REVIEW

Could personalised risk prediction for type 2 diabetes using polygenic risk scores direct prevention, enhance diagnostics, or improve treatment? [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract
Over the past three decades, the number of people globally with diabetes mellitus has more than doubled. It is estimated that by 2030, 439 million people will be suffering from the disease, 90-95% of whom will have type 2 diabetes (T2D). In 2017, 5 million deaths globally were attributable to T2D, placing it in the top 10 global causes of death. Because T2D is a result of both genetic and environmental factors, identification of individuals with high genetic risk can help direct early interventions to prevent progression to more serious complications. Genome-wide association studies have identified ~400 variants associated with T2D that can be used to calculate polygenic risk scores (PRS). Although PRSs are not currently more accurate than clinical predictors and do not yet predict risk with equal accuracy across all ethnic populations, they have several potential clinical uses. Here, we discuss potential usages of PRS for predicting T2D and for informing and optimising interventions. We also touch on possible health inequality risks of PRS and the feasibility of large-scale implementation of PRS in clinical practice. Before PRSs can be used as a therapeutic tool, it is important that further polygenic risk models are derived using non-European genome-wide association studies to ensure that risk prediction is accurate for all ethnic groups. Furthermore, it is essential that the ethical, social and legal implications of PRS are considered before their implementation in any context.

Keywords
Type 2 diabetes, polygenic risk score, genetics, risk prediction, diverse ancestry, precision medicine, personalised medicine
Introduction
Type 2 diabetes mellitus (T2D) is a major global health issue. Since the 1990s, the number of people with diabetes has more than doubled globally, with 439 million people estimated to be suffering from the disease by 2030, 90–95% of whom will have T2D. The International Diabetes Federation estimated that as of 2015, 1 in 11 adults aged 20-79 worldwide had diabetes mellitus. This pandemic, which for many affected people is debilitating and ultimately lethal, must urgently be addressed with effective public health measures. Diabetes is a major cause of cardiovascular and renal failure, retinopathy, blindness and limb amputation, and is ranked 7th in the top 10 global causes of premature death in 2016.

Patients with diabetes have a 15% increased risk of all-cause mortality, which is twice as high (30%) in individuals under the age of 55. This is particularly concerning considering that T2D is increasingly being observed in children and young adults, especially in certain ethnic groups. Heritability of T2D is estimated to be between 25 and 40%; however, it is predominantly behavioural and environmental changes resulting from worldwide socioeconomic shifts that have fuelled this growing pandemic. Indeed, two-thirds of all diabetes cases will occur in low-to-middle-income countries in 2030, with China recently having overtaken India as the global epicentre.

In recent years, efforts have been made through genome-wide association studies (GWAS) to identify genetic variants associated with an increased risk of T2D, with the aim of using these variants to calculate individualised polygenic risk scores (PRSs). These scores represent a weighted sum of the number of risk alleles carried by an individual, where weights are defined by each allele’s measured effects in GWAS. Thus, PRS calculate the genetic component of an individual’s overall disease risk and can be used to describe both a person’s absolute risk as well as an individual’s relative risk compared to the rest of a population. The potential utility of PRS lies in three main areas. PRS can be used to enhance the timeliness and prediction-accuracy of disease onset and progression monitoring, to improve therapeutic management through the selection of interventions aimed at preventing, curing or containing disease, and they can inform genetic counselling and family planning.

Although there are wide-ranging potential applications for PRS, there remain some significant limitations; PRS are currently significantly more accurate in predicting risk for European than non-European populations because of bias in the ethnicities of GWAS participants. According to the GWAS catalogue, around 79% of all GWAS participants are European, despite making up only 16% of the global population. Polygenic risk models have been shown to be inaccurate when applied to populations different to those used for their derivation. Considering that the majority of diabetics reside in non-European countries, this data gap must urgently be filled before PRS can be reliably used in a clinical context. Recent efforts, such as the H3ABioNet in Africa and The Slim Initiative for Genomic Medicine in Mexico, have aimed to diversify GWAS whilst simultaneously ensuring that additional data and insights generated do not solely provide benefits to high-income countries. Taken together, it is now timely to discuss the potential advantages in deploying PRSs for risk prediction and treatment optimisation whilst reflecting on remaining challenges related to wide-scale implementation in clinical practice as well as socio-ethical implications.

