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Precision Diabetes Is Slowly Becoming a Reality

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Significance of the Study

- Till recently, a "one-size-fits-all" approach was used to treat most forms of diabetes. With the availability of big data and analytic tools like genomics, epigenetics, metabolomics and proteomics, precision diabetes is now slowly becoming a reality. Precision diabetes is already being applied to monogenic forms of diabetes like maturity-onset diabetes of the young, neonatal diabetes mellitus and congenital hyperinsulinaemic hypoglycaemia. In many such cases, this can be a life changer, as insulin can be stopped completely and be replaced with oral glucose-lowering agents. In other forms of diabetes like type 2 diabetes, precision diabetes promises to be of use in personalised therapy for people affected with the disorder.

Keywords
Precision medicine · Personalised medicine · Personalised diabetes · Precision diabetes · Monogenic diabetes · Neonatal diabetes · Maturity-onset diabetes of the young

Abstract
The concept of precision medicine is becoming increasingly popular. The use of big data, genomics and other "omics" like metabolomics, proteomics and transcriptomics could make the dream of personalised medicine become a reality in the near future. As far as polygenic forms of diabetes like type 2 and type 1 diabetes are concerned, interesting leads are emerging, but precision diabetes is still in its infancy. However, with regard to monogenic forms of diabetes like maturity-onset diabetes of the young and neonatal diabetes mellitus, rapid strides have been made and precision diabetes has already become part of the clinical tools used at advanced diabetes centres. In patients with some monogenic form of diabetes, if the appropriate gene defects are identified, insulin injections can be stopped and be replaced by oral sulphonylurea drugs. In the coming years, rapid advances can be expected in the field of precision diabetes, thereby making the control of diabetes more effective and hopefully leading to prevention of its complications and improvement of the quality of life of people afflicted with diabetes.

Introduction

The National Institutes of Health (NIH), USA, define precision medicine as an emerging approach to disease treatment and prevention that takes into account

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individual variability in genes, environment and lifestyle [1]. This concept is not new, and in the past, patients were prescribed optimal treatment by clinicians based on the available data and resources. In its crudest sense, conducting blood transfusion based on the specific blood group of a recipient is an example of precision medicine [2]. The crux of precision medicine is custom delivery of healthcare, with tailored treatment at the level of the individual patient. However, in spite of extensive epidemiological and physiological characterisation and elucidating pathophysiological pathways, we are still far away from predicting prognoses, or even selecting the most effective medicines for a given patient. Most therapeutic approaches are based on population averages, which unfortunately do not fit everyone [3].

Since these current methods of disease categorisation are outmoded and have not achieved their objectives, a new concept has arisen in the recent years. It is recognised that individuals who share the same diagnostic labels may have very heterogeneous presentations and clinical courses and may respond differently to therapeutic interventions. This has led to the concept of personalised medicine, which, when further refined by scientific inputs, becomes precision medicine [4].

Precision medicine refers to collecting specific information about a patient and prescribing a specific treatment. This involves defining disease subtypes and biomarkers that can identify patients who are likely to benefit from a specific treatment or those who are likely to experience a particular side effect. Application of genotypic and phenotypic information forms the basis of precision medicine [5]. Personalised medicine not only incorporates the principles of precision medicine but also takes into account patients' preferences and social context, as well as other factors such as affordability of therapies.

Big Data and "Omics" Technologies in Precision Medicine

One of the important reasons for the rapid development of precision medicine in recent years is the availability of big data and the advancement of technologies to mine these data [6, 7]. It is believed that traditional sources of medical information, such as patient history, physical examination and laboratory workup, when augmented by data mining of deep phenotypic data and genomic analyses coupled with epigenetic, metabolomic, proteomic and transcriptomic data, can help deliver precision medicine to individual patients [4, 8].

A plethora of transformative and disruptive technologies such as DNA sequencing, functional investigation, the emerging field of epigenetics, genome-wide association studies and miRNA scans, as well as a range of "omic" measurements, can help in the detailed in vivo dissection of physiology and pathology, and this improves diagnosis and treatment. They can also provide the basis for refinement of disease subtypes and support the effective optimisation of disease management to match an individual pathology or genetic make-up [9]. The field of oncology has been one of the first to adopt precision medicine, but other fields, including endocrinology, are catching up fast.

