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Review

Personalized medicine- future of diagnosis and management of T2DM

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Personalized medicine (PM) is a major thrust area for treating diseases. In PM, specific information is collecting from a particular patient and then providing a specific treatment to the patient for better treatment outcome. It can eliminate trial-and-error approach in the clinical practices, which are not life-threatening but frustrating for the patients who are not getting satisfactory response to drug and suffered from the various side effects [1,2]. PM offered an approach for redefining disease subtypes and biomarkers that can identify patients who are most likely to benefit from a specific treatment. PM enriched the preventive and therapeutic measures by utilizing biological information *i.e.* genetic biomarkers, proteomics as well as metabolomics. Personalized medicine is aiming and endeavoring to sub-divided patients into different categories based on their "molecular make up", *i.e.* using biomarkers. This type of categorizing enables us to make a decision to have a unique and precise treatment for each patient [2,3].

Currently, disease analysis done at molecular levels using large scale approach are being employed by some clinicians and pathologist. PM assist the individual on personalized basis and thus, patients treated according to their own genetic basis. Various technology *i.e.* whole genome sequencing, next gen-sequencing, proteomics, metabolomics, trnscriptomes and epigenetic came in on ground level and help to create a data base [2,4]. Active participation of scientist, doctor and patients create a particular characteristic which play as a marker for the disease (Fig. 1). Various genetic panels may be identifed in this process which account for a particular disease, which leads to produce a highly individualized disease therapy and drug treatment according to their genetic profiling. If the physician could be armed with specific personalized information about that patient, including information about their genetic makeup, then treatments could be tailored for each individual patient [2,5]. This approach would then lead to better outcomes without wasting time on ineffective therapy. Outcome statistics, which indicate that a certain percentage of patients will respond to a specific treatment, are not always meaningful for a given individual. Genetic tests and biomarkers can be utilized for predicting the diagnosis and for monitoring the course of diabetes [2].

Patients who are identified by genetic testing to be at high risk for diabetes can be directed to preventative measures, such as lifestyle modifications or medications, in order to delay or prevent the disease.

1. The personalized approach to diabetes mellitus

Diabetes mellitus is a group of metabolic diseases, which include phenotypic elements *viz.* β cell dysfunction, and insulin resistance that leads to alterations in carbohydrates, lipids, and protein metabolism [6,7]. It is also described as a syndrome due to clustering of several complications like hyperinsulinaemia, hyperglycemia, increased very low density lipoprotein (VLDL), increased triglycerides (TG), decreased high density lipoproteins (HDL) cholesterol, high blood pressure, micro albuminuria, hyperuricaemia, fibrinolytic and coagulation abnormalities [8]. The chronic hyperglycemia is associated with long term damage, dysfunction and failure of various organs, heart, kidneys, nerves, especially eyes and blood vessels [9,10].

The global burden of diabetes mellitus is presently 425 million affected people, expected to rise to 629 million in 2045 and about 193 million people are undiagnosed. The Indian estimate shows

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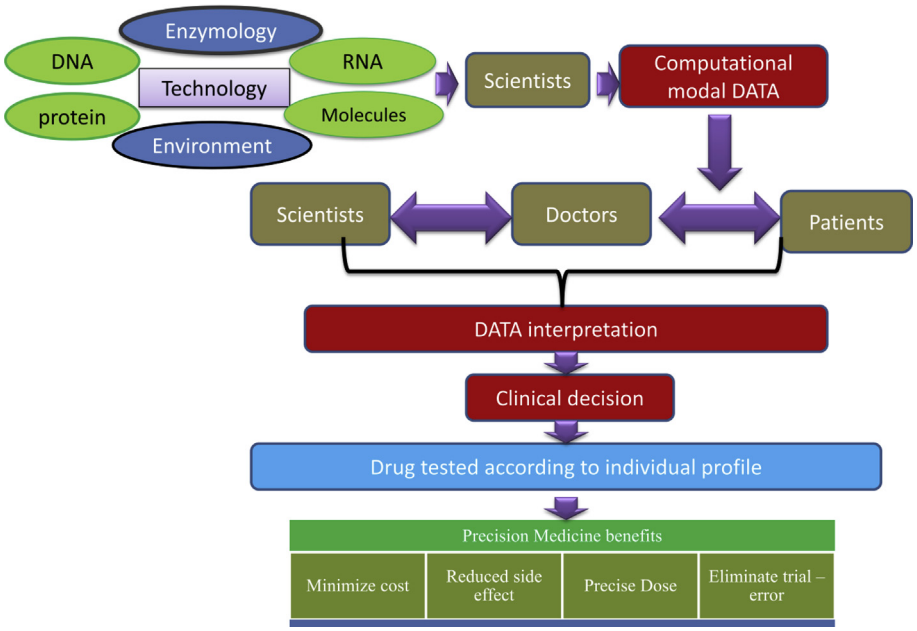

