

Article History

Received:
January 15, 2024

Revised:
February 28, 2024

Accepted:
March 22, 2024

Available Online:
June 30, 2024

ADVANCES IN PRECISION MEDICINE FOR TYPE 2 DIABETES: INTEGRATING GENOMIC, EPIGENETIC, AND METABOLOMIC DATA FOR PERSONALIZED THERAPEUTIC STRATEGIES

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Abstract

Type 2 diabetes (T2D) is a global health problem that has heterogeneous disease progression and response to therapy. Precision medicine using multi-omics data such as genomics, epigenetics, and metabolomics is promising for the development of customized therapies. The present review examines these omic technologies in integration, particularly in stratifying patients, discovering biomarkers, and optimizing treatment. Highlighting advances in pharmacogenomics, pharmacometabolomics, and pharmacoepigenomics in the integration of those data for T2D patients, its applications face limitations, including standards for data, among others ethical issues. Notwithstanding, precision medicine sounds to be a revolutionized approach to application with respect to T2D management when interventions are tailored to specific interventions based on the possible profiles that individuals were known molecularly.

Keywords: Type2 Diabetes, Precision Medicine, Pharmacogenomics, Pharmacoepigenomics, Metabolomics

INTRODUCTION

Millions of people worldwide are suffering from type-2 diabetes (T2D) while contributing above morbidity and mortality rates [3]. There is alarming increase in the figure of adults with diabetes in 2045, according to International diabetes federation (IDF), which definitely adds urgency for the development

of more advanced diagnostics and therapeutics [5]. This condition is largely multifactorial, meaning that they occur due to genetic, epigenetic, and environmental factors that basically bring this disease into reality as stated by World Health Organization (WHO) [4].

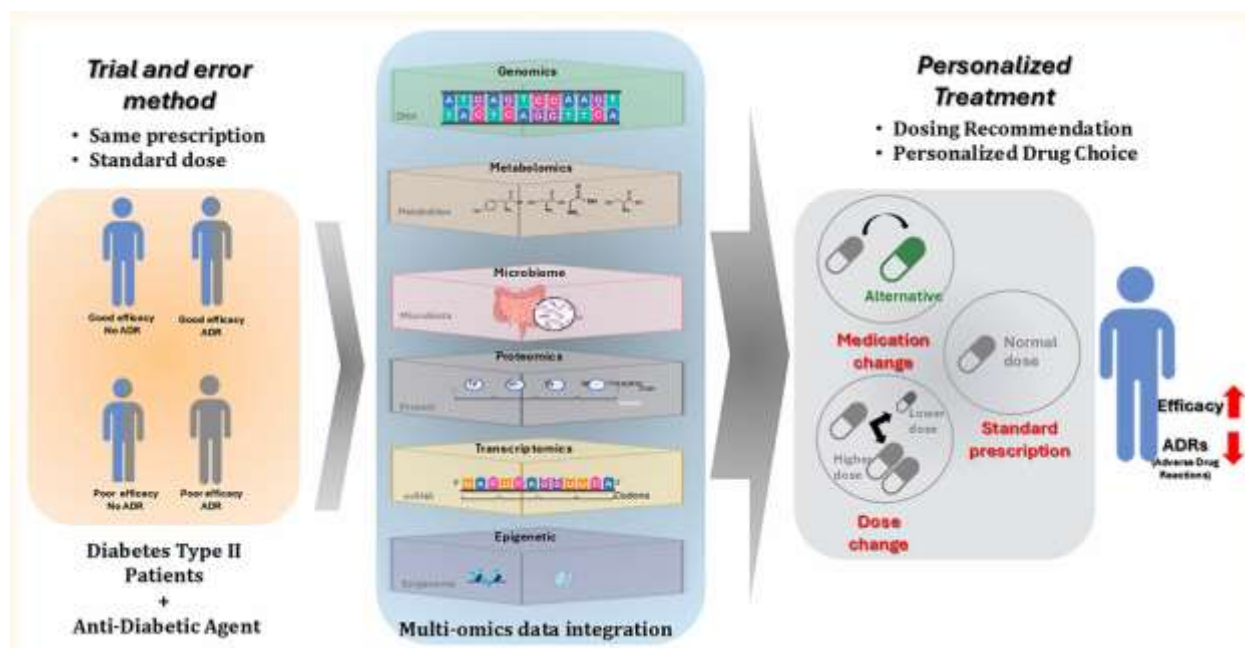


Figure 1. Advancing T2D management through multiomics integration in personalized treatment versus standard therapeutic approaches

