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Review Article

Precision Medicine: Unveiling Progress Amidst Challenges

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ABSTRACT

Precision medicine is an approach to provide individualized treatment to the patient for a specific disease based on the genotypic, phenotypic and also psychological factors which in turn enhances the patient care to several folds. Apart from providing personalized treatment, it can also be used to accurately diagnose a disease state in a patient. Precision medicine can be employed to improve the health status of both individual patients and general population at high risk. However, several ethical considerations have to be looked upon while employing precision medicine at the same time it required more cutting-edge methodologies for the accurate execution of the same.

Keywords: Precision Medicine, Personalized Medicine, Individualized Treatment Plan, Pharmacogenomics, Pharmacogenetics.

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INTRODUCTION

In recent years, the concept of "Precision Medicine" (PM), formerly known as the personalized medicine has been gaining enormous popularity.[1,2] A few definitions of precision medicine state that they are "treatments tailored to the needs of specific patients based on genetic biomarker, phenotypic and psychosocial factors that differentiate an individual from other individuals with similar clinical presentations." i.e., emphasizing on results or individualized treatment plans.[3,4] some claim that, Precision medicine is a framework that integrates clinical observations and supplementary data to categorize patients into innovative subgroups (Figure 1). The aspiration is for these subgroups to exhibit common underpinnings in terms of disease vulnerability and manifestation, which in turn could facilitate the implementation of meticulously tailored therapeutic strategies.[5-7] Precision medicine attempts to maximize the quality of medical care by customizing each medical procedure to each patient's independently evolving health state. A wide range of treatment- or care-related choices, including which medication to use, how much to take, when to take it, whether to recommend a specific diet or kind of exercise, or other possibilities, could be seen as potential actions.[8-10]

Evolution of Precision Medicine

The universal approach to treatment means that everyone who presents with a certain constellation of symptoms will get the same care, however, the practice of PM or personalized medicine practice has sparked a desire for more accurate methods of diagnosis and therapy, so that individuals with specific symptoms can receive more individualized care.[11,12] In many aspects, PM's objectives have long been aligned with the supervision of communicable illnesses, which aims to pinpoint the etiological agents and build data warehouses to guide targeted therapy for infections. In order to learn more about resistant organisms and to safeguard populations, technology has been introduced into infectious disease management over time.[13] The gathering of a lot of health data will move us closer to Sir William Osler's goal of linking the enormous reservoirs of information, so that they may be readily accessible for both the prevention and the treatment of disease.[14] Particularly DNA sequencing techniques have greatly boosted the amount of data available that could help with illness prevention and treatment. The sequencing of the initial human genome in 2001 incurred an expenditure of $95 million (Figure 2). Since then, costs have decreased as sequencing methods have become more automated. Whole exosome sequencing now costs less than $1,000, which has sparked a wave of innovation that aims to use these results to improve how people receive healthcare.[15] PM aims to integrate technology into healthcare to build an ecosystem of data that can more accurately diagnose and treat a patient's ailment. This method seeks to seamlessly combine biological data with clinical characteristics, including imaging, laboratory testing and medical records. The justification is to provide "a new classification of human diseases based on molecular biology.[16] As per the 2011, National Research Council

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Report, this approach would augment comprehension regarding the etiology of diseases, facilitate finer diagnostic precision, enhance the selection of therapeutic interventions and catalyze the development of innovative pharmaceutical agents. Over the years, PM has influenced how noncommunicable diseases are treated, too. In theoretical terms, precision medicine methodologies are anticipated to contribute to the enhancement of disease classification and refinement of our understanding of disease progression for intricate conditions such as obesity, cancer and cardiovascular disease. This could potentially lead to a transformative change in medical treatment strategies, aiming to optimize disease management while minimizing adverse effects.[17] Researchers have developed novel trial structures, such as basket and umbrella trials, that have been employed in various precision oncology research endeavors. These trial formats aid in drug exploration via studies guided by precision medicine principles.[18-20]

Concerns have been raised by others in the public health field regarding the validity and generalizability of these results.[21] Because genomic factors have a very limited impact on overall health compared to behavioral or social aspects, which are typically disregarded in PM discussions, there has been worry about PM's primary focus on genomic advancements.[22]

Novel therapies of Precision medicine

The effect of PM-led therapy is examined to concern both, persons with disease and those in the general public who are thought to be at high risk.