Fig. 1. Integrated model of precision medicine. Doctors, Scientists and patients are actively participated in the integrated process.

that 74.3 million people were affected in 2017 [11]. This rise in the number of diabetic patients is associated with economic development, ageing population, increasing urbanization, dietary changes, reduced physical activity and changes in lifestyle pattern.

Personalized medicine for diabetes included four step processes for diabetes management. Step first included identification of biomarkers and genes for diabetes, which is greatest risk factor for type 2 diabetes. Second step include identifying the predictors of diabetes and highrisk individuals on basis of their genetic makeup. Third step is selection of individualized therapies on the basis of molecular diagnostics clinicians decided that which drug should be prescribe, what dose of drug to use, which diet to prescribe and which drug is least likely to cause side effects or toxicity for affected individuals. Fourth step include monitoring of therapy by measurement of circulating biomarkers of diabetes (Fig. 2) [4].

2. Genomics and pharmacogenomics

Several genes are known (~3206) to be associated with Type 2 diabetes mellitus (T2DM) and related complications [12–15]. It is important to identify the genetic polymorphisms in different geographic populations and ethnic groups since there are differences between populations regarding susceptibility and development of disease. Genetic profiling of patient' can suggest the precise selection of drugs or treatment plan which result into minimize harmful side effects or ensure more successful outcomes [16]. Genome-wide association studies (GWAS) are important tool for analysis of characterise and the genetic component of T2DM by using bioinformatics and clinical symptoms [17]. Recent GWAS study with ~16 million genetic variants of European ancestry in 62,892 T2DM cases and 596,424 controls showed that 4 rare and 139 common variants associated with T2DM. GWAS results identifies 33 putative functional genes for T2DM after Integration of the gene expression data (Genome-wide association analyses identify 143 risk variants and putative regulatory mechanisms for type 2 diabetes [17]. As Asian Indians have a greater susceptibility to diabetes and have increased insulin resistance, they are a unique population for carrying out genetic studies [11,18]. Genomic analysis can reveal the individual risk for the disease and suggest potential targets for the PM. Whole genomic sequence can reveal chronic disease and their therapeutic targets for the treatment. Several studies showed that gene polymorphism can be used as a genetic predictor for the disease. Effective drug response determined on the basis of reaching capability of drug at site of action in a sufficient concentration. It might be possible that drug transport genes and metabolism genes variation accounting for altering drug concentrations and subsequently to alter drug action and side effects [1].

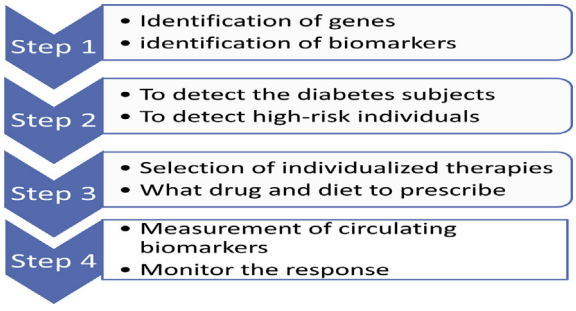

Fig. 2. Personalized medicine for diabetes included four step processes for diabetes management.