Developing PRSs for T2D
Early disease detection and prevention are fundamental goals of any public health strategy. Genetic risk represents the earliest measurable alert for potentially avoidable heritable diseases in later life and is thus a useful tool for predicting who should be actively targeted with preventative interventions. Recent studies suggest that, for a subset of diseases, our knowledge of underlying genetics is comprehensive enough now to enable polygenic risk profiling based on PRS for personal and clinical use (Figure 1). Considering the condition’s prevalence, it is useful to consider whether polygenic risk profiling for T2D is currently reliable enough to be introduced into clinical practice or health and life insurance companies’ risk underwriting methodologies.

The aim of polygenic risk modelling is to accurately predict the probability of an individual developing T2D based on specific single nucleotide polymorphisms (SNPs) in their genome. GWA studies identify SNPs that are statistically associated with the disease, after which algorithms allow selection of the SNPs that should be included in the PRS model. This step is important because GWSA don’t exclusively identify causal variants, and inclusion of non-causal variants would significantly reduce the predictive performance of PRS models. Subsequently, the weights of the selected SNPs are calculated according to their corresponding estimated regression coefficients.

GWAS provide limited information on the genetic architecture of a disease because the genes or functional DNA elements through which detected variants exert their effects on the traits predominantly remain unidentified. This is mainly a result of linkage disequilibrium (LD), where two SNPs are inherited together more commonly than would be expected if they were independent and assorted randomly, leading to the inclusion of SNPs that are in LD with a causal gene, rather than being causal themselves. Several approaches have been used to resolve this issue, most recently by combining summary-level data from GWAS with expression quantitative trait locus (eQTL) studies to identify genes whose expression levels are associated with a complex trait. These methods are based on the idea that if the expression level of a gene is influenced by a genetic variant, there will be differences in gene expression levels among individuals carrying different genotypes of the variant.

As recently as 2013, the degree of T2D heritability explained by identified genetic variants amounted to only 10%. Thus, it was assumed that rare variants may yet be undiscovered. However large-scale whole genome sequencing initiatives in following years covering five ancestry groups did not support the idea that rare variants have a major role in predisposition to T2D. It is also important to note that GWAS do not assess intrauterine effects, gene-gene or gene-environment interactions, which may account for an additional portion of T2D heritability. Nevertheless,
as of 2019, over 400 genetic variants were known to account for 20% of T2D heritability, most likely a result of the expansion of GWAS efforts looking at larger and more ethnically diverse groups.

Recent efforts have attempted to account for additional heritability by including SNPs below the accepted genome-wide significance level to form a ‘global extended polygenic score’; however, this risks the inclusion of variants not associated with the disease. For example, if there are unaccounted for differences in the population structure of the control and diseased populations in a GWAS, SNPs included in the model may be linked to population structure rather than the disease. Regardless, studies have suggested that lowering the SNP significance threshold does not significantly increase predictive ability.

Are PRSs an improvement over traditional clinical predictors of T2D?
Clinical predictors, such as age, sex, body mass index, glycaemia and family history of T2D, are typically used to predict T2D risk. PRS do not currently allow estimation of risk more accurately than by these traditional factors, nor does the addition of risk scores to these factors significantly improve prediction accuracy. Predictive models of T2D are typically assessed by their area under the curve (AUC), which represents the probability that a randomly selected individual with T2D will have a higher calculated risk than a randomly selected individual without T2D. The AUC of clinical models that take into account biomarkers as well as nominal factors typically range between 0.7 and 0.9, whilst the AUC of three published global, extended polygenic risk models not adjusted for age and sex reached only between 0.64 and 0.66. Even when two of these models were adjusted for age and sex, the AUC increased to only 0.73. Despite these findings, a study by Lyssenko et al. that added a 16 SNP PRS to clinical risk scores was able to reclassify 9% and 20% of Swedish and Finnish subjects respectively to a higher risk category, despite the addition of the PRS only increasing the AUC from 0.74 to 0.75. Additionally, the AUC for the clinical model decreased for the same individuals over time, while the AUC of the genetic risk score increased. Regardless of these results, the AUC is not necessarily the most appropriate measure of the clinical utility of PRS. The AUC is a measure of the ability of PRS to act as a sensitive diagnostic test, or in other words the likelihood that the onset of disease will occur in an individual, despite the real value of the risk scores lying in prognosis.

