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Precision Medicine for Metabolic Disorders in Low– and Middle-Income Countries: Areas of Opportunity and Challenges for the Future

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ABSTRACT

The purpose of this perspective is to analyze the use of precision medicine and its potential for the next few decades with a special focus on the low– and middle-income countries, using diabetes as a paradigm. Precision medicine has improved the diagnosis, prevention, treatment, and prognosis of several malignant neoplasia. Furthermore, this approach is useful in the management of monogenic diabetes. However, its impact in the current practice for the majority of the cases of diabetes is quite limited. Precision medicine has not fulfilled the expectations because it implies a long-term process composed by several feedback loops, and a number of internal and external validations and calibrations to target specific populations. If we want to obtain the expected benefits, the academic community and science agencies should work together to create the budgets and infrastructure that warrant the transfer of knowledge to the whole of society. (REV INVEST CLIN. 2021;73(5):316-20)

Key words: Precision medicine. Omics. Low/middle income countries. Diabetes. Personalized medicine.

INTRODUCTION

Precision medicine is an approach to optimize the diagnosis, prediction, prevention, or treatment of diseases by integrating multidimensional data, accounting for individual differences[1]. A variety of sources of information are useful in precision medicine, ranging from genomics, metabolomics, transcriptomics, or any other omics technology to functional imaging or electronic medical records. Data should lead to identification of clusters of individuals with the same medical condition that may have a similar progression, response to therapy or outcomes. The result is a refinement in the selection of medical procedures or therapies[2].

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The interest for precision medicine was triggered by the publication of the "Human Genome Project." The main premise is that most human diseases have an underlying genetic component, which can modulate disease onset, progression, presence of certain complications, and treatment response. This is particularly true for common diseases, like type 2 diabetes (T2D). More than 70 genes and close to 130 gene variants have been associated with T2D. However, T2D represents a group of heterogeneous phenotypes. Through the availability of large genotyping data, at least five distinct patient groups have been identified that differ in insulin secretion capacity, disease progression, and even in the risk for chronic complications[3]. The cluster analysis was enriched when clinical data were included. Based on these findings, targeted therapy could be applied to certain individual subgroups[4].

Francis Collins proposed in 1999 that "due to precision medicine, in 15 or 20 years, you will see a complete transformation in therapeutic medicine[5]." However, besides a few exceptions, precision medicine remains a promise. The purpose of this manuscript is to discuss the possible use of precision medicine in the next several decades, with a special focus on low- and middle-income countries. We will discuss some strategies that our scientific communities may adopt to contribute and avoid delays in the implementation of the state-of-the art practices in precision medicine. We will use diabetes as an archetype, based on the high social impact of the disease and the advances of precision medicine in this topic.

APPLICATIONS OF PRECISION MEDICINE IN METABOLIC DISORDERS

Precision diagnosis

T2D (as the majority of the metabolic diseases) is largely a polygenic disease. A small proportion of cases is explained by monogenic defects. Precision medicine allows their identification which has clinical implications. Maturity Onset of the Young (MODY) is a form of early-onset diabetes transmitted as a Mendelian dominant trait. Al least 14 different genes have been found responsible for this heterogeneous disease, although three genes account for most cases (*HNF1a, HNF4a,* and *GCK*). At present, the majority of the MODY patients are misdiagnosed (as type 1 diabetes [T1D] or T2D). The correct diagnosis has therapeutic and clinical implications. MODY cases carrying *HNF1a* mutations have a selective response to sulfonylureas[5]. In addition, the identification of *HNF4a* mutations implies the search for extra pancreatic abnormalities (i.e., renal cysts among others). Guidelines have been developed for pregnant women carrying different MODY gene mutations. A form of precision medicine is the development of MODY calculators[6] in which clinical, biochemical, and other variables may help to identify the cases that require genomic studies. Its use is limited by the different diagnostic performance observed between ethnic groups[7]. The proper selection of the cases is critical to make the genetic studies (i.e., MODY multigene panel) cost effective.

Furthermore, precision diagnosis may be helpful to distinguish major phenotypes (i.e., T1D vs. T2D). Several multigene panels in combination with biochemical (i.e., plasma or urinary C-peptide concentrations) or immunologic tests (i.e., several anti-islet cell antibodies) have been used for this purpose[8]; their use may avoid a delay in starting insulin therapy. However, these diagnostic tools are limited to reference centers due to the required infrastructure, the polygenic nature of these diseases and its cost.