3. Gene polymorphisms associated with pharmacogenetics of anti-diabetic drugs

3.1. Metformin

Metformin used as a first line of drug for newly diagnosed T2DM cases. It have various beneficial effects on cardiovascular risk factor, cancer and polycystic ovary syndrome. Metformin reduced the gluconeogensis without affecting insulin secretion. It is transported through organic cation transporter (OCT1 and OCT2), OCT act as a poly-specific transporters of small and hydrophilic organic cations, including toxic substances and endogenous compound [19]. Metformin activated AMP-activated protein kinase (AMPK) cause increase fatty acid oxidation and inhibit lipogenesis [20].

3.1.1. Organic cation transporter 1 (OCT1) and OCT2

Metformin drug response determined by variation in organic cation transporter 1 (OCT1). Drug transporter gene polymorphism might be possible accounting for variation in drug response [1]. Several diabetes studies have focused on genetic association with the different anti-diabetic drug. Studies suggested that OCT1 play a major role in hepatic effects of metformin. Organic cation transporters 1(OCTs) is responsible for the hepatic uptake of metformin In the kidney whereas OCT2 is expressed on the basolateral membrane and it involved in the uptake of many xenobiotics from the bloodstream into renal epithelial cells [21]. Metformin showed reduced distribution to the liver in Oct1−/− mice when compared to controls (wild-type mice). OCT 1 belong to solute carrier family (SLC22A), it has been mapped on chromosome 6q26, consist 11 exons. Although the precise mechanism of the action of metformin remains unclear, it is believed that hepatic uptake is an essential step in reducing hepatic glucose production as well as the occurrence of life-threatening side effects such as lactic acidosis [22–24]. Genetic variation may cause to differ in protein folding pattern, Seven nonsynonymous variants were found in OCT1 gene to alter metformin uptake [25]. Four SNPs ie. S14F, S189L, G401S and M420del caused decreased uptake activity of Metformin where as R61C, G220V and G465R are nonfunctional variants (Table 1) [1,19,25]. Shikata et al. reported that three variants of exon 1 ie.123C > G, 243C > T, 350C > T and one variant of intron 10 ie.26C > T showed good responder for metformin [19]. Recent studies have showed that P341L had decreased ability to transport compound whereas P160L and M408V were unchanged [19]. In south Indian population individuals having A allele at rs622342 showed better efficacy for metformin [26]. Individual with the AA genotype of rs628031 (1222A > G) was significantly associated with the metformin side effects in Latvian population whereas no association was found in Indian and Iranian population (Table 1).

3.1.2. Multidrug and toxin extrusion protein 1 (MATE1)

Multidrug and toxin extrusion protein 1 (MATE1) is an apically expressed poly-specific proton antiporter which mediates the efflux of diverse substrates, primarily organic cations, in the kidney and the liver. Following its relatively recent discovery, MATE1 has rapidly emerged as an important transporter in the renal and biliary excretion of endogenous and exogenous organic cations, particularly metformin. It appears that clinical inhibitors of organic cation transporters (OCTs) are also potent inhibitors of MATEs, and therefore modulation of the activity of both OCTs and MATEs, or predominantly of MATEs, may better describe DDIs currently ascribed to OCTs. MATE1 has been shown to mediate the cellular uptake of structurally diverse, low molecular weight organic cations, such as metformin, tetraethylammonium (TEA), paraquat, agmatine, atenolol, serotonin, cimetidine, N-methylphenylpyridinium (MPP+) and oxaliplatin. C allele of rs2252281 variant, a common genetic variants in the promoter region of solute carrier family 47, creates a repressor binding site and disrupts an enhancer element which decreases MATE1 expression. C allele of rs2252281 was associated with higher metformin level in hepatocytes which leads to significantly glucose-lowering response during an oral glucose tolerance test (OGT) [27,28]. Individuals with the AA genotype showed slow eliminators of metformin which result in to better responder to drug [29]. *SLC47A1* rs2289669 GG genotype patients and rs594709 'A' allele carriers showed a better efficacy in improving blood lipid [30]. The *SLC47A1* rs2289669 G > A polymorphism was significantly associated with the lower HbA1c level in metformin treated T2DM individuals (Table 1).

