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PRECISION MEDICINE: REVIEW ARTICLE

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ABSTRACT

Since the drop in mortality from infectious, chronic, and non-communicable diseases, the healthcare system has altered, having an immediate effect on both public health and individual health care expenses. A system that targets the disease before it starts and treats the disease in a tailored fashion if it cannot be avoided is now required in place of traditional reactive medicine based on symptoms, diagnosis, and therapy. This new approach to medicine is called precision medicine. In order to present a current overview of this topic, this study does a detailed literature analysis. It then explores the implications of using genetics and genomics for nursing practice, medical education, clinical research, and ethical concerns. I conversed. The concepts of prediction, prevention, personalization, and involvement are added to the Precision Medicine model in this article. In the end, we shall decision-making paradigm

With a focused healthcare delivery model, the traditional manner of allocating resources for health is challenged in terms of safety, efficacy, and efficiency. Concerning unique variations in pathology, the foundation of precision medicine. Promotion Decision-making and health policy must change to reflect this new health frontier. Ensuring the reduction and improvement of health care inequity, the overarching public health goal Achieving population health requires efficient and equitable distribution health savings. The latest uses of precision medicine are covered in this work. Additionally, the possible effects of these public health decisions and policies Patients with uncommon illnesses and cancers are the main emphasis. Writers

After that, make the necessary adjustments and offer public health's accuracy as a link between them.

Discuss the various fields of precision medicine, how it is used in developing nations, and how it affects public health and medical education. Traditional public health has faced difficulties as a result of advances in precision medicine. Apparently competitive fields.

Keywords*: Precision Medicine, Medical Education, Molecular Biology, Genetics, Genomics*

1. INTRODUCTION

Precision medicine has sparked intense debate about the benefits and reality of more personalized medicine. Approach to healthcare. One camp has an ideology that believes in medical utopia May exist in a world where patient omics-related information such as the patient's genome and exponomics exists Metabolomics can guide real-time individual prevention and treatment for improvement All results (1, 2). In the other camp, there are people who speak lessons because of their current incompetence.Harmonize dreams and reality (3, 4). Especially with relevance Impact of personalized precision healthcare approaches on populated public health Traditional focus for funding-requiring interventions and decisions for health initiatives Rationalize within a finite budget. Precision Public Health (PPH)

This was mainly due to advances in science and technology leading to improved sanitary conditions, new therapies and drugs (such as antibiotics), new imaging methods (starting with the X-ray, which won the Nobel Prize in 1901), and the introduction of preventive medicine including vaccination campaigns and, later in the century, the promotion of healthy lifestyles [3,4].

Standing at the peak of healthcare evolution, one might wonder if this increase in life expectancy will continue. Moreover, within the current limits of the lifespan, we are already paying the price for living longer. Currently, we spend approximately 50% of the budget dedicated to healthcare on treating terminal illnesses such as cancer, heart failure, and other degenerative diseases [5,6]. The single factor common to all of these diseases is aging. To better target the issues related to this increase in life expectancy, medicine in the 21st century must focus on attaining the 4 Ps stated by Dr. Leroy E. Hood: prediction, prevention, personalization, and participation [7–9]. We must now transition from traditional reactive medicine based on symptoms, diagnosis and treatment to a system that targets the disease before it occurs and, if it cannot be avoided, treats the disease in a personalized manne