Precision Diabetes

Diabetes mellitus broadly encompasses four categories, namely, type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), monogenic diabetes and gestational diabetes.

T1DM is an autoimmune disease with progressive destruction of β-cells, leading to polyuria, polydipsia, weight loss and hyperglycaemia. T1DM requires lifelong administration of insulin injections several times a day as endogenous insulin secretion becomes near zero. Making a proper diagnosis of T1DM with clear evidence of β-cell destruction through the presence of islet cell autoantibodies and demonstration of absent β-cell function as measured by levels of C peptide and prescribing the appropriate doses of insulin are the basis for precision medicine in the case of T1DM, although some heterogeneity exists even here.

T2DM is a heterogeneous group of disorders predominantly due to insulin resistance and some degree of an insulin secretion defect. T2DM has a range of risk factors, aetiologies and clinical presentations.

There are also several forms of monogenic diabetes, which are caused by highly penetrant single gene defects; the three major types maturity-onset diabetes of the young (MODY), neonatal diabetes mellitus (NDM) and congenital hyperinsulinaemic hypoglycaemia (CHH) are the most common. It is with these forms of diabetes that precision diabetes has already come to be used in the clinical setting [10].

This review will first describe the role of precision medicine in T2DM and then deal with the monogenic forms of diabetes.

Precision Diabetes in T2DM

Defining subgroups using molecular testing is much more difficult in T2DM, as it is a polygenic disorder and the clinical phenotype reflects environmental as well as genetic influences [11]. One approach for precision medicine in T2DM is to categorise patients based on differential responses to drugs, and to then investigate the molecular underpinnings of each subgroup using next-generation sequencing platforms and gene arrays. In clinical practice this approach is not easy to implement, although pharmacogenomic developments continue to be made [12].

In contrast to monogenic diabetes, where the gene mutation is causal and has a high phenotypic correlation, T2DM involves multiple, common, low-impact risk variants. The emerging availability of genomic and electronic health data from large populations, the so-called big data, is a powerful tool for bringing precision medicine to T2DM [13, 14]. For example, recently, at least five clusters of T2DM with differing clinical features have been identified [15].

A common nonsense mutation in the *TBC1D4* gene that substantially increases the risk of T2DM was recently identified in a Greenlandic Inuit population [16]. This variant is shown to exclusively increase postprandial glucose levels. The frequency and effect of the *TBC1D4* mutation on glucose metabolism and T2DM were determined in two related populations: Canadian Inuit and Alaskan Inuit [17]. The mutation in the *TBC1D4* gene is common among North American Inuit, and results in elevated postprandial glucose levels and an underdiagnosis of T2DM unless an oral glucose tolerance test is performed. This is one example of how precision medicine may be applied at the population level.

Some pharmacogenomic advances have been made in relation to antidiabetic drugs. Variations in the cytochrome P450 (CYP) enzymes contribute to oral antidiabetic drug metabolism in the liver and affect drug disposition and efficacy. Genetic variants in CYP2C9*2 (I359L) and CYP2C9*3 (R114C) have been shown to be associated with reduced blood sulphonylurea (SU) clearance [18, 19]. Furthermore, variants in CYP2C8 were found to influence the efficacy of repaglinide and rosiglitazone [20].

Various studies have shown that rs12208357, rs34130495, rs34059508 and rs72552763 are related to the *SLC22A1* gene, which encodes organic cation transporter 1, and are genetic markers for the efficacy and excretion of metformin [21–24].

The SNP rs11212617, which is located near the ATM locus, was found to be associated with HbA_{1c} levels in response to metformin in a large-scale genome-wide association study conducted in European T2DM populations [25]. One study has demonstrated that the *PAX4* variants rs6367136 and rs10229583 and the *PSMD6* variant rs831571 were correlated with the therapeutic efficacy of repaglinide and rosiglitazone in Chinese T2DM patients [26, 27].

Dujic et al. [28] demonstrated the impact of genetic factors on gastrointestinal tolerance to metformin. The Genetics of Diabetes Audit and Research in Tayside Scotland (GoDARTS) study [29] had also shown that reduced-function alleles of the *OCT1* gene are associated with increased intolerance to metformin. Recently, it has been suggested that serotonin reuptake transporter might also be involved in intestinal metformin absorption. The number of low-expressing serotonin reuptake transporter alleles significantly increased the odds of metformin tolerance. These results suggest that gastrointestinal side effects of metformin could be related to the reduced uptake of intestinal serotonin [23].