3.1.3. Multidrug and toxin extrusion protein 2 (MATE2)

MATE2 is a primarily of organic cations and act as a poly-specific efflux transporters for diverse substrates. It is an important player for renal excretion of exogenous and endogenous organic cations, mainly for metformin. MATEs may act in concert with OCT2 to mediate the excretion of some drugs. Variants in *MATE2*, particularly a promoter region variant rs12943590, have also been associated with altered glucose - lowering response to metformin in human [28]. SNPs 485C > T (P162L) and 1177G > A (G393R) were associated with reduced transport of metformin, while a polymorphism in the basal promoter region 130G > A enhanced the promoter activity, which leads to faster metformin elimination [31] (Table 1). Two other *MATE2*-K variants were identified: G211V, which shows low expression levels and seems to inactivate transport function, while the other variant K64 N presents a decreased transport activity [32]. SNP rs12943590 G > A associated with a gain-of-function promoter polymorphism which show slow glycemic response to metformin treated patients with type 2 diabetes.

3.1.4. 5′- adinosine monophosphate (AMP) activated protein kinase (AMPK)

Metformin act on lipid metabolism by reducing hepatic steatosis [33,34]. Geerling et al., reported that metformin exerts a beneficial effect on circulating lipids by lowering plasma triglycerides, through selective increases in VLDL-tri-glyceride uptake and fatty acid oxidation [35]. AMPK act as a master regulator of cell and body energy homeostasis, glucose uptake, insulin synthesis and secretion in pancreatic islet β-cells and induced various pathways to maintain energy balance. AMPK has also regulated various other pathways *ie.* the hippo pathway, growth related pathway, JAK-signal transducer and activator of transcription (STAT) pathway. Metformin induced reduction of lipid storage mediated by 5′-adinosine monophosphate (AMP) activated protein kinase (AMPK), AMPK is a heterotrimeric complex having one catalytic α-subunit and 2 regulatory β and γ subunits [36]. Studies suggested that *AMPK* rs2746342 is significantly related to the susceptibility to T2DM in the Chinese Han population whereas some were showed not significant association with the disease.

Altogether, it appears that genetic variants of *OCT1, OCT2,*

Table 1
Gene polymorphisms associated with pharmacogenetics of Metformin drugs.

S.No.	Gene	Polymorphism	Polymorphism	Phenotype responce	Reference
1	OCT1	rs3798174	C > T	linked to reduction in metformin effect on initial A1C and lipid responses	[19]
		rs2282143	P340L	Decreased ability to transport compound (Metformine)	[19]
		rs622342	C > A	Better efficacy for metformin	[26]
		rs628031	M408V	Not show any effect	[19]
2	MATE1	rs2252281	T > C	Decreases MATE1 expression	[19]
		rs2289669	G > A	'A' allele carriers showed a better efficacy in improving blood lipid	[30]
				Lower HbA1c level in metformin treated T2DM individuals	
3	MATE2	rs12943590	G > A	Lowering response to metformin in human	[28]
				Glycemic response to metformin treated patients with type 2 diabetes	[28]
4	AMPK	rs2746342	G > A	Susceptibility to T2DM	[37]

MATE1, MATE2 transporters and *AMPK* genes may be important determinants for metformin response.

3.2. Suphonylureas

Sulfonylureas have long been used for the treatment of type 2 diabetes and were the first oral anti-hyperglycemic agents to be introduced into clinical practice. They are still widely used and are first- or second-line drugs if the hemoglobin A1c (HbA1c) target is not achieved after metformin monotherapy. Sulfonylureas stimulate insulin secretion by binding to sulfonylurea receptor 1. This binding depolarizes the cell membrane and close the ATP-sensitive potassium (KATP) channels leading to Ca2+ influx and insulin secretion in a glucose-independent manner [38]. In neonates, inactivating mutations in genes encoding *Kir6.2* (KCNJ11) and *SUR1* (ABCC8) are responsible for T2DM, while activating mutations lead to hypoglycemia (Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes [39]. Polymorphisms in the genes *ABCC8, KCNJ11, CYP2C9, TCF7L2,* have been reported for altered response to SUs. Impairment of Kir6.2 (*KCNJ11*) and SUR1 (*ABCC8*) will lead to improper signaling cascade of insulin resulting in abnormal glucose levels.