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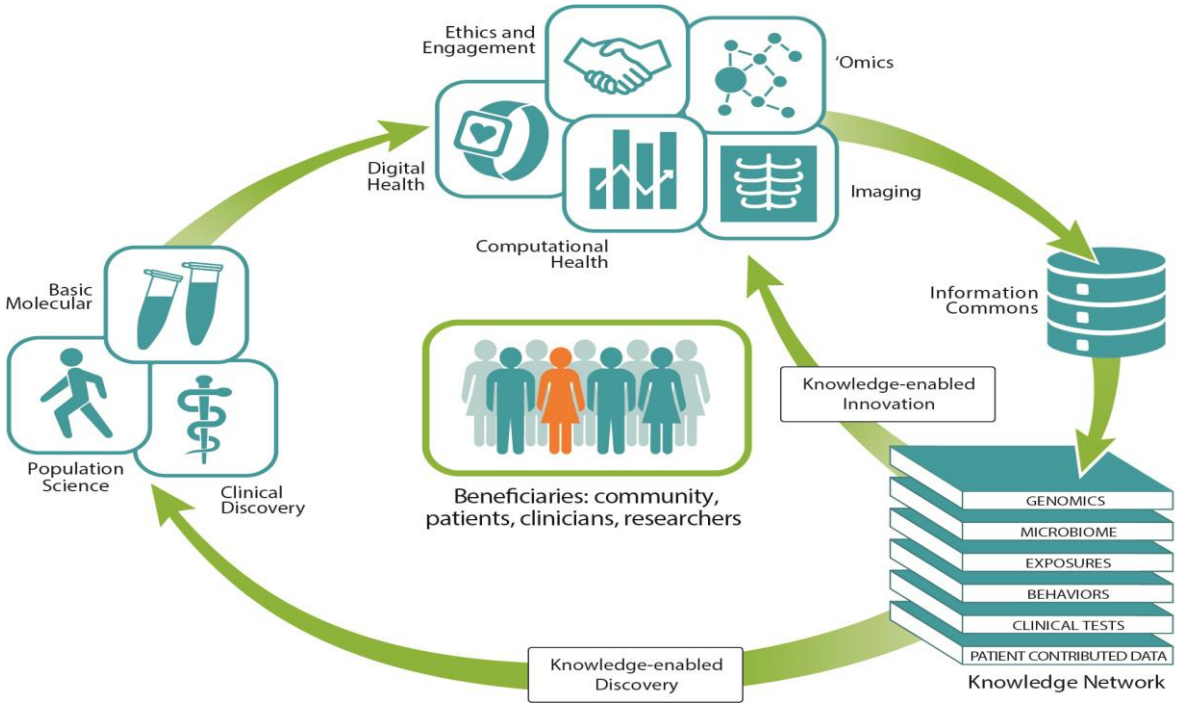
2. THE ELEMENTS OF PRECISION MEDICINE

Precision medicine, as envisioned by UCSF, is a fluid, circular process. Findings from basic, clinical, and population sciences research, data from digital health, 'omic technologies, imaging, and computational health sciences and ethical and legal guidelines are integrated into a knowledge network, creating a sort of "Google maps for health," which informs both science and care for individuals and populations.



3. THE CONTRIBUTION OF GENETIC TESTS AND THERAPIES TO PRECISION MEDICINE

Advances in the development of genetic tests and therapies provide the potential to transform medicine and create unprecedented ability for detection, prevention, and treatment of diseases. Therapy approaches based on genetic variants and specific biomarkers have been increasing over the last few decades in association with the increasing availability and affordability of genomic sequencing technology. In this context, there has been growing interest in and advocacy for precision medicine approaches (13).

This interest is highlighted by the World Economic Health Forum's Precision Medicine Programme, which "aims to support the development of policy frameworks and governance protocols to realize the societal benefits, and mitigate the risks from, precision medicine" (14). Consideration of individual level variation, of both the person and/or their disease, is at the heart of precision therapies. For example, tumors have been eloquently described as "malignant snowflakes," which articulates that no two cancers will have the same molecular profile (15). Subsequently, therapeutic regimens must consider this inevitable variation in disease, with an individualized therapeutic approach likely to produce better health gains (15). Similarly, there are thought to be up to 6,000 rare diseases, many of which have underlying genetic causes and which may require different therapeutic approaches. Furthermore, genetic variants have been shown to influence metabolism of drugs and a range of drugs include information on their labels about adverse drug reactions or different dose recommendations based on a person's genomic profile (16, 17). It is possible that an individual's genomic information could be used to rationalize and guide therapeutic options and dosing at the point of prescribing.

However, the approval and use of such precision therapies is often reliant on "companion" diagnostic tests that are able to identify who is likely to benefit from a particular medicine, requiring parallel mechanisms of assessment and regulation for diagnostic and therapeutic approaches. Some recent examples of precision therapies and interventions are explored below.