Individuals Affected by Disease

A key aspect of PM's promise is the idea that it can find new treatments for diseases that were previously incurable. In cancer therapy, precision has come to mean different things over time. The terminology was initially employed to delineate the strategic formulation of therapy directed towards distinct characteristics of organ-specific tumors. Notably, the identification of therapeutic agents such as erlotinib or gefitinib, which address lung cancer displaying an amplified EGFR mutation, has arisen from the shift from organ-based classification to molecular profiling. This transformation has introduced an alternative to conventional chemotherapy approaches.[23,24] Imatinib, a treatment for Chronic Myeloid Leukemia (CML), is another medication created using rational drug design. The Philadelphia chromosomal mutation, which results in an overactive Breakpoint cluster region-Abelson (Bcr-abl) fusion protein, is the main contributor to this disorder. An imatinib, categorized as a tyrosine kinase inhibitor, exhibits a predilection for binding to the hyperactive protein. Prior to the year 2001, a third of patients diagnosed with Chronic Myeloid Leukemia (CML) experienced a five-year survival rate subsequent to their initial diagnosis. Recent investigations revealed that the expected 6-year life expectancy rate after imatinib clinical trials in CML was 83%.[25] The potential to steer treatment strategies based on information derived from the distinctive characteristics of the patient and the biological attributes of their tumor, independent of the organ of disease origination, has recently garnered attention due to its potential within the realm of precision medicine. Certain medications, including Olaparib, have been licensed for use in some individuals who express the BRCA mutation.[26]

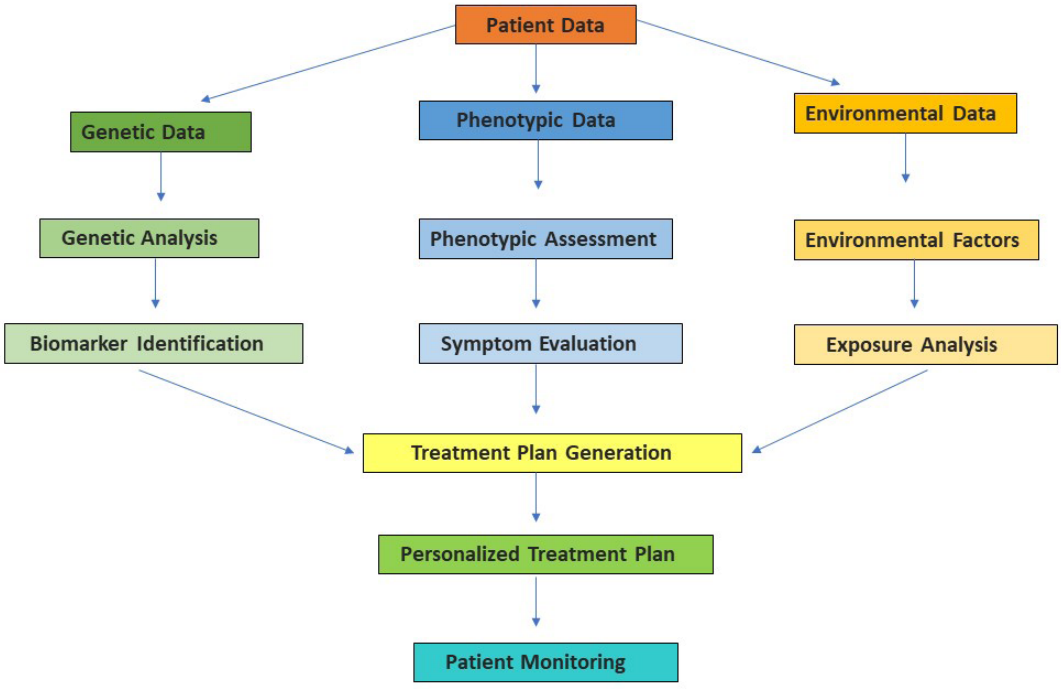

Figure 1: Conceptual Framework of Precision Medicine.