Because of heterogeneity among patients, conventional treatment strategies for T2D, including lifestyle modifications and pharmacotherapy, were unsuccessful in achieving optimal glycemic control in most patients [9]. Recent advances in multi-omics technologies, such as genomics, epigenomics, and metabolomics, were harnessed to formulate personalized therapeutic strategies that could assist in treatment efficacy and reducing the adverse drug reaction [10]. Pharmacogenomics, which is the study of how an individual's genetic inheritance affects their response to drugs, is built around such findings; polymorphisms in genes such as SLC22A1, which is an uptake transporter of

metformin, and ATM are associated with variability in metformin response [13].

Metabolomics, a developing area of research in precision medicine, highlights metabolic changes that may accompany T2D progression and response to therapy [31]. Machine learning models that utilize metabolomic data have been shown to enhance the discrimination between disease classification and biomarker discovery, thereby expediting early diagnosis and treatment optimization [2]. Epigenetic modifications, such as DNA methylation and histone modifications, are also associated with

insulin resistance and β -cell dysfunction, providing candidates for further therapeutic targeting [6].

Table1. Proteins bind small molecules and carry out functions essential for all living systems.

Pharmacological Drug	Mechanism of Action	Genes	Main Effects	SNPs	Clinical Utility
Metformin	Inhibits gluconeogenesis through AMPK activation and other AMPK independent pathways	SLC22A1 (OCT1)	Located in the epithelial inner surface of the gut, renal tubules, and hepatocytes. OCT therefore allows the transport of the hydrophilic molecule across cell membrane barriers	Highly polymorphic with upto 34 identified polymorphic SNPs across different populations. Among the common SNPs are: rs628031, rs622342, rs12208357, rs72552763, rs2297374, rs4646272, rs34130495, rs2282143, rs1867351, rs594709, rs200684404, rs34104736, rs2297373, rs622591, rs2197296, rs4709400, rs461473, rs1443844, rs9457843, rs6937722	Studies are highly controversial on the effect of polymorphism on the effectiveness and tolerance of metformin in different population cohorts
Metformin		SLC22A2 (OCT2)		rs316019, rs316009, and rs145450955	