BIOMARKER SPECIFIC THERAPIES:

In 2017, the Food and Drug Administration (FDA) United States (USA) approved higher accuracy Dosing and companion test compared to the previous year (18). One example is pembrolizumab (Keytruda) This was the first solid cancer treatment approved for use Based on the presence of specific biomarkers,

Tumor localization (19). The same was true for trastuzumab-dskt (OgivriTM). Approved as the first biosimilar to act on both stomachs, Breast tumors that may overexpress the HER2 gene Promote competition and reduce medical costs (20). Because these tests depend on a more specific entity Biomarkers, therefore, they depend on companion genes test. Two examples of accompanying tests are MSK-IMPACTTM. (Screening 468 genes) and Foundation One CdXTM (screening 324) Gene), both solid tumor testing and first massively parallel testing

A sequence of in vitro diagnostic tests. Both tests are screened multiple times Oncogenes to identify mutations that may be useful in clinical applications Patient management and identification of specific patients Tumor types that may benefit from approved targeted therapies

GENE THERAPY:

Significantly, three of the 2017 FDA approvals were the first gene therapies ever approved by the FDA, including voretigene neparvovec (LuxturnaTM) for retinal dystrophy, the first to treat an inherited disease. Spark Therapeutics gave LuxturnaTM a list price of US$425K per eye, making it the most expensive medicine in the USA per dose (23). The FDA also gave fast track designation and priority review in 2016 for two orphan drugs for genetic neuromuscular diseases (both antisense oligonucleotides), representing significant advances in the treatment of rare diseases. In September 2016, the FDA provided accelerated approval for eteplirsen (Exondys 51TM) for Duchenne muscular dystrophy (24), and nusinersen (Spinraza R) was approved in late December for early fatal spinal muscular atrophy (25). Both these treatments need to be delivered for the remainder of a patient's life. Exondys 51TM costs around US$300K per patient per year, and in the second quarter of 2018 it generated Sarepta Therapeutics over US$73 million in net revenue (26). Spinraza R has a list price of US$125K per injection, translating to US$750,000 in the first year of treatment per patient, and US$375K for each subsequent year.

In Australia, Spinraza R was listed on the Pharmaceuticals Benefits Scheme from 1 June 2018 (27), meaning patients pay less than AU$40 per script. However, in August 2018, Britain's healthcare cost agency (National Institute for Health and Care Excellence; NICE) deemed Spinraza R too expensive, and its long-term effectiveness too uncertain, for routine use within the National Health Service [NHS; (28)]

GENE EDITING :

Currently, the emphasis is on precision treatment of the genome. Focusing on editing or engineering, three genomic modification techniques, all utilizing programmable nucleases, This can be thought of as a "molecular tool". These are CRISPR Cas9 (clustered, normally spaced, short palindromes). Replay-CRISPR; CRISPR-related protein 9-Cas9); zinc Finger nucleases (ZFNs); and transcriptional activator-like effectors Nuclease (TALEN). All these nucleases have been translated About patient care to some extent. The cells constructed with TALEN B-cell acute lymphoblastic leukemia (B-ALL) (29). very Promising findings led to the drug tisagenlecleucelle) FDA approved in August 2017, along with others Approved for use in large-cell B-cell lymphoma in May 2018 (30- 32). Tisagenlecleucelle approved by the European Union B-ALL will be available within 2 weeks after August 2018 NHS England has reached a commercial agreement with this drug Novartis, a manufacturer that provides medicines for advanced children Leukemia (33). First human in November 2017 as part of Phase 1/2 trial Infused ZFN gene editing tool into her bloodstream Attempts to treat previously incurable, rare metabolism of the patient Illness [Hunter Syndrome; (34)]. Other studies with ZFNs

Technology is also underway [eg B. Severe hemophilia B (35), Hurler syndrome type I (36) and transfusion-dependent beta-thalassemia (37)]. Some intriguing reports are emerging We have succeeded in treating the disease using CRISPR-Cas9. Prevention or reversal in preclinical models, eg with B. mice[for example. B. Embryo (38) and postnatal (39) birth] and dogs (40)

A model of the Duchenne muscular dystrophy. However, the first Description of the CRISPR-Cas9 gene technology used for modification Human embryo with causative gene mutation (41) Hypertrophic cardiomyopathy is controversial (42). yet Current clinical studies on CRISPR-Cas9 gene editing Adult techniques include techniques for advanced esophageal cancer Cancer (43); Leukemia and lymphoma (44); Transfusion-dependent beta-thalassemia (45); and relapsed refractory Multiple myeloma, synovial sarcoma and mucous-like / round cells Liposarcoma (46). New treatments like these offer effective treatment options

For patients with serious, rare illnesses if they were there before There was not. However, based on the current price, this is unlikely that these diagnostics and therapeutics present viable options to patients or their families, especially on an ongoing basis. Therefore, patients are reliant on governments and health insurers to cover the majority of the cost. Policymakers need to carefully evaluate the test or treatment's affordability, whilst appreciating the additional advantages it might bring to an affected person and the wider population.