In some cases, information on family history may be difficult to obtain, either because the individual is not in contact with direct
family members or because the individual is young and family members may not yet display symptoms of T2D. Regardless, considering that the majority of T2D cases are highly polygenic, parent and child generations may carry significantly different overall risks because only half of their genes will be inherited from each parent. Additionally, unlike phenotypic factors, which may be subject to confounding effects of disease and treatment, PRS are stable and can be used throughout the life course.

Although polygenic risk models do not improve existing predictive methods, they may nevertheless be useful in a clinical context. Because the effects of BMI and polygenic risk for diabetes are additive, they can be used in combination to distinguish risk between individuals with similar clinical characteristics. For example, an individual with average BMI and a high PRS may have the same overall risk as an individual with high BMI and low polygenic risk, potentially allowing identification of risk factors with cumulative impact as well as factors that can be traded-off against one another. The combination of clinical risk factors with PRS may reclassify some individuals to exceed the thresholds that justify certain medical interventions.

**Partitioned polygenic scores (pPS) for improving T2D prediction**

Clinical progression to T2D can be caused by multiple pathophysiological processes. For example, some genetic variants increase T2D risk by promoting obesity, whilst others impact insulin sensitivity, insulin secretion, islet function or incretin signalling. Genetic variants associated with T2D can be broadly grouped into pathophysiology-based clusters by hierarchical clustering and GWAS that test the association between variants and non-disease outcomes. For example, early efforts to group variants in this way identified a pathophysiological process that contributes to T2D risk through co-causing insulin resistance characterised phenotypically by lower levels of adiposity. This represents a case where pPS may be more effective than clinical factors in accurately predicting likelihood of T2D and facilitate earlier diagnosis.

pPS information could become especially useful if correlated with downstream morbidities and endpoints associated with T2D. Indeed, cluster associations linked to insulin resistance have been correlated with coronary artery disease, stroke and the renal complications of diabetes. Genetic identification of the risk of specific diabetes-related complications could direct targeted therapeutic preventative interventions and be used to determine by which laboratory parameters and how closely an individual’s disease progression should be tracked. For example, individuals with cluster associations linked to renal complications might want to have more frequent serum creatinine and urea, as well as urine albumin and glucose tests to detect any deterioration in kidney function as early as possible. It may also be useful to screen kidney transplants for specific genes before passing them on to patients with diabetes currently on dialysis.

As T2D is highly polygenic, it is more useful to strive for a graded model of disease risk than distinct categories. Each pathophysiological process contributing to the onset and deterioration of T2D can be seen as an individual axis, where a patient will be positioned at a particular point ranging from high to low T2D risk. Although non-genetic factors also contribute to T2D risk, the degree of risk across combined pathophysiological axes may inform both disease presentation and progression. Progression along axes could potentially be tracked in real time if process-specific biomarkers were linked to pPS. For example, low-density lipoprotein cholesterol is used as a biomarker for the influence of genetics and environmental factors on adverse cardiovascular event risk. The rising amount of large proteomic and metabolomic data sets will facilitate further linking of biomarkers to pathophysiological processes in future.

Most treatment plans for T2D aim primarily to maintain a steady serum glucose level in order to prevent any damage to the epithelium of small arteries and capillaries. However, pPS could provide additional, potentially more specific, information to inform the treatment or preventative measures of T2D patients or probable future patients. Indeed, in a study of 14,813 individuals with T2D, one-third fell within the top decile of T2D risk for at least one cluster, and of these, 75% were placed in the top decile for one specific cluster. This suggests that there is a realistic opportunity to improve T2D treatment through targeted interventions. However, drugs that target particular pathways, for example sulfonylureas and thiazolidinediones, appear to be equally effective in individuals with complementary gene clusters as in those without. This is likely because the overall accounted for heritability of T2D is still too low to predict differential therapeutic outcomes.

