gaining regulatory approval for new prediabetes biomarkers requires that researchers foster close and frequent communications with the regulatory agencies to ensure candidate biomarkers have the possibility to progress through the regulatory process.

### *Legal, social and ethical*

Balancing the interests of society and its citizens, the risks and benefits, legislation and individual freedom, as well as the risk of exasperating disparities, are central to many commentaries on the legal, social and ethical aspects of precision medicine.

Precision medicine research is heavily dependent on biobanked data and tissues. Oftentimes, the original informed consents were obtained many years before modern omics technologies existed, at a time when many research questions germane to precision medicine were inconceivable. Often, the informed consents were broad, and ethics committees have concluded that these modern research questions are within the scope of the consents. As new, ever larger and interconnected cohorts are being formed, the desire many researchers share for broad consenting and/or to bank data or samples for unspecified future research must be placed in context with several important ethical realities: the need to maintain participants' confidentiality, appropriately handle incidental findings, determine who owns the samples and data, consider cultural sensitivities, return results to participants, engage society, and ensure unused material is properly disposed of(64).

Much as precision medicine was inconceivable when many existing cohorts were formed, it is impossible to accurately predict how contemporary cohorts will be used in the future. Furthermore, many precision medicine initiatives involve the hybridization of academia, health care and industry, which may challenge some of the more altruistic motivations of participants in academia-led biomedical research. Moreover, much of the highly sensitive data collated by these initiatives will eventually be made available through managed-access portals to a wide-range of end-users who were not part of the data collection process. Thus, much of this highly sensitive data will be widely disseminated and used by distant end-users to address a plethora of diverse research questions that cannot yet be conceived, factors that need to be considered during the informed consent process. These are challenges for



historical biobanks as well as new precision medicine cohorts that consent only at enrollment. To help overcome this, a process called *dynamic consent* has been developed, which allows consents to be progressively updated as projects evolve, but requires fluid communication with participants throughout the life-course of a study(65).

A major concern about genetic data is its linkage to databases that enables inferences about a person's social, cognitive, moral, cultural, health, or sexual identity, which participants had not consented to, or for such inferences to be made about family members without their consent(64). Indeed, ensuring genomics data is used in a way consistent with appropriate ethical standards is a core feature of most current health data protection legislation(66). Notwithstanding these risks, there are major benefits associated with big data, which include the discovery of novel disease mechanisms and therapeutic targets, many of which only become visible when datasets scale to massive proportions. Thus, rather than constrain the growth and responsible utilization of big data, emphasis is being placed on implementing legislation that protects privacy and helps prevent data breaches, whilst facilitating the safe and responsible storage, transfer and utilization of data. In the European Union, for example, the General Data Protection Regulation was implemented in May 2018 to harmonized data privacy laws across Europe. A key feature of this legislation as it relates to precision medicine research is that the analysis of sensitive data requires explicit opt-in consent, whereas for non-sensitive data, unambiguous (implied) consent is sufficient.

## **Summary & Conclusions**

Diabetes medicine is likely to evolve dramatically in the coming years, ideally because evidence emerges from the major precision medicine initiatives to support its utility in preventing or treating diabetes, but no doubt also because of the major commercial interest in seeing precision medicine grow. One of the possible outcomes will very likely be the replacement of current classifications of diabetes with empirically-derived sub-classifications that can be coupled with treatment regimens that, compared with conventional medicines, are more effective, less costly and convey fewer unnecessary side-effects. As genetic databases grow, genetics will be increasingly used to discover new drug targets. At this time, the clinical application of genetics is confined to the diagnosis of and therapeutic guidance for rare forms of diabetes, as well as the prediction of adverse drug reactions. The ways in which genetics may or may not guide prevention and therapy in common forms of diabetes is unclear. However, because characterizing variation in a patient's nuclear genome is inexpensive and easily achieved, and DNA variation remains constant across the life-course, it is likely that genetic sequences will feature in most patient's clinical records.

Given this, genetic data will likely be deployed in diverse ways in the diabetes clinic of the future. The roles other omics technologies, digital imaging devices, and wearables will play in precision diabetes medicine are harder to forecast, as research in these areas is less advanced and the cost of obtaining some of these data will likely remain high relative to genetics. Finally, although many precision medicine initiatives focus predominantly on pharmacotherapy, optimizing lifestyle (and possibly surgical) interventions using biotechnologies also has great potential for optimizing type 2 diabetes prevention and treatment.