Additionally, balance is needed when deciding on the pricing of therapeutics to ensure access to excellent health care for patients, whilst also supporting biopharmaceutical innovation and investment into new therapeutics.

4. DECISION-MAKING APPROACHES FOR MAXIMIZING POPULATION HEALTH

In publically funded healthcare systems two broad priorities for decision-makers are "to do the most, for the most" (47), and to "reduce health inequity" across the population (48). Within the constraints of finite resources, the maximum number of people should receive the maximum benefit

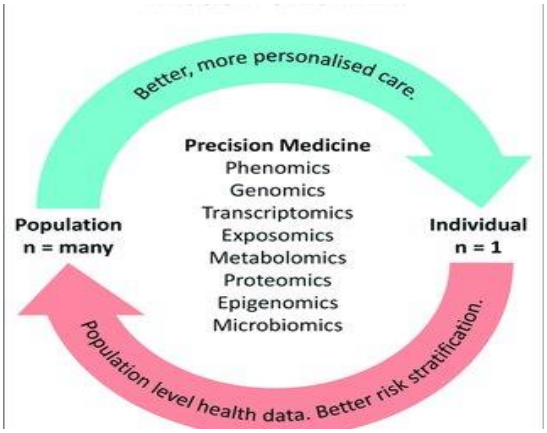
from the health programs and therapeutics that are publically funded. In other words, this is the "n of many" approach for optimizing population health outcomes. However, decision-making should not exacerbate existing health disparities and targeted investment is often required to address health inequities that emerge through societal mechanisms, including healthcare decision-making mechanisms. To assist with this, decision-makers rely on tools to allow for transparent, fair and reproducible decisions to determine which programs and therapeutics should receive public investment.

The economic evaluation of healthcare initiatives allows decision-makers to evaluate the cost of providing an intervention or therapy, and determine what the outcomes will be if that particular therapy or program is chosen over another (49). In short, it allows decision-makers to seek which outcomes can be "purchased" for the population and at what financial cost. Crucial to this paradigm is the need to evaluate which benefits to the population are foregone when one intervention is chosen at the expense of another (the "opportunity cost") (50). Ultimately, cost thresholds that determine which programs or therapeutics will be funded are somewhat flexible.

However, in situations where interventions are costly or where there is a lack of available evidence for utility or cost-effectiveness, there is a greater reliance on other tools for decision-making, such as the determination of social values and the influence of the political agenda. The incorporation of social values into decision-making is less defined than economic evaluations, given the inability to attribute a standardized weighted value to social concepts.