**Using PRSs to inform interventions**

PRS for T2D can be used to identify the most suited therapies and preventative behavioural interventions. A study by the Diabetes Prevention Program Research Group assigned 3,234 nondiabetics with elevated fasting and post-load plasma glucose concentrations to placebo, metformin or lifestyle modification programme groups. After 2.8 years, the lifestyle intervention had reduced T2D incidence by 58%, while metformin reduced T2D incidence by 31% compared to placebo. In an intervention like this, PRS could be used to more effectively assign individuals to either metformin or the lifestyle modification groups. For example, those with a high BMI but low PRS could be selectively assigned to the lifestyle modification group, whilst those with a high PRS might benefit more strongly from taking metformin as well as being advised on lifestyle changes. Those with a high PRS and therefore lifelong risk may benefit from a longer-term interventional programme that comprises preventative pharmacological as well as lifestyle interventions.

A significant barrier preventing the clinical implementation of PRS is the lack of consensus as to whether behavioural interventions aiming to minimize the environmental component of T2D risk are adequately effective. As part of a randomized clinical trial, individuals with a high phenotypic risk for T2D were genetically tested and enrolled in a 12-week US Diabetes Prevention Programme (DPP), if they were shown to be in the highest or lowest risk quartiles. Interestingly, the 6-year follow-up results suggested a lower diabetes incidence in the
control group among patients enrolled in the DPP without prior genetic testing. The mixed evidence around the effectiveness of behaviour change interventions may be influenced significantly by the duration and content of the DPP, but the lack of consensus suggests that it will be very difficult to create a T2D prevention programme motivated by genetic risk scores.

Recently, attempts have been made to identify SNPs that have pleiotropic associations with several phenotypes or diseases. Verma et al. developed a network of associations from a large phenome-wide association study (PheWAS) on electronic health record (EHR) derived phenotypes from the Geisinger’s Biobank. Whilst previous similar studies relied on EHR summary statistics from disparate studies, this research benefitted from utilising a single source of EHR data. Associations were identified between 632,574 common variants and 541 diagnosis codes. Using these associations, pairs of diseases were connected based on their shared associations with a given genetic variant. This research may serve as a basis for more targeted studies to test for comorbidities related to specific phenotypes, which would be particularly relevant for T2D. Future research to expand these network analyses to link genetic variants with laboratory tests for biomarkers will also improve the prospects for targeted therapeutic interventions and/or treatment.

Identifying effective behavioural interventions is particularly useful in T2D because overall risk can be significantly modified through physical exercise and a healthy diet. Although a recent large-scale meta-analysis found that genetics-based risk estimates do not motivate behaviour change, and behavioural interventions aiming to increase physical exercise levels are usually not successful in the long term, individuals at high risk of T2D could instead be referred to incentive-driven behaviour change interventions, which are generally more successful in motivating change. This approach has recently been rolled out in the UK, where the South West London Health and Care Partnership has joined up with Sweatcoin, a phone-based fitness app that rewards users with vouchers and cash based on their step count. Early results from a cohort of 70 individuals show a 90% retention rate after three weeks. Another advantage of such an incentive-driven intervention approach is its cost-effectiveness. The study suggests that the rewards will cost the NHS an average of £25 over 10 weeks per patient and will save £3,000 for each year that Diabetes onset is delayed. Individuals who are identified before the onset of clinical predictors to have a high polygenic risk for T2D could easily be referred to this programme as a preventative measure, with a positive return on investment for the NHS.

Digital approaches to T2D prevention have a number of advantages over face-to-face behavioural interventions. To be successful, face-to-face interventions require sustained active input over long periods of time. This may be difficult for people with long working hours or care commitments to sustain, and for some there may be stigma associated with ‘needing’ behaviour change counselling, potentially prompting them to drop out of lifestyle modification programmes. Moreover, face-to-face programmes are labour-intensive and thus expensive, particularly when implemented on a large scale, in contrast to digital programmes. In response to these challenges, the NHS is now trialling five digital intervention programmes to combat T2D, combining phone calls, automated prompts, digital support groups and digital activity monitoring. In future, if proven effective, routine polygenic risk testing could become the basis for assigning high-risk individuals to bespoke combinations of cost-effective behavioural intervention programmes. Moreover, direct-to-consumer genetic testing companies that provide information on T2D risk could develop new service lines directing high-risk individuals to suitable self-help digital applications.