Another pharmacogenetic approach to treatment response in T2DM was demonstrated with the use of thiazolidinediones (TZDs), compounds that are transported into the liver by OATP1B1 (encoded by the *SLCO1B1* gene) and metabolised by the CYP450 2C8 enzyme (encoded by the *CYP2C8* gene). Although variants in the *CYP2C8* gene (the *CYP2C8*3* allele) have been shown to alter TZD pharmacokinetics, the *CYP2C8*3* allele has not been shown to alter its efficacy. In an elegant study [30], 833 patients with T2DM treated with pioglitazone/rosiglitazone were genotyped for *CYP2C8* and *SLCO1B1* functional variants. The *CYP2C8*3* variant was significantly associated with reduced glycaemic response to rosiglitazone and less weight gain, whereas the *SLCO1B1* 521T>C variant was associated with enhanced glycaemic response to rosiglitazone. Patients with both genotypes (super-responders) had a significantly greater HbA_{1c} reduction. Interestingly, neither of the variants had a significant impact on pioglitazone response. This highlights the importance of studying transporter and metabolising genes as a predictor of treatment response by identifying those individuals who can benefit from the therapeutic advantages of TZDs.

There are also reports showing that genetic polymorphisms, such as *TCF7L2* polymorphisms, may influence the response to dipeptidyl peptidase-4 (DPP-4) inhibitors [31–33]. There are also some studies suggesting that gene polymorphisms may mediate the response to GLP-1 (glu-