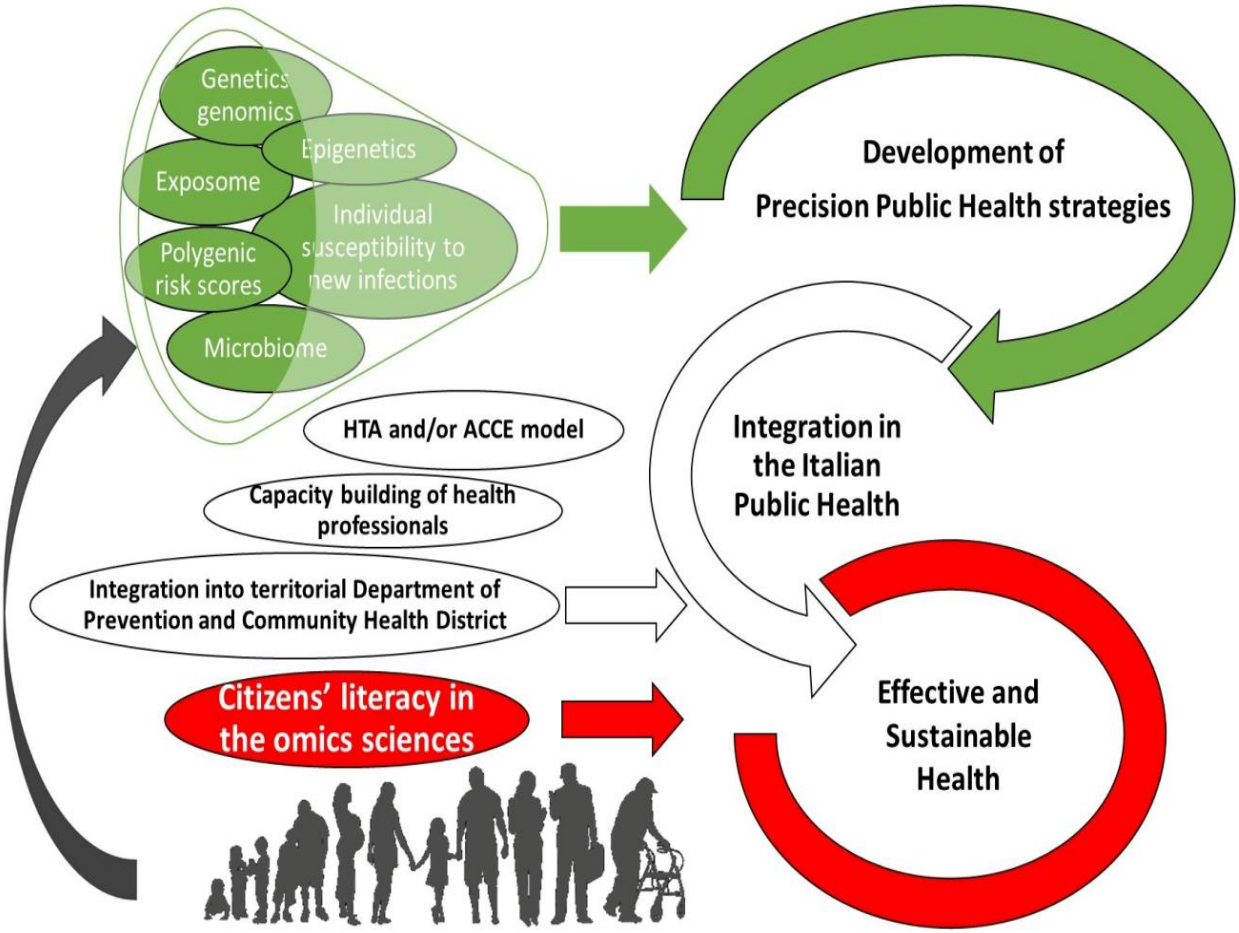
However, research has occurred to quantify social preferences, although these methods are as yet not widely adopted (49). Examples of such social concepts include whether an intervention targets a population of unmet need; whether the intervention satisfies the "rule of rescue," i.e., patients for whom there is no other therapeutic option, or whether the program may target a population considered at higher risk such as lower socioeconomic groups. It is for such patients that standardized health care decision-making paradigms become challenged.

An additional consideration for decision-making in the event of unfavorable economic evaluations is the inability to attribute value to political goals for health care, which may catalyse innovation incentives and funding for conditions on the political agenda (51). Uncertainty of leadership, changing agendas and political factions can lead to the reliance on political will, which is arguably the most volatile tool for decision-making. While the window of political will is open, health systems could proceed with haste to sustainably integrate new methods into the delivery of healthcare to better the health of the population.



Therapeutic efficacy and outcomes used in economic evaluation and decision-making are traditionally determined through the results of large randomized controlled trials (RCTs) or systematic reviews of RCTs. Given the reliance of decisionmaking on large numbers of participants in RCTs, this presents a disadvantage for conditions and populations in which large numbers are difficult to achieve, such as has occurred for patients with rare diseases and uncommon cancers (52). In these situations it is difficult to generate enough data in support for the public funding of therapeutic agents, often leaving this subset of patients without the same therapeutic options as patients with more common conditions (53). This scenario fails the goal of equity of access to care, as a disparity will exist when only those who can privately afford these treatments are able to access them.

In the oncology patient population, particularly for those with rare and uncommon cancers, or common advanced cancers where therapeutic options have been exhausted, the cost of an intervention may be high, the outcomes may be relatively poor, and the evidence base may be minimal



5. APPLICATIONS OF PRECISION MEDICINE

What is already happening: The cases of oncology and psychiatry?