3.2.1. Potassium inwardly-rectifying channel, subfamily J, member 11

KCNJ11 is a transmembrane ATP-sensitive potassium channel (KATP) located on pancreatic β-cells encoded by *KCNJ11* gene. The *KCNJ11* gene is located on chromosome 11p15.1 in humans. The KCNJ11 transporter is associated with insulin secretion [40]. Till date 219 single nucleotide polymorphisms have been reported in *KCNJ11* gene and many of them were found to decrease or completely stop the metabolic sensitivity of β cell K_{ATP} channel function, leading to a constant depolarization of the cell membrane and a persistent insulin secretion even at very low plasma glucose concentrations. Examples of few SNPs in *KCNJ11* gene found to be associated with T2DM are rs5210, rs5215, rs5218, rs5219, rs886288, rs2285676 [41] (Table 2) Among the different polymorphisms, the most widely studied genetic polymorphism of *KCNJ11* for sulfonylurea response is E23K (i.e., rs5219) located in exon 1 [42]. Studies have reported that the mutant K allele carriers respond better to sulphonylurea treatment in comparison with the EE homozygous wild-type carriers who had higher chances of treatment failure [43,44]. Apart from rs5219 polymorphism in *KCNJ11* gene, the rs5210 SNP have also been widely studied in context with sulphonylurea response. This SNP is located on 3′- untranslated region (UTR) region of *KCNJ11* gene. A Chinese study had reported a positive association of this gene polymorphism with Gliclazide response [45].

3.2.2. ATP binding cassette subfamily C member 8 (ABCC8)

Sulphonylurea Receptor 1 (SUR1) is a regulatory subunit of K_{ATP} channel. It is encoded by the ATP-binding cassette, subfamily C, member 8 (*ABCC8*) gene, located on chromosome 11. A study reported that loss of function mutations in *ABCC8* gene were found to result in closure of K_{ATP} channel and hypersecretion of insulin causing hyperinsulinemic hypoglycemia of infants [46] in context to sulphonylurea treatment, Ser1369Ala (T > G, exon 33) polymorphism in *ABCC8* gene have been associated with differential response with sulfonylurea in T2DM patients. The homozygous mutant Ala/Ala genotype of Ser1369Ala polymorphism was found to be associated with decreased insulin secretion [47] (Table 2). on the other hand a study on 115 T2DM patients taking 40 mg of gliclazide twice a day for 2 months showed a greater decrease in Hb_{A1c} levels after 8 weeks in Ala allele carriers (−1.6%) compared with Ser/Ser homozygotes (−0.76%; p = 0.044) [48] Apart from this, rs1799854 (intron 15, exon 16 -3C/T) and rs1799859 (exon 31) polymorphisms of *ABCC8* gene have also shown to alter treatment response of sulphonylurea drugs in T2DM patients with Caucasian ethnic background [49,50].

3.2.3. Transcription factor 7 like 2 (TCF7L2)

This is the most widely studied candidate gene for T2DM. Various polymorphims of *TCF7L2* gene in different ethnicities like India [51], Japan [52] (Hayashi et al., 2007), France [[53] United States [54], the Netherlands [55]] etc have been studied and found to be associated with T2DM. a arecent study conducted in Egypt reported that rs7903146 variant of *TCF7L2* gene was associated with therapeutic response to SUs and it was observed that the most frequent allele in the nonresponders group was the T allele, whereas the most frequent allele in the responders group was the C allele [55] Another study by Pearson and colleagues on two different polymorphisms of *TCF7L2* gene reported that rs12255372 and rs7903146 influence therapeutic response to sulfonylureas. The SNPs rs12255372T and rs7903146T were represented to be significantly associated with enhanced expression of *TCF7L2* gene in beta cells, altering insulin release and predisposing individuals to T2DM(Table 2) [56]. Among these T2DM-associated *TCF7L2* variants, rs7903146 (intron 4) showed the strongest association with T2D [57] a study reported Significant reductions in HbA1c and fasting plasma glucose levels in T2DM patients taking a combination of sulfonylurea and metformin carrying the wild type CC genotype and those with CT/TT genotype [58].