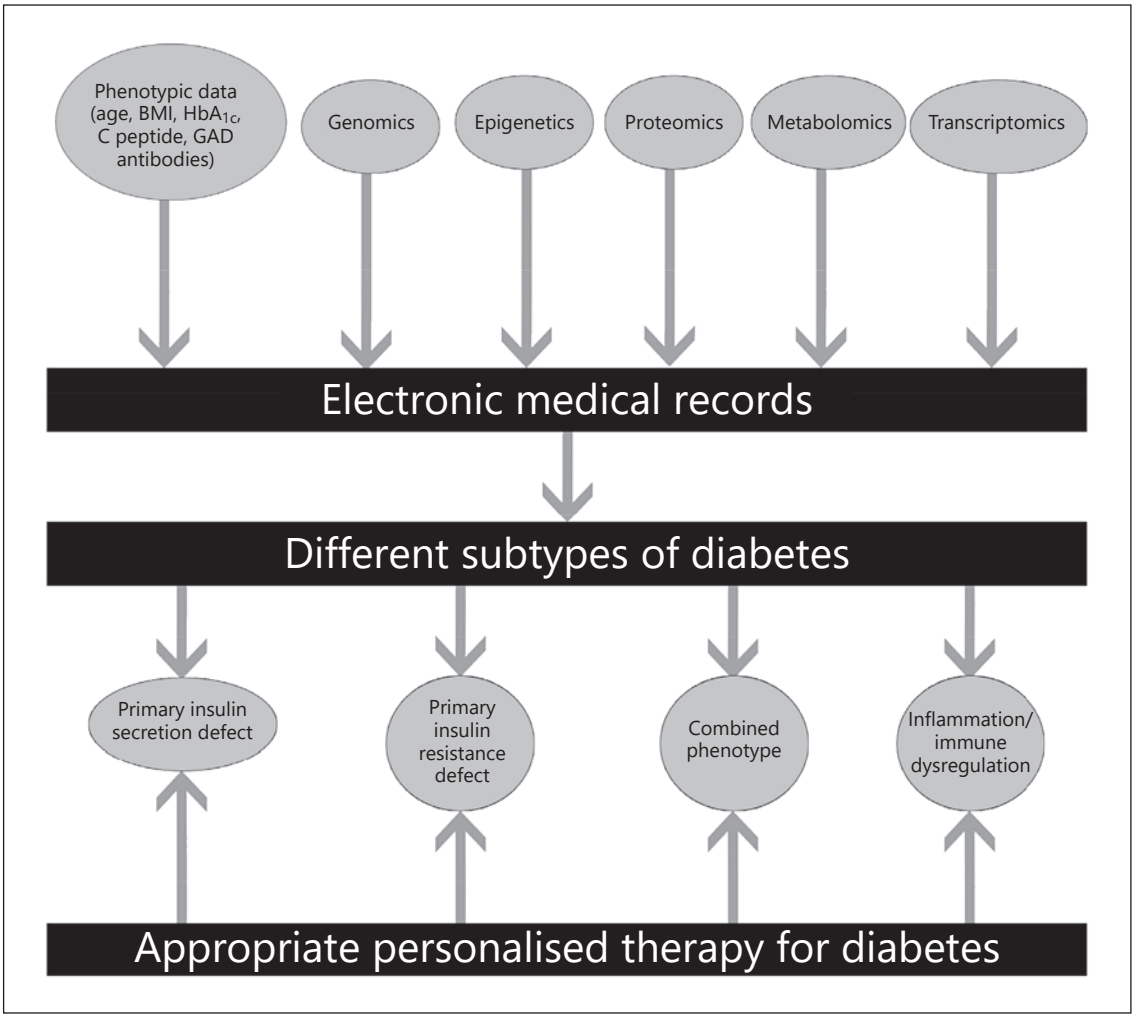

Fig. 1. Precision diabetes: a futuristic model. Adapted from Schwartz et al. [44].

cagon-like peptide-1) receptor agonists [34] and DPP-4 inhibitors [35].

A multitude of newer antidiabetic agents are now available. These include DPP-4 inhibitors, sodium/glucose cotransporter 2 (SGLT2) inhibitors and GLP-1 receptor agonists. It is now known that there are at least 8 pathophysiological defects in T2DM. These drugs help address several of the defects. It is also known that there could be ethnic differences in the response to these drugs; for example, the DPP-4 drugs seem to work better in Asians than in Europeans [36–40]. This could be because β-cell dysfunction is more severe in Asians, particularly in Indians [41]. Indeed, it has been shown that Asian Indians and Pima Indians represent two extreme phenotypes of T2DM, one leaner with more insulin deficiency and the other obese with severe insulin resistance [42]. This suggests that an insulin secretagogue would be preferable for the former and insulin sensitisers for the latter. This is one sample application of personalised or precision medicine at the population level.

In a brilliant review, Schwartz et al. [43] make out a case for a new classification system of diabetes and discuss the rationale for and implications of the β-cell-centred classification schema for T2DM. They also emphasise the concept of epigenetics and inflammation, as well as the role of inflammation and immune dysregulation, in the pathophysiology of T2DM [44]. They suggest how data from "multiomics" could be integrated with electronic medical records to provide "dynamic decision support" for recommendations regarding the treatment

of T2DM. They envisage that in the not-too-distant future, data on genomic, epigenomic, proteomic and metabolomic markers could be available on a chip. This will help to classify individuals with diabetes more accurately, and thus make diabetes treatment more patient centred and precision medicine in diabetes a reality.

Figure 1 summarises the concept of a futuristic model of precision diabetes which could be applied at a diabetes clinic to offer personalised diabetes care [44].

Monogenic Diabetes: The Field where Precision Diabetes Has Already Become a Reality

In contrast to the polygenic forms of diabetes like T2DM and T1DM, where precision diabetes is still an evolving field, there are many forms of monogenic diabetes where precision diabetes has already found a place in clinical practice. We will deal with three of these conditions: (1) NDM, (2) CHH, and (3) MODY.

Neonatal Diabetes Mellitus

NDM is defined as diabetes which develops in neonates under 6 months of age. About 50% of the patients with NDM have mutations in the K_{ATP} channel genes, namely, *KCNJ11* and *ABCC8* [45]. Patients with mutations in these two genes respond to high-dose SUs and show excellent glucose control without any increase in hypoglycaemia and glucose variability [46]. Improvements in neurological function are also seen in these patients after treatment with SU [47, 48]. In such patients, treatment with insulin reduces the glucose level but does not elicit an optimal response – and, more specifically, the neurological functions do not show any improvement [49]. SUs close the SU channel in the cells so that exocytosis of insulin takes place, thereby correcting the defect. Since K_{ATP} channels are present in β-cells, the brain, the liver, etc., all cells are corrected simultaneously, thus improving their functions as well. This is an excellent illustration of precision diabetes and one of the most exciting clinical situations in diabetology. Switching a child aged just a few weeks or months to oral tablets, from what would otherwise have meant lifelong insulin injections, is nothing short of a miracle to the child and the family, and we have been able to help many such children [50].