Cancer is a leading cause of death worldwide, accounting for 8.8 million deaths in 2015 19. Research examining the mechanisms involved in the pathogenesis of cancer, including the understanding of oncogenes and epigenetic clues in oncogenesis, has been performed continuously and at an increasing pace over the last several decades 20. Therefore, the discovery of potential targets for drug development - aiming to block the expression of those oncogenes by inactivating them or their pathways - is one of the promising aspects of precision medicine. One example of this concept, which is already being clinically applied, is the treatment of chronic myeloid leukemia (CML). Allogeneic bone-marrow transplants had long been considered the best treatment option, but they were indicated only for younger patients and continued to cause significant mortality 21. However, the discoveries of molecular predispositions that generate a variety of diseases, such as CML, made possible the development of more specific medications aimed at new molecular targets. Currently, the administration of a competitive inhibitor of the Bcr/Abl tyrosine kinase - an oncoprotein expressed in 95% of patients with CML and the molecular target for this disease - is able to achieve an 80% success rate of a complete cytogenetic response in newly diagnosed patients 22

Among psychiatric illnesses, post-traumatic stress disorder (PTSD) is being extensively studied in the USA due its prevalence in soldiers returning from combat, which can reach 18.5% in this population according to data of Vietnam veterans 23. Animal research has already shown that in a stressful environment, epigenetic alterations in the hypothalamic-pituitary-adrenal axis can modulate the stress response 24. Other research has shown that combat veterans present an epigenetic alteration (hypomethylation) in the exon promoter region NR3C1-F1 of the glucocorticoid receptor gene, which could explain the changes in the neuroendocrine response of these soldiers 25. In contrast, the same exon NR3C1-F1 is the site of hypermethylation in suicide victims with a history of childhood abuse 26. These two subpopulations from different stress environments may be seen comparable if only the signs and symptoms are considered. The knowledge that these groups present opposing epigenetic modifications to the same gene makes it possible to approach treatment of these patients while taking into consideration their particular disease mechanisms and developing more efficient treatments for each group.

What is going to happen: Tissue engineering and regenerative medicine

Tissue engineering and regenerative medicine are fields that can make important contributions to developments in precision medicine. Among the innumerable possibilities within these research areas, there are two topics of interest: organs-on-a-chip and personalized stem cell therapies.

Organs-on-a-chip are 3D tissue-engineered platforms with microfluidic network systems that can be used to study the effect of virtually any substance on a specific tissue [27,28]. This technology has gained great interest mainly due to the limitations inherent to the use of animal models during safety and efficacy testing, such as the poor translational potential and the ethical issues raised by animal experimentation [29]. Although organs-on-a-chip have been increasingly utilized for preclinical testing of drugs, they present an even more interesting potential for use in precision medicine. The creation of patient-specific organs-on-a-chip would allow testing drug therapies *in vitro* before proceeding to the actual clinical treatment [30]. Using induced pluripotent stem cells (iPSCs) from adult tissue, such as skin or blood, and differentiating them into any target tissue, from liver cells to neurons, it would be possible to create a patient-specific organ-on-a-chip to study how different drugs act on the patient's own tissue and, based on this screening, to define a better therapeutic approach to treat a given disease, which can also be simulated *in vitro* [31–33]. The New York Stem Cell Foundation (NYSCF) recently took an important step toward making personalized organs-on-a-chip closer to clinical application by creating a high-throughput robotic platform to automate the process of transforming patient samples into iPSCs and later into the target tissue cell types [34]. The final development of the organs-on-a-chip technology would be the creation of a whole body-on-a-chip, thus allowing the investigation of not only a drug's efficacy on the targeted tissue but also its adverse effects on other tissues of the patient [35].