**Using PRSs to optimise treatment of T2D**

As well as being used to inform preventative therapeutic interventions, PRS can be leveraged to optimise treatment after the onset of disease. T2D has two major underlying pathophysiology. One involves impaired insulin secretion, whilst the other involves downstream insulin resistance. GWAS has identified variants distinctly associated with dysregulation of both of these pathways. Using pPS, an individualised ‘palette’ can in theory be generated to quantify the level of genetic risk affecting each of these two pathways. Drugs that are currently prescribed to treat T2D individually target these specific pathways. For example, sulfonylureas and meglitinides stimulate insulin release while metformin and thiazolidinediones improve insulin sensitivity.

Additionally, individual variants revealed by polygenic risk assessment could also be used to direct treatment. If the function of an individual exonic SNP is known, its pathophysiological effects can be pharmacologically targeted. However, in practise, linking T2D SNPs to their mechanistic functions has been difficult and has yielded mixed results. For example, the human mutation SLC30A8 protects against T2D, whilst it is associated with an increased risk of disease in mice. On the other hand, a variant in the ADRA2A gene has been identified as impairing insulin secretion in GK rats through the over-expression of the α2A-adrenergic receptor in islet cells. Humans carrying the variant were subsequently treated with yohimbine, an inhibitor of the receptor, resulting in a dose-dependent improvement in insulin secretion.

However, specific pharmacological targeting is not straightforward. It is likely that during clinical progression of T2D, one primary pathophysiological pathway modulates the other. For example, an inherited increased resistance to insulin may result in epigenetic regulation to increase the production of insulin, thereby skewing the ‘palette’ and reducing the effectiveness of targeted therapies. This idea is supported by evidence that sulfonylureas initially overcome insulin resistance reflected in a significant HbA1c decline, but subsequently HbA1c levels gradually rise again, possibly as a result of the drug’s acceleration of β-cell failure. Moreover, the long-term modifying effects of pharmacological treatments on underlying physiology becomes increasingly complicated when a patient is being treated with several medications, as multimorbidity is common in patients with T2D. Regardless, the low accounted for heritability of T2D means that it is unlikely that treatment targeted to one pathophysiological pathway will cause detectable improvements in treatment outcomes.

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In recent decades in affluent health systems, T2D patients have increasingly been enrolled in structured disease management programmes (DMPs) comprising a broad range of elements, such as disease awareness and self-monitoring training, lifestyle behaviour-change programmes, therapy-compliance monitoring and motivational prompts, medical appointment scheduling, and/or even reward schemes for positive risk-reducing behaviour. Such programmes have been shown to increase the number of T2D patients effectively medicated with stable HbA1c levels within the healthy range, reduce the number of necessary hospital admissions, and delay the onset of T2D complications. However, the capacity of health systems to fund and deliver such DMPs is obviously limited due to cost.

**Health inequality risks of PRSs**

As a result of a strong European bias in the ethnicities of GWAS participants, current PRS models are significantly more accurate in predicting disease risks in European populations than other ethnicities. When prediction accuracy for 17 traits was assessed across an ethnically diverse population sourced from the UK Biobank using European summary statistics, genetic prediction was on average 1.6-fold lower in South Asians, 2-fold lower in East Asians and 4.5-fold lower in Africans than in Europeans. The same study also found that prediction accuracy is consistently higher when using GWAS summary stats from an ancestry-matched population.

In the case of T2D, the lack of predictive accuracy is particularly concerning considering that three quarters of the global burden of the disease falls in low- and middle-income countries, and the diabetes-related mortality rate is more than twice as high in low- and middle-income countries compared to high-income countries. Moreover, the prevalence and incidence of T2D varies considerably by ethnicity, with significantly higher rates observed among people of South Asian, Indigenous Australian, and African origin.