Precision oncology's main objective has been to find medications that selectively target the causes of mutations on cells with cancer that increase survival. According to anecdotal reports, some individuals who had their tumours genetically sequenced reacted to targeted medicines identified by the tumor's features.[27]

Patients with certain uncommon disorders, like haemophilia B, may benefit from gene therapy or gene editing procedures because they directly target the faulty gene. In a Phase I clinical investigation involving individuals with a medical condition, cells containing Adeno-Associated Virus serotype 8 (AAV8)

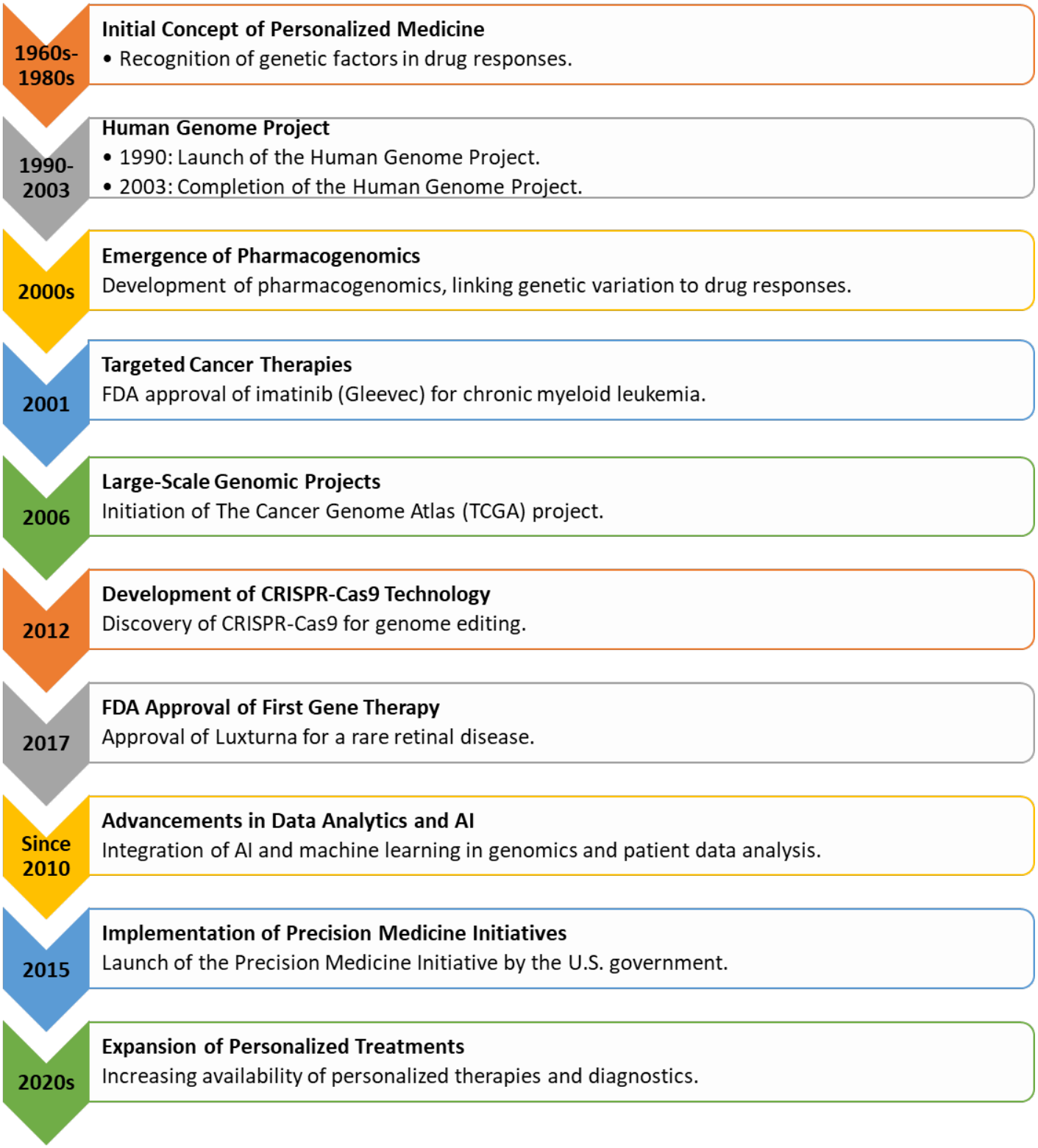

Figure 2: Evolution of Precision Medicine.

vectors were administered intravenously as part of a gene therapy initiative. These cells exhibited an ability to infiltrate the liver and augment the levels of deficient clotting factor IX.[28] This strategy may be a long-term option for individuals who need frequent clotting infusions, lowering expenses and medical issues as well as potentially lowering morbidity and death. Ivacaftor and lumacaftor, two novel treatments that target the CFTR gene, have been approved for the treatment of other uncommon disorders like cystic fibrosis. These therapies, which have been found to enhance respiratory function in patients with particular CFTR mutations, can be combined.[29] Multiple challenges hinder the applicability of precision medicine methodologies in this manner. Firstly, it remains uncertain whether these approaches yield comprehensive effectiveness. Patients have not benefited from cancer trials that were explicitly created to examine the utilization of genetic information alterations to guide therapy as stated by PM.