Table 2
Gene polymorphisms associated with pharmacogenetics of sulphonylurea drugs.

S.No.	Gene	Polymorphism	Polymorphism	Phenotype responce	Reference
1	***KCNJ11***	rs5219	C > T	K-allele carriers had signifi cantly higher decrese in HbA1c compared with EE homozygotes	[43]
		rs5210	G > A	Significantly associated with decrease in FPG (Fasting Plasma Glucose)	[45]
2	***ABCC8***	rs757110	C > A	Significantly associated with decrease in FPG (Fasting Plasma Glucose)	[45]
		rs1799854	C > T	Carriers of wild-type CC genotype had significantly lower HbA1c levels compared to patients with TT genotype	[49]
		rs1799859	C > T	Patients with wild-type GG genotype had signifi cantly higher HbA1c levels compared to patients with AA genotype	[49]
3	***TCF7L2***	rs7903146	C > T	Significantly higher reduction in HbA1c and FPG in patients with CC genotype compared to the CT and TT genotype	[58]
		rs12255372	G > C	T allele was signifi cantly more frequent in patients who failed to respond to SU than in the control subjects	[59]
4	***CYP2C9***	rs1057910	A > C	Carriers of *3 allele required lower doses of tolbutamide to regulate glucose levels as compared to *1/*1 genotype	[63]
		rs1799853	C > T	More likely to achive a treatment HbA1c <	[65]
		rs1057910	A > C	7% (53 mmol/mol) than patients with wildtype Genotype	

3.2.4. Cytochrome P450 2C9 (CYP2C9)

Cytochrome P450 2C9 (*CYP2C9*) are a class of drug metabolizing genes that metabolize different classes of SU drugs like tolbutamide, glimperide, glipizide and glibenclamide to active metabolites in the liver [59]. Other studies have shown that two variants of *CYP2C9* gene, *i.e.*, rs1057910 *(CYP2C9*3)* and rs1799853 *(CYP2C9*2)* were significantly associated with decreased metabolism of SUs in healthy volunteers [60]. The *CYP2C9*3,* Ile359Leu and Arg144Cys variants of *CYP2C9* gene were found to enhance risk of hypoglycemia or cause a major reduction in renal clearance of glibenclamide suggesting lower doses of this antidiabetic drug to decrease the risk of hypoglycemia [61–64] (Table 2).

4. Challenges, opportunities and future direction

Personalized medicine is growing field which will be future of the medicine industry. PM combined the bioinformatics and clinical data for identifying the biomarkers for diseases. Emerging technologies provided the unmined sources of information. Precision medicine clinics will channel new sources of information assembled into clinically focused data sets and will use the emerging data streams to deliver individualized treatments for patients with phenotypically similar but genotypically and molecularly dissimilar diseases [4]. Personalized medicine aim to reduce the burden of disease by targetting prevention and treatment more effectively through the integration of inputs from multiple data source. However, personalized medicine might be decreases the health cost and improve the therapy by eliminating trial-and- error method for the treatment. Drug-response studies were mainly centered on the transporter protein that regulated metformin transport and most of the work focused on organic cation transporters (OCTs) to understand the role of candidate genes. It will be helpful to have an understanding of the pharmacokinetics and pharmacodynamics of metformin and sulfonylurea. PM will change the whole treatment plans for the disease. Worldwide Healthcare systems will need to consider this technology for adjusting and evaluative methods for developing new treatments and services.

5. Conclusion

In this review we summarized the importance of personalized medicine and determining the pharmacogenomic and drive for interindividual variation in drug response. Proper molecular diagnostic can lead targeted treatment which increase efficacy of treatment and avoid unnecessary drug trial and insulin therapy. In this review we found that *OCT1, OCT2, MATE1, MATE2* transporters and *AMPK* genes may play important role in metformin response whereas *ABCC8, KCNJ11, CYP2C9, TCF7L2* are reported for alters response to sulfonylurea. So by identifying these markers we can personalize diabetic treatment.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.06.017.

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