The lack of non-European participants in GWAS affects the quality of PRS for Europeans as well as non-Europeans. Previous studies have shown that GWAS derived from non-Europeans contribute a disproportionately high number of GWAS associations compared to Europeans. Furthermore, non-Europeans may carry some gene variants of large frequency or effect that have a relatively low frequency or effect in Europeans. For example, the SIGMA Type 2 Diabetes Consortium identified SLC16A11 as a novel locus associated with T2D that is present at ~50% frequency in Native American samples and ~10% in East Asian samples, but is rare in European and African samples.

Differences in T2D risk related to ethnicity mean that the absolute ranges of risk categories depend essentially on the reference population. An absolute score which in one population indicates a very high risk may in another population represent a much lower risk. A study by Reisberg et al., which developed a polygenic risk model for T2D and tested it on different populations, found that when the absolute genetic risk cut offs from the European population were applied to individuals with African ancestry, all these individuals were identified as having an extremely high genetic risk. Although T2D incidence does vary by ethnicity, the difference in rates does not explain such a large variability in PRS distributions.

One way to tackle this issue is to simply recalculate absolute PRS distribution cut-offs for the assessed population by using only data from a matched ethnic population. This would solve the problem relatively easily for a homogenous population. In admixed populations, however, where individuals tend to have a mixed set of SNPs originating from multiple ethnicities, no appropriate reference population is likely to be found. In such cases, one would in theory first have to identify each individual’s personal ancestry and then adjust risk scores accordingly. However, this requires a complicated trans-ethnic understanding of disease-associated SNPs supported by extremely large data sets.

Carlson et al. argue that such high-risk scores are observed in non-European populations because of the LD in GWAS. LD between causal and associated SNPs varies in different populations, and because the majority of available GWAS data is based on Europeans, current models will mainly include non-causal variants that reflect European patterns of linkage disequilibrium. This means that the effect size of approximately a quarter of SNPs will be overestimated in non-European ancestries. This clearly illustrates the predictive inaccuracy of PRS in their current state; incorrectly defining an entire population as having an extremely high risk of disease would likely lead to stigma and exacerbation of existing health inequalities.

The prevalence of overweight or obesity is generally lower in most Asian than white populations, and Asian individuals tend to develop T2D at a lower BMI than Europeans, suggesting that the overall risk of developing T2D in Asians is higher compared with Europeans at any given BMI level. The attenuated predictive power of PRS in non-Europeans should urgently be addressed by researchers as T2D risk in Asian populations is clearly more difficult to predict using clinical factors than in European populations. In the UK, where the implementation of PRS currently appears most feasible following the UK Health Secretary’s outlined plans for a ‘genomic revolution’, 7.5% of the population in 2018 was Asian and 3.3% was Black (African and Caribbean), meaning that rolling out polygenic risk models in their current forms would risk exacerbating ethnic health inequalities and disadvantaging those who are likely to have the highest T2D risk based on their ethnicity.

Recently, various public health initiatives have been launched to expand genomic testing and research capacity in low- and middle-income countries especially focussing on those populations currently disadvantaged by this lack of predictive ability. In 2010, the US National Institute of Health (NIH) and the Wellcome Trust established a partnership to support population-based genetic studies in Africa. The Human Heredity and Health in Africa Project (H3Africa) received more than $216 million to study common non-communicable disorders (including Diabetes) using genetic, clinical and epidemiological screening tools. The
The worldwide epidemiology of type 2 diabetes, as well as mapping the regional variation of cardio-metabolic disease-related risk factors\(^a\). In the same year, a second similar initiative was launched in Mexico. The Slim Initiative for Genomic Medicine, a collaboration between Mexico’s National Human Genome Research Institute and the US Broad Institute is enabling researchers to study Latin American populations\(^b\). These two international projects will hopefully yield valuable new insights greatly increasing the applicability of T2D PRS in the future.

**How feasible is the implementation of PRSs?**

Thus far, we have covered the advantages of using PRSs for T2D intervention. The use of PRSs in a clinical setting is not without challenges. First, there is an issue on the cost effectiveness of PRS.