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## Tables and Figures

Name	Region	Start date	Funding	Initiative	Population (in thousands)
Australian Precision Medicine Initiative	Australia	2016	A\$25 million	Public-private	-
Chinese Precision Medicine Initiative	China	2016	US\$ 9 billion	Public-private	2
Innovative Medicines Initiative (IMI) (diabetes projects only)	EU	2008	EUR 200 million	Public-private	>100
Nordic Precision Medicine Initiative	Nordic (Denmark, Estonia, Finland, Iceland, Norway and Sweden)	2015	-	Public-private	>1000
Estonian Personalised Medicine Initiative (Nordic Precision Medicine Initiative)	Nordic (Estonia)	2015	EUR 33 milion	Governmental	100
FinnGen (Nordic Precision Medicine Initiative)	Nordic (Finland)	2017	EUR 60 million	Public-private	500
Genomic Aggregation Project in Sweden (Nordic Precision Medicine Initiative)	Nordic (Sweden)	2015	-	Public	160
Saudi Human Genome Project	Saudi Arabia	2013	US\$ 40 million	Governmental	100
Genomics England	UK	2012	US\$ 523 million	Public-private	75
UK Biobank	UK	2006	US\$ 122 million	Public-private	500
Project Baseline	US	2017	>US\$ 41 million	Public-private	10
US Precision Medicine Initiative	US	2015	US\$ 215 million	Public-private	1000
Accelerating Medicines Partnership	US	2014	US\$ 52.8 million	Public-private	150
Million Veteran Project	US	2011	US\$116 million	Public-private	612

**Table 1:** Global precision medicine initiatives of relevance to type 2 diabetes



## **Figure legends**

**Fig. 1:** Global precision medicine initiatives of relevance to type 2 diabetes

**Fig. 2:** The path to precision medicine in type 2 diabetes

Figure 1.

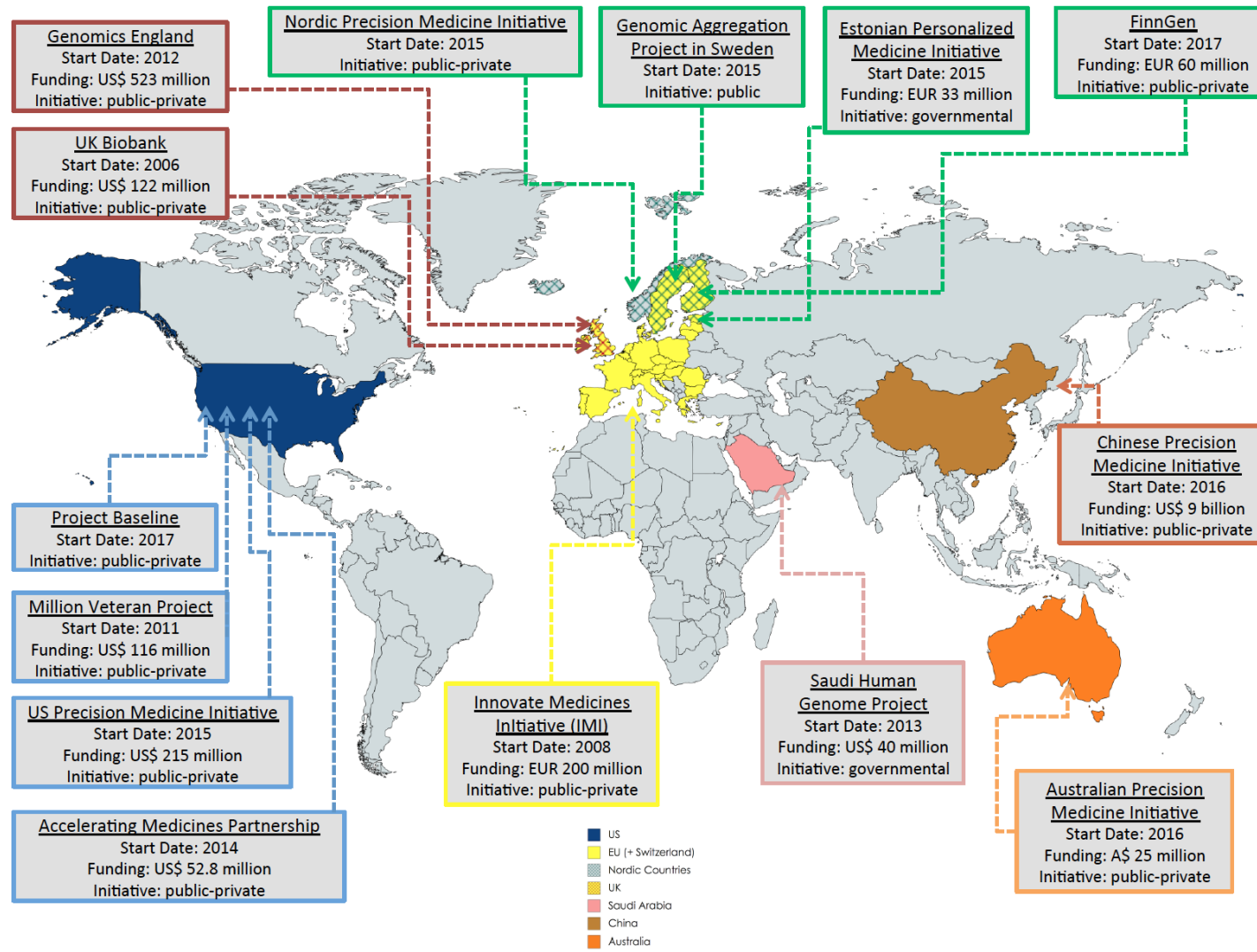


Figure 2.