[30] Based on mutations or medicines chosen by the patients' doctors, the SHIVA study assigned therapy to individuals with metastatic cancer.[31] The groups exhibited a progression-free survival rate of less than 3 months individually, upon comparative analysis. Furthermore, the comprehensive impact of treatment on individuals afflicted with these diseases might not be adequately represented by employing progression-free survival as a surrogate measure for overall survival. The effectiveness of medications like lumacaftor in helping cystic fibrosis patients achieve better results is also unknown. Enhancements in overall survival rates within cystic fibrosis can be ascribed to therapeutic protocols that prioritize the management of infections and the provision of appropriate nutritional supplementation. This is due to the fact that pharmacological advancements impact only a small fraction of the patient population. Second, whereas PM methods can be used to generate new medicines, they can also be used to produce diagnostic and prognostic biomarkers that assist doctors guide tailored treatment for a patient's illness or avoid hazardous therapies.[32] However, both in clinical and experimental settings, these biomarkers are frequently challenging to assemble and evaluate.[33] A lack of consensus persists regarding the significance and credibility of various present serological indicators, encompassing tumor markers. It is plausible that these recently identified biomarkers could encounter a similar fate.[34] Given the absence of broad applicability, the adoption of precision medicine-derived biomarkers in clinical practice might face resistance, notwithstanding their specificity and sensitivity.