Whether or not to integrate and promote the use of PRS in T2D prevention and treatment decisions is ultimately a question of whether PRS can be made accessible to genetic counsellors, physicians and of course, patients in a cost-effective and timely manner, and can provide equal or better predictive accuracy than relying solely on clinical predictors for T2D. In some respects, the price of genetic testing reflects the predictive power of polygenic risk models and whether PRS are reliable enough for clinical use, in so far as prices will go down faster the more testing is performed. Second, the proposed application of PRS warrants significant ethical and social considerations. The potential for psychological harm resulting from T2D risk prediction is supported by evidence that 52\% of Americans with T2D report experiencing stigma\(^c\). Furthermore, 57\% of low-income African American diabetics reported at least one experience of stigma from a family member\(^d\). Within the group reporting stigma, incidence was strongly linked to BMF\(^e\), suggesting that negative psychological effects associated with T2D prediction could be linked to a fear of being/becoming overweight rather than of T2D itself.

**Conclusions**

There is little evidence that PRS currently enable more accurate prediction of T2D risk in adults than relying on traditional clinical factors. But as GWAS cohorts become more diverse, and large samples become more easily “correlatable” with patient journey data through accurately codified EHRs, it is by no means unlikely that over time this may change. Additionally, there is a rationale to further develop and track the accuracy of PRS-based predictions for all non-communicable diseases over longer periods of time in light of the NHS’ commitment to moving towards personalised, genomics-based medicine. More research should also therefore be conducted on pPS, genetic clusters that could predict T2D complications based on relationships between genetics and EHRs, to inform better monitoring (in combination with new biomarker discoveries) or choice of therapeutic interventions. Furthermore, PRS could potentially be deployed to assign those with highest genetic risk to effective DMPs, and direct-to-consumer testing can also steer high-risk individuals to effective DMPs, incorporating digital interventions, which are cheap and effective especially if supported by compliance-enhancing tools and incentive schemes.

Despite their potential, the implementation of PRS face significant challenges. PRS are not yet as accurate at predicting risk in non-Europeans as in Europeans. More GWAS are needed in low- and middle-income countries, especially as the number of individuals with diabetes is growing most rapidly in many Asian and African countries. However, in these countries available healthcare funding is predominantly focussed on acute care needs of the population. Therefore, GWAS initiatives should be combined with efforts to improve research infrastructure and scientific training in many affected but underrepresented regions of the globe. In addition, internationally agreed policies accompanied by effective enforcement controls should be called for in projects to expand GWAS to low- and middle-income countries.

Finally, despite the multitude of potential uses for PRS, implementation is ultimately a trade-off between their clinical validity and utility, and their cost effectiveness. Health systems with constrained budgets are forced to make difficult ethical decisions to set a price limit for each quality-adjusted life-year they are willing to gain from an intervention or medication, and existing peer-reviewed frameworks must be deployed to assess whether the overall benefit of a genetic test outweighs its costs. Under current guidelines, PRS have a significant way to go before they fulfil the criteria for widespread implementation.

**Data availability**

No data are associated with this article.

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This is a very nice review by Mathilde Boecker and Alvina G. Lai, which describes the potential applications of PRSs in clinical practice for type 2 diabetes diagnosis, management, and prediction of complications and the challenges to applying them. Overall, the review focuses more on the difficulties and disadvantages of using PRSs than discussing solutions or suggestions scenarios for future implications.

It would be interesting to know how many GWAS (or sequencing studies) or the sample size needed for calculating PRS with enough confidence level to be applied for clinical practice? While the answer to this question might be complex; however, it is crucial to have a general idea about establishing a focus-shift from "populations or groups" to individuals with an acceptable confidence level. In other words, it is essential to validate PRSs first before using them.

Concerning the previous point, I guess the authors might look at how some extensive databases (e.g., 23andMe or Impute.me) provide individuals with PRSs as a "Direct-to-consumer (DTC)" approach, given that they have extensive databases. The answer to how accurate these providers are will give insights into the future of using PRSs in clinical practice. Besides, this also shows how the PRS concept might move to an individual-to-practice direction rather than the opposite way (i.e., an individual may come to a clinical facility carrying his own PRSs, which he/she got from 23andMe, for example, asking for a consultation). Overall, this might indicate that dealing with PRSs will be soon inevitable.