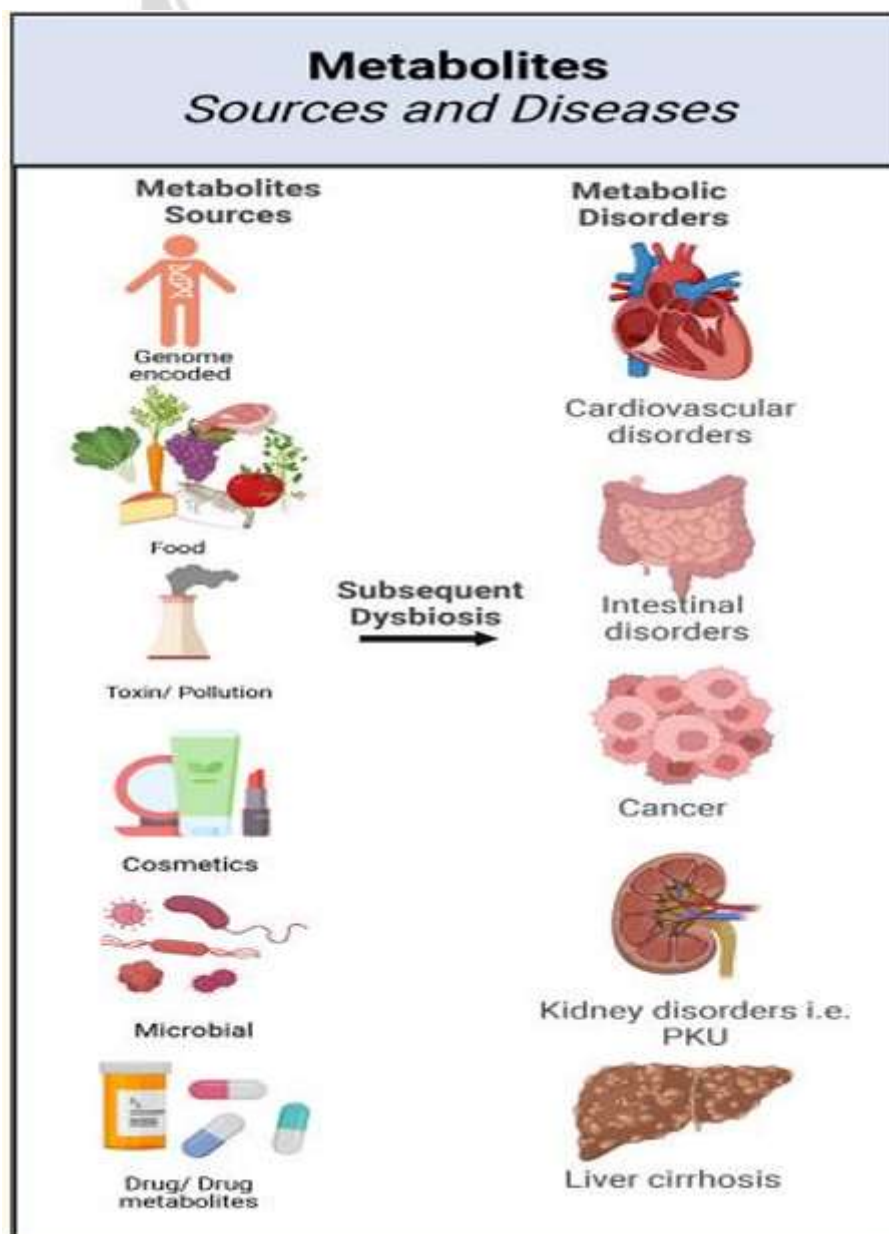
Pharmacological Drug	Mechanism of Action	Genes	Main Effects	SNPs	Clinical Utility
GLP-1 analogues	Stimulates glucose-dependent insulin release from pancreatic islets	CNRI	Cannabinoid type 1 receptor present in adipose tissue	rs1049353	No changes in glycemic outcomes, but changes in body weight are noted
		GLPIR	Glucose-dependent insulin release regulation. GLP1 RA genes also may contribute to delayed gastric emptying and increase satiety, while ARRB1 genes may affect beta cell proliferation	rs6923761 rs10305420	Controversial, rs6923761G may be implicated in A1c reduction, or greater weight reduction and more marked delayed gastric emptying. while rs10305420 is unlikely to be associated
		TCF7L2		rs7903146	Controversial
		SORCS1		rs1416406	Possibly affect glycemic control outcomes including A1c, fasting glucose and post-meal glucose
DPP4 inhibitors	DPP-4 inhibition promoting glucose regulation	GLPIR	GLP receptors	rs6923761, rs3765467	Possibly affect A1c reduction
		TCF7L2	Impairment in insulinotropic actions of incretin hormones, which are vital in DPP 4 inhibitor actions	rs7903146	Possibly affect A1c reduction
		PNPLA3	PNPLA3 gene has been associated with insulin resistance	rs738409	Possibly affect A1c reduction and PNPLA3 may additionally affect lipid profile and changes in liver aminotransferase
		DPP4	Drug inhibition site gene	rs2909451, rs759717	Likely higher DPP4 activity, may affect A1c reduction
		CDKAL1	Genotypes associated with higher DM incidence	rs7754840, rs7756992	Possibly affect A1c reduction
		KCN	Potassium gene family, that affects the release of insulin from pancreas	rs734312, rs2285676, rs163184	Possibly affect A1c reduction
PRKD1	Kinase G-protein coupled receptor mediates insulin release	rs57803087	Possibly affect A1c reduction		

The integration of Artificial Intelligence (AI) in precision medicine increases the power of such systems to analyze interactions between a huge number of genetic, epigenetic, and metabolic markers [2]. Most AI-driven predictive models can stratify patients according to their molecular characteristics with a very high degree of accuracy and have thus been used to develop individualized treatment regimens to improve outcomes for patients [11].