Personalized stem cell therapies, in turn, join the potential of regenerative medicine, which aims to replace or regenerate cells, tissues and organs, to the tailored approach used in precision medicine. While stem cell therapies are already, by default, a type of personalized therapeutic approach, since cell sources are, in most of the cases, autologous, methods exist to make these treatments even more personalized. The most interesting is the use of gene editing technologies to enhance stem cells or cure genetic disorders before the delivery of cells into the patient. Briefly, the process is characterized by isolating patient cells from any tissue, reprogramming them into iPSCs, modifying or correcting the cell genotype (or epigenetic factors) using technologies such as Zinc finger nucleases (ZFN), Transcription activator-like effector nucleases (TALEN) and Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR associated protein 9 (CRISPR/Cas9), differentiating them into the desired tissue and implanting them back into the patient [36,37]. Some of the best examples of the potential of this approach are in the treatment of hematological diseases [38,39]. While clinical trials are still not a reality, the technique has already been demonstrated to be successful for the treatment of sickle cell disease [40] as well as the correction of β-globin gene mutations in subjects with thalassemia [41–44]. Advances in gene editing technologies, together with the improvements in iPSCs generation, will soon allow a wide range of diseases to be targeted by personalized regenerative medicine approaches.

6. INITIATIVES IN PRECISION MEDICINE WORLDWIDE

The development of algorithms to predict and treat diseases based on a subpopulation-specific set of characteristics, such as genetics, drug responses, lifestyles, and social demands, requires a vast amount of information. Thus, instead of performing a series of separate and independent research protocols, initiatives aiming to create and integrate data from different medical centers are necessary. Using currently available tools, such as cloud computing, artificial intelligence, and big data, the collection and analysis of different databases will allow the creation of algorithms to direct clinical practice.

To contribute towards the development of precision medicine, the National Institutes of Health (NIH) announced, in 2015, the Precision Medicine Initiative (PMI), a program for delivering resources to projects aimed at creating new methods to improve healthcare by applying technologies that maximize effectiveness by taking into account individual variability in genes, environments, and lifestyles.

The initiative focused not only on cutting-edge technologies but also on the interdisciplinary context of the research topics. Since then, researchers of various fields have been working together to break through this new frontier of medicine [45–47]. The California Initiative to Advance Precision Medicine (CIAPM) is another initiative, launched in 2015, aiming to build a centralized information base. This initiative, a partnership among the University of California, the state of California and other entities, is expected to stimulate collaborations among clinicians, scientists, and patients to improve healthcare outcomes and foster innovations in the biomedical field.

One of the issues involved in building these large and centralized databases is related to consent, confidentiality and intellectual property. An immense ethical challenge exists in organizing these databases and giving access to different clinicians and researchers while protecting patient information from third party interests, as well as protecting the intellectual property of the scientist or clinician who collects the data.

Although the problem of limited genomic data from populations of developing countries is mainly due to the high costs, several startup companies are seeking to increase the amount of genomic data generated from Asian populations. The GenomeAsia 100K, a nonprofit consortium of companies and academics, wants to create reference genomes of all major Asian ethnic groups starting with the sequences of 100,000 people.

Finally, it is important to note that the significant advances in precision medicine produce concerns that must also be considered. Again, ethical issues are a critical problem, considering that all of the genetic, environmental, and lifestyle information of each patient will be stored in a database in the future. How should this information be kept safe and confidential? Taking this concept one step further, the possibility to genetically engineer patients and therefore create “super-humans” is not far away and fuels heated ethical debates. Considering this possibility, diseases will be able to be predicted,

and we will also have the tools to prevent them before they occur; addressing this possibility is not something we are currently used to and is thus another skill we still need to develop.

7. CONCLUSION

- Translational precision medicine brings with it a paradigm shift from one-size-fits-all to biomarker-guided medicine patient-centered medicine. One of the most important success factors for applying this principle in pharmaceutical drug development is the combination of forward and backward movement

Translation, the classification of disease states as multi-omics defined endotypes, the integration of AI and algorithm-based R&D concepts, the implementation of digital biomarkers as clinical endpoints and the Development of companion diagnostics. The rise of datadriven and algorithm-based research and development requires the establishment of a new mindset regarding data mining and AI Tools can be used effectively to discover and develop new things drugs. Whether and how, the near future will show These emerging AI-based digital tools will reveal new things Targets, pathogenic disease signatures, clinical optimization Study designs and general implications for drug development Pharmaceutical Industry. Convergence of patient-centric Real-World Evidence (RWE) tools, EHRs, multi-omics Profiling, digital biomarkers and AI-based data analysis will pave the way to biomarker-assisted algorithm-based precision research and development.

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