Identification of sub-phenotypes of both T1D and T2D has become very attractive for several research groups. Data-driven cluster analyses have been used to identify 5 T2D sub-phenotypes (autoimmune diabetes, aging-related, obesity-related, insulin resistance-related, or severe insulin deficiency related)[9]. Each one has a different probability to have chronic complications and could be identified using risk calculators. The cluster analyses are based on accessible clinical variables that may change over time; as a result, patient classification will transit between clusters. Using population-based data, we found that the most common phenotype in Mexican living with T2D is the severe insulin deficiency group. However, if patients improve their glycemic control they will change to another phenotype[10]. As a result, the long-term implications become uncertain. Long-term follow-up data coming from electronic medical records of cases treated in national health systems will be required to produce the best possible definition of the T2D subphenotypes.

Precision prevention

Many efforts have integrated clinical, genomic, metabolomics, and/or microbiome data to construct predictive models to identify individuals with the higher risk for incident T2D diabetes. Although the inclusion of the omics variables improves performance of the scores, the change is not significant over the information obtained from clinical data[11]. Moreover, the effectiveness of prevention therapies is the same in cases with or without high genetic risk scores[12]. Additional studies with larger sample sizes and longer follow-ups are needed to evaluate the usefulness of more developed predictive scores.

Precision treatment

This is the area in which precision medicine has had greater achievements. This is the case for some malignant neoplasia (i.e., breast cancer). Furthermore, improved efficacy or safety has been achieved by taking into account the polymorphisms or mutations of the genes involved in the absorption, conversion or excretion of drug therapies[13]. The Pharmacogenomics Knowledge database (PharmGKB) contains information regarding drug metabolism and general usage guidelines of the pharmacogenomics information[14]. In the diabetes field, the identification of some monogenic forms of diabetes could help to select (sulfonylureas of *HNF1A* mutations) or to avoid (insulin in *GCK* or *HNF1A* mutations) therapies. Cluster analyses have been proposed to guide the selection of diabetes therapy; the insulin resistance phenotype may have a greater response to PPARγ agonist than to other glucose-lowering agents such as sulfonylureas. Precise molecular diagnosis of pregnant women with MODY gene mutations has also resulted in specific therapeutic guidelines. For example, sulfonylureas are known to cross the placenta; hence, their use should be avoided in *HNF4a* and *HNF1a* carriers, as these drugs can result in neonatal hypoglycemia. Furthermore, in a woman carrying *GCK* mutations, it is advised to know the mutation status of both, the pregnant woman and the fetus to define the treatment options. The use of insulin is recommended only in those pregnancies where the fetus has not inherited the mutation. In such cases, the fetus will be exposed to maternal hyperglycemia and might present diabetes-related complications if the mother is not treated[15].