For all their advances, issues remain in actually inducing precision medicine into routine practice in the clinic. These include the captured problems of standardization of data, regulation, and ethics to be resolved for equitable access and implementation [28]. Future research should involve biobank enlargements, multi-ethnic mega-studies, and merging EHRs with multi-omics data to improve real-world applications of precision medicine in T2D management [29].

Precision medicine can involve genomic, epigenetic, and metabolomics material. Bring transformation to T2D therapy- personalized interventions as opposed to generalized therapeutic interventions will be the way forward. As this field of research unfolds, it is critical that collaboration between clinicians, researchers, and policymakers happens for this to maximize clinical utility and result in better diabetes care across the globe [1,2,16,].

Figure 2. Metabolites Sources and Disease



METHODOLOGY

A thorough literature review was undertaken involving peer-reviewed articles and current research studies on the pharmacogenomics, metabolomics, and epigenomics domains in T2D. Data sources included recent results from published reviews and empirical studies on omics-driven precision medicine approaches [1,2,17,33].

Pharmacogenomics. It includes the study of how differences in genotype can serve to alter the metabolism of drugs or their effects.

Polymorphisms in the SLC22A1, SLC47A1, and ATM genes have been shown to account for variability in metformin action [7-9,11]. Several genome-wide association studies (GWAS) are identifying key SNPs that modulate glycemic control and drug reactions in patients with T2D [25-28]. By identifying these markers, the clinicians can prescribe the best-suited drug with an appropriate dosage and thus minimize the chances of such treatment failures arising. Metabolomics has its own contributions into the metabolic pathways influenced by T2D and the response mechanisms. Liquid chromatography-mass spectrometry (LC-MS) studies revealed distinct metabolite profiles differentiating metformin responders from non-responders [22-23]. Machine learning based on artificial intelligence has been involved in metabolomic biomarker discovery to enhance predictive accuracy of drug response and disease progression [30]. Epigenetic alterations, like DNA methylation and histone modification, are also linked with gene expression and drug responses in T2D. Recent studies are indicating CpG methylation patterns that predict tolerance to metformin-tolerant and glycemic response [9]. In addition, epigenetic

treatment by inhibiting histone deacetylases (HDACs) and DNA methyltransferases (DNMTs) is expected to enhance insulin sensitivity and β -cell function [19]. AI and Machine learning have gained importance in using multi-omics data for precision medicine applications. High prediction accuracy for T2D subtypes and treatment responses has been achieved using supervised learning models with transcriptomic and metabolomic datasets [2,21]. Deep learning networks do well in further refining patient stratification and, thus, developing personalized treatment algorithms [2,24].

Limitations and Research Gaps

While there has been immense progress in integrating multi-omics data formats, challenges of reproducibility in such data continue to exist in diverse populations [10,15-21]. Thus, ethical concerns concerning genetic privacy and data security require regulatory frameworks that guard patient information [2]. More extensive clinical studies are needed, however, to establish the clinical implications of precision medicine in T2D management [29].

Future Directions

It is envisaged that high-throughput sequencing and AI-powered analytics will revolutionize precision medicine in T2D [1,31,36,]. Additional integration of the electronic health record (EHR) with multi-omic data may facilitate real-time treatment adjustments at an individual level. In the future, further research should focus on the expansion of biobanks globally and on multi-ethnic studies, ensuring inclusivity in all precision medicine strategies [6,8,18-22].