Not all mutations in the *KCNJ11* and *ABCC8* genes, however, lead to NDM. Only some mutations are clinically actionable. This needs to be investigated by functional methods and through segregation analysis. The knowledge of causal mutations has helped in the successful transfer of children from insulin to SUs, as shown in studies by Hattersley and Ashcroft [51] and recently by our group [52]. Patients with transient neonatal diabetes due to 6q24 methylation abnormalities can be treated with low-dose SU when they relapse, while patients with other subtypes of neonatal diabetes require insulin treatment [53]. The ability to explain additional clinical abnormalities that are associated with the underlying genetic cause is one of the major benefits of precision medicine. One such example is cardiac defects in patients with *GATA6* mutations and remission of transient diabetes in patients with 6q24 methylation abnormalities [54].

Patients with transient neonatal diabetes due to 6q24methylation abnormalities can be treated with low-dose SUs [55] when they relapse, whereas patients with NDM due to K_{ATP} channel mutations require high-dose SU and those with non-K_{ATP} channel mutations require insulin treatment [56].

Congenital Hyperinsulinaemic Hypoglycaemia

Another important area where precision diabetes is playing a role is CHH. Here, hypoglycaemia (low blood glucose) manifests just after birth or in the first few months of life. This hypoglycaemia can be severe, debilitating and persistent. In many of these neonates with hypoglycaemia, definite mutations can be identified that are responsible for the condition. We reported on a series of CHH cases from our centre [57]. Some of these neonates respond to diazoxide, while others require subtotal pancreatectomy. Before such a drastic procedure, it is useful to confirm the diagnosis by genetic testing, and this is where precision diabetes plays a role [57].

In the case of conditions such as thiamine responsive megaloblastic anaemia syndrome, an early genetic diagnosis and treatment with thiamine help in the control of diabetes [58]. For IPEX and some severe monogenic autoimmune syndromes, a genetic diagnosis helps in early detection and allows consideration of early curative bone marrow transplantation before patients become severely affected [59].

Maturity-Onset Diabetes of the Young

By its classic definition, MODY presents in non-obese individuals before the age of 25 years, is inherited in an autosomal dominant manner, is primarily due to β-cell dysfunction and can be treated without insulin for at least 5 years [60]. Since the presentation of MODY has characteristics of both type 1 (early onset, lean) and type 2 (family history of diabetes, with β-cell function), it is often misdiagnosed. After the discovery of the MODY genes, a

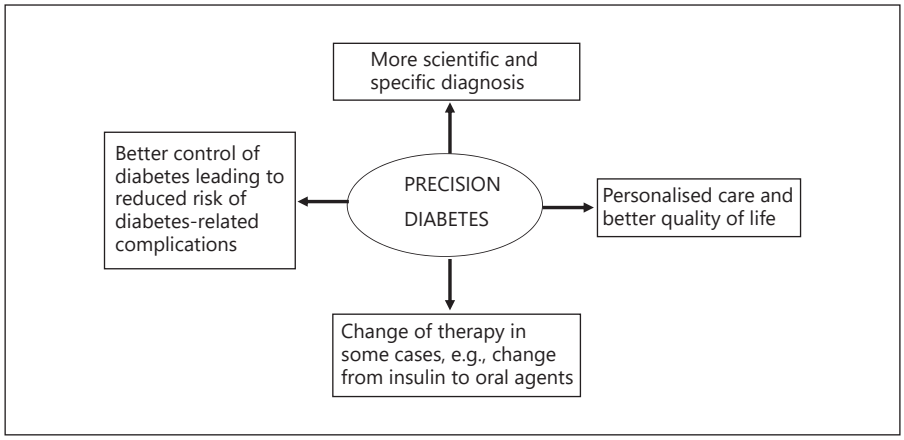

Fig. 2. Advantages of precision diabetes applications.