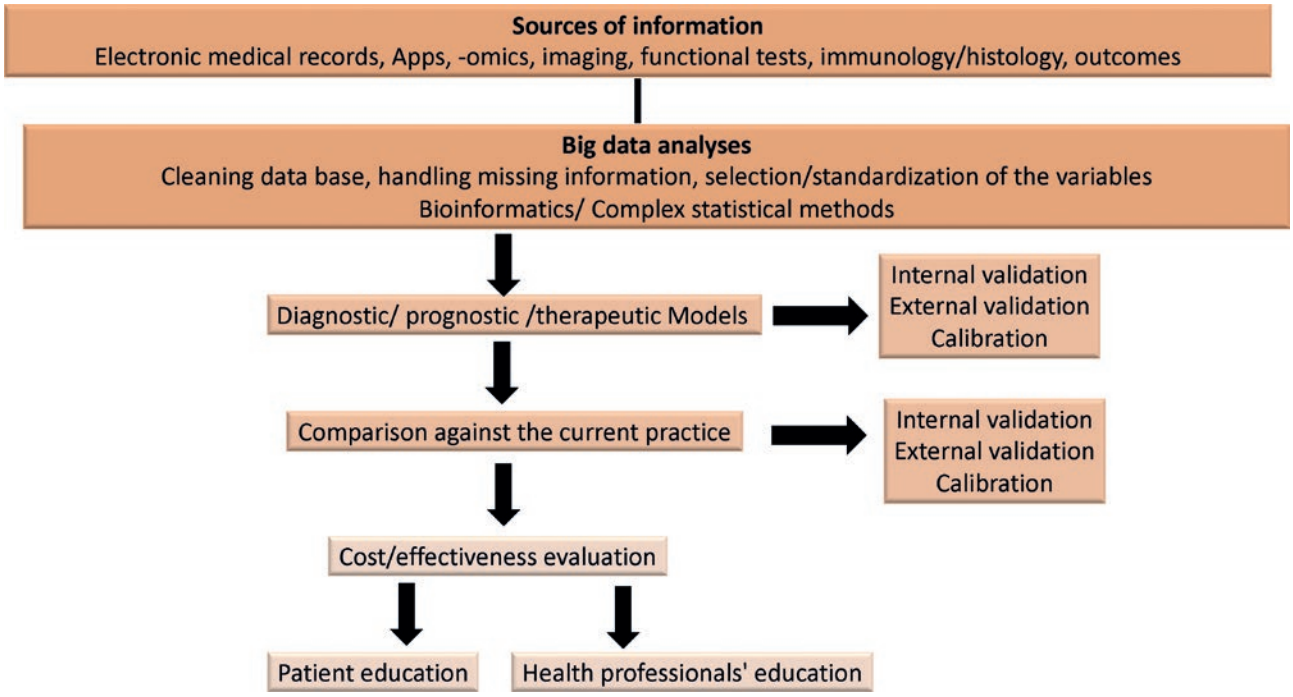
Precision prognosis

Precision prognosis is broadly used in medical oncology where large sets of data are analyzed to identify groups of mutations, miRNAs, or gene expression signatures from tumor subtypes[16]. This approach is useful in clinical practice to inform on cancer progression and prognosis[17]; however, it is difficult to be applied for metabolic disorders, due to the multifactorial and time-dependent nature of the chronic complications. Precision prognosis estimates may require large longitudinal studies in which newly diagnosed patients are evaluated at different time points, and extensive information is recorded including medical, biochemical, and environmental data.

CHALLENGES, AREAS OF OPPORTUNITY, AND POTENTIAL BENEFITS IN LOW– AND MIDDLE-INCOME COUNTRIES

Precision medicine has not fulfilled the expectations because it implies a long-term process composed by several feedback loops, a number of internal and external validations and calibrations to target special populations[18] (Fig. 1). Many precision medicine studies are limited to the description of a tool or model, with the translation process being left for the future. Furthermore, the sampling process should be representative of the subjects in which the product will be applied. Many precision medicine studies relied on a previously collected set of variables not related to the precision medicine approach. This issue is solved by collecting large-scale data sets, but this strategy may not include the whole spectrum of the population. In addition, the analyses could be complicated by the effect on the results caused by sample storage, missing variables, and different analytical methodologies. Big data analyses heavily rely on complex statistics and bioinformatics. In the process, critical decisions may influence the outputs; cleaning the database, handling missing data, and the selection/standardization of the variables require experience and the participation of several researchers with complementary expertise. Models should be built considering the resources that are available in the clinical scenario and to be as simple as possible. A common mistake is to include a large list of variables that may interact between each other or that are highly correlated, which may cause unexpected results. The models should

Figure 1. The process and cycles of personalized medicine.



pass internal and external validations, which is a crucial but difficult to accomplish step of the process. For precision therapeutics or precision prognosis projects, the study design should include randomized controlled trials or pragmatic studies (based on medical records of large medical providers). Several Phase III studies will be needed to validate a new indication or an alternate therapeutic scheme. This process is challenging and costly.

To confront the complexity of the process, a joint effort of multiple partners is required. Multiple consortia in the US and Europe have been created[19,20]. In the diabetes field, the Precision Medicine in Diabetes Initiative (PMID) was created in 2018[1]. Initially, the goal was to publish a consensus report in which milestones, deliverables, and research gaps were identified (2018-2019). In the current phase (2020-2023), study protocols are executed and granted by PMID. The translational studies are expected for 2024-2025. The process will finish with physician and patient education programs (2025 and beyond). Regrettably, the study samples fell short to be representative of all ethnicities. Reference centers from Latin America may have a prominent role in this process to increase the representativeness of the resulting products[21]. As a result, it is highly desirable that reference centers of our countries should seek for their inclusion in the consortia and to develop the infrastructure to warrant an active participation. The institution will benefit from its involvement by getting exchanges of training, personnel, and knowledge. Unfortunately, financial support for these initiatives is quite limited. Science agencies should update their policies to create specific calls to ensure that our countries are represented in such international efforts. The consortia participants should be involved in the whole process that concludes with the incorporation of the end-product in clinical practice[22].

The Native American background of the Latin American populations will result in additional challenges during the translation process due to the differences in the allele frequencies and the existence of ethnic-specific rare variants. This feature should be seen as an opportunity rather than an obstacle[23]. The concentration of research resources in reference centers limits the wide spread of the resulting products if these include any –omics variables. On the other hand, the increasing use of electronic medical records in the

largest health systems will allow the inclusion and follow-up of large data sets and the collection of real-life evidence. Cluster analyses and artificial intelligence methods will be invaluable tools to use this resource to improve medical care, even with the limited access to the omics methods[24]. Biobanks should be considered as a priority in the preparation of any precision medicine effort. These organizations should have a bioethics committee that warrants the proper management of the biological materials and the information of the participants[25].

CONCLUSIONS

Precision medicine remains a promise to be fulfilled especially in low- and middle-income countries. If we want to obtain the expected benefits, the academic community and the science agencies should work together to create the budgets and infrastructure that warrant the transference of knowledge to the whole of society.

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