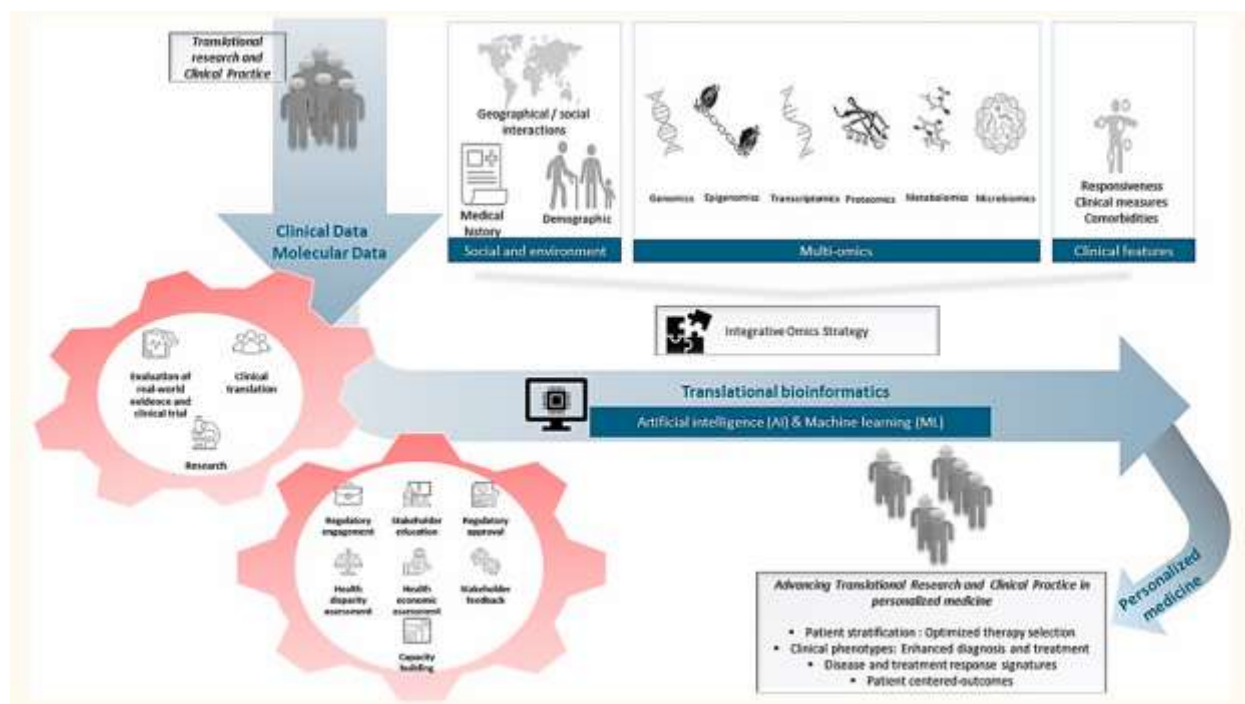


Figure 3. Integrative omics strategy in precision medicine.

CONCLUSION

Precision medicine is going to be a marvelous pillar of T2D intervention through precision health: the tailoring of interventions to genetic, epigenetic, and metabolomics profiles. New methods-pharmacogenomics, metabolomics, and their integration data-will genuinely increase therapeutic approaches towards personalized outcomes for patients using them. Utilizing more comprehensive molecular mechanisms knowledge of T2D, precision medicine practices promise improved treatment regimens, adverse drug reaction reductions, and better disease monitoring. Thus, massive barriers remain to be crossed, making the journey to successful implementation of such precise medicine in clinical practice today. Data standardization, interoperability of health documents, and ethical considerations around patient privacy and data security are critical. Above this, large clinical trials and studies on diverse populations will still have to be initiated to ascertain efficacy and generalizability on personalized

treatment approaches. Yet, as precision medicine advances, this could shape the future of diabetes care for individuals across the world, taking it to greater heights in proactivity and patient-centeredness, resulting in better lives for patients and reducing the burden of T2D worldwide-on an extent and nature that is yet unimagined.

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