Table 1. Usefulness of precision diabetes in monogenic diabetes

I.	**Neonatal diabetes mellitus**
1.	Helps to differentiate transient neonatal diabetes from permanent neonatal diabetes
2.	Helps to stop insulin administration and switch to high-dose sulphonylurea if the children have *KCNJ11* or *ABCC8* mutations
3.	Diabetes caused by *SLC19A2* gene mutations can be successfully treated with thiamine
4.	Early detection and treatment of Wolcott-Rallison syndrome ensures earlier detection and management of liver abnormalities
5.	Developmental disorders of the exocrine pancreas require replacement of pancreatic enzyme in addition to insulin
6.	Helps detect various genetic syndromes associated with neonatal diabetes mellitus
II.	**MODY**
1.	Patients with *HNF1A* and *4A* MODY can be taken off insulin and treated with low-dose sulphonylurea
2.	*GCK* MODY patients require only a diet regimen and all pharmacological treatment can be stopped, except if they become pregnant

MODY, maturity-onset diabetes of the young.

genetic workup helps in classifying MODY accurately. This is very important, since some of the MODY subtypes entail specific therapeutic recommendations based on the genetic aetiology. The transcription factor genes *HNF1A* (MODY 3) and *HNF4A* (MODY 1) promote transcription of multiple genes related to glucose metabolism, insulin secretion and insulin production. Diagnosis of MODY 1 and 3 is important for clinical therapy, as patients with those types are very sensitive to SUs [61–67]. This is due to decreased expression of the target genes *HNF1A* and *4A* in the liver, leading to decreased uptake of SUs, in turn resulting in increased circulating levels of SUs [68]. Therefore, *HNF1A* and *4A* MODY patients need lower doses of SUs, which are the first-line treatment for MODY 1 and 3 [69]. It has been demonstrated that switching of treatment from insulin to SU improved HbA_{1c} levels in MODY 3 and MODY 1 patients. In a randomised trial, Pearson et al. [70] showed that SUs lead to a 4-fold greater reduction of fasting plasma glucose levels in *HNF1A* MODY patients compared to T2DM patients matched for age, BMI and blood glucose levels.

GCK MODY (MODY 2) patients do not require insulin or oral drugs, as these patients have a regulated blood glucose set at a higher threshold level [71, 72]. They respond to diet and exercise and rarely develop complications from diabetes. Only during pregnancy do *GCK* MODY women need insulin [73]. However, its validation in non-European populations has not been tested.

In Asian Indians, T2DM occurs earlier and often overlaps with MODY, and hence understanding and recognising MODY subtypes in this population gains more importance. Our work has revealed important insights into the molecular genetics of MODY by showing the presence of novel mutations in the *HNF1A* (MODY 3) [74] and *HNF4A* (MODY 1) [61] genes. We showed that about 9% of clinically diagnosed MODY subjects had MODY 3 [75], while 3% had MODY 1. We also identified MODY 5 in some of our patients [76]. We have recently reported on a comprehensive analysis of all 14 MODY genes and have also reported on what is likely to be a new MODY

gene, with a mutation in the *NKX6-1* gene, located on chromosome 7 [77].

Table 1 summarises the usefulness of precision diabetes in monogenic forms of diabetes. Advancements in genetic testing due to the development of next-generation sequencing have made comprehensive analyses of all known genetic bases for monogenic diabetes possible. This technology has also helped in reducing the turnaround time for genetic testing. A rapid and precise genetic diagnosis is now possible even before the development of all clinical features [49, 51]. Figure 2 summarises the advantages of precision diabetes.

Conclusions

Rapid strides are being made in the field of precision diabetes. While it is still too early to say that we have reached a stage where every patient with diabetes can be given a personalised form of treatment, we are beginning to understand that one size does not fit all. In the case of T2DM, clustering of the disorder has now been identified as the first step in precision diabetes. In the case of monogenic forms of diabetes, particularly in MODY, NDM and CHH, genetic testing has come to stay and can be life-changing for those individuals with certain genetic variants. In the years to come, precision diabetes can be expected to play a big role in improving the quality of life of people with all forms of diabetes and help them achieve better control of their diabetes and thereby prevent complications arising from the disorder.

Disclosure Statement

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