Also, it would be interesting to add a point about machine learning in relation to PRSs in assessing predictive scores for diseases.

The authors clearly show that other factors are essential for calculating the "absolute risks" for a disease or its progressions, like lifestyle or biochemical tests. Hence, it would be better for authors to point more to using PRSs to generate "prediction risk models."
The authors pointed very well to the psychological impact of PRSs on individuals. I want to add to this the magnitude of information of all possible diseases, which will also be given to individuals in the future. The current incentive systems described in this review are not convincing and with relatively small sample size. In addition to the behavioral interventions and incentive systems, it would be necessary to know how PRSs for various diseases should be prioritized and delivered to individuals? When will it be essential to introduce behavioral changes or decide to treat/or not to treat? For example, if a PRS is high for coronary artery disease for an individual who is 30 years old, should behavioral changes or pharmacological interventions be introduced at this age? Or if they identify a high risk for breast cancer, does that change the mammography test's starting age and frequency?

On page 8, the authors discussed the feasibility of the implementation of PRSs in clinical settings. I would suggest adding another issue: the availability of the bioinformatic facilities and the number of skilled personnel trained to deal with massive amounts of data and conclude results. This is a really challenging problem.

On page 5, this sentence, "It may be useful to screen kidney transplants for specific genes before passing them on to patients with diabetes currently on dialysis," is vague and not informative.

On page 7, I feel that the paragraph starts with "Carlson et al. argue that such high-risk ...etc." should be before the section before it which begins with (one way to tackle this issue is to simply ...etc.). The discussion before that was in the variability in PRS on different ethnicities, and the study by Carlson et al. explains the reasons for this. So, it might be better to shifts these two paragraphs.

Also, concerning the variability of the PRSs among different ethnicities, I would like to point to a recent study in the Qatari population (Thareja et al., 2021) where they used European PRS to replicate them in the Qatari population for 11 traits. The authors showed that the tested traits showed lower performance when applied to Qatar Biobank data with an average performance of 64.7% than when applied to Europeans. I hope this point helps the authors regarding the ethnicity issues.

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**Is the topic of the review discussed comprehensively in the context of the current literature?**
Yes

**Are all factual statements correct and adequately supported by citations?**
Yes

**Is the review written in accessible language?**
Yes
Are the conclusions drawn appropriate in the context of the current research literature?
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Genetics of metabolic diseases, type 2 diabetes, personalized medicine

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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○ This is a nice review of the potential utility of PRSs in type 2 diabetes (T2D). I have some general suggestions for improvement:

○ In general, the language can be tightened up a bit to be factual while still conveying the reviewers opinions. This generally applies to the areas where interventions / clinical deployments are suggested but where no evidence has yet been generated in clinical studies.

○ For example, the first paragraph of "Using PRSs to inform interventions" suggests one way of stratifying patients based on the combination of clinical and genetic risk factors. But given that outcome studies have not been done - it might serve the reviewers to be broader in the types of relationships they suggest. For example, high genetic risk could also be associated with calorie seeking behavior and thus perhaps behavioral intervention.

○ Throughout the review I would suggest the reviewers consider the possibility that behavioral interventions themselves may be driven by genetics or partitioned genetics.

○ The authors get to this some degree when discussing the balance of BMI vs genetic risk - I think it would be worth addressing the utility in lean diabetes directly.

○ The results discussed in this same section (reference 37) seem to be misinterpreted. This review cites about 8 prior studies that show T2D risk prediction can be improved by PRSs. The statement regarding the relationship between prior genetic testing and T2D incidence is odd.

○ The conclusion starts off rather negative given the various areas of potential utility
identified by the reviewers. Perhaps it is better stated that the blind application of T2D PRSs to risk prediction is not useful while there are several scenarios of prognostic utility etc.

**Is the topic of the review discussed comprehensively in the context of the current literature?**
Yes

**Are all factual statements correct and adequately supported by citations?**
Yes

**Is the review written in accessible language?**
Yes

**Are the conclusions drawn appropriate in the context of the current research literature?**
Partly

*Competing Interests:* No competing interests were disclosed.

*Reviewer Expertise:* genetics, quantitative genetics, individualized medicine

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.