General population and high risk

The usefulness of PM strategies for enhancing population health depends on their ability to be applied to large populations and, ideally, for the prevention of diseases. In this sense, there is some promise. For instance, therapeutic strategies to lower the risk of developing cancer have been made possible by the identification of genetic abnormalities linked to familial cancer syndromes. Achieving cessation of medullary thyroid cancer in individuals diagnosed with multiple endocrine neoplasia type 2 necessitates the execution of a comprehensive thyroidectomy.[35] Individuals harboring BRCA mutations had the option of undergoing prophylactic bilateral mastectomy and salpingo-oophorectomy as preventive measures to mitigate the risk of developing breast and ovarian cancer, respectively. In instances where a woman carries a deleterious mutation in either the BRCA1 or BRCA2 gene, the adoption of bilateral prophylactic mastectomy diminishes her susceptibility to breast cancer by a minimum of 95%.[36,37] Routine surveillance or the utilization of tamoxifen as an antiestrogen pharmaceutical agent are two noninvasive ways to avoid cancer. The latter has been proven to be advantageous primarily for women with BRCA2 mutations and decreased the incidence of breast cancer by 62%.[38] Administering a daily dosage of 600 mg aspirin for the purpose of reducing the susceptibility to colorectal cancer in individuals with Lynch syndrome is one of the additional chemoprevention strategies for familial cancer syndromes.[39] Nevertheless, when employed across entire populations, these strategies exhibit certain limitations. Initially, it is noteworthy that merely 5-10% of individuals with breast cancer possess the BRCA mutation.[40] making it impossible for the majority of patients to benefit from these cancer risks reduction techniques. Additionally, only a small part of the general population is impacted by these therapies. As per assessments, the origins of approximately 15-20% of global malignancies can be attributed to infectious agents.[41] Notably, precision medicine methodologies have yet to be integrated into initiatives concerning hepatitis B or Human Papillomavirus (HPV) immunization campaigns. Cervical cancer screening and the quadrivalent HPV vaccine have both proved effective in lowering the incidence of cervical cancer.[42,43] Second, if the fundamental tests have not been sufficiently validated, PM strategies or genetic testing may result in interventions that are harmful to people. A case study demonstrates the unwanted effects of PM.[44] Family members undertook genetic testing after a young patient's untimely death, which was determined to have been caused by cardiac causes. The findings revealed that a genetic variation, suggestive of long QT syndrome in family members, was present. An Implanted Cardiac Defibrillator (ICD) was put in as a preventative measure for the deceased patient's brother. It became clear that the initial assessment was flawed when the family showed up for a second opinion. Administering an Implantable Cardioverter-Defibrillator (ICD) as a preemptive measure was deemed ill-advised and invasive, causing harm to an asymptomatic individual. The report's authors stress the value of using clinical information rather than only genetic test findings to guide care, such as electrocardiograms that ruled out long QT syndrome. This instance emphasizes the requirement for continuing medical professional education in the analysis regarding the outcomes of genetic testing. In order to prevent any potential adverse effects on the population, the credibility and authenticity of precision medicine and its outcomes need to be established.

Ethical issues in PM

The diagnosis, mitigation and/or treatment of diseases rely on individual genetic, environmental and behavioral variations. It is a natural progression from current research profiles and identifies therapeutically useful markers using multiomics-based laboratory tests. In essence, the objective is to gather genotypic and phenotypic data to guide precise and efficient patient therapy. Usually, extensive and complicated testing would be needed before any practical clinical applicability to patients. Precision medicine's integration into healthcare will heavily rely on clinical laboratories. Reflex testing based on algorithms or specific case judgements is frequently required for laboratory work. The integration of test results and clinical data will create the basis for interpretation. A more participatory role for the clinical laboratory as a partner in clinical care is required as a result of both indirect and direct transmission of test data to patients. To adapt to these exciting changes, clinical lab technicians will need to rely more on their ethical judgement. Globally, formal instruction in ethics has been inconsistent, frequently constrained or lacking from many training programs.[45] As a result, many clinical laboratory professionals feel underequipped to integrate ethics into their skill set. More ethical education is one method to make this situation better. Extensive datasets encompassing research findings and clinical data, coupled with a plethora of laboratory examinations rooted in multiomics methodologies, serve as the foundation for both research and the emerging clinical practice of precision medicine. This environment may lead to moral conundrums involving questions like justice, autonomy, new findings and consent. Precision medicine's requirements must be balanced with the idea that patients' interests come first, which can lead to conflicts that frequently go unresolved. In precision medicine, data collection and analysis go further than is required to look into specific clinical conditions. Over time, the data gathered and research objectives frequently change. This makes it difficult to gain informed consent based on proper counselling. A dynamic consent that can alter over time could be able to address some of the issues. In other circumstances, presumptive consent shall be deemed sufficient. Although there are many different data sets used in precision medicine, genomics still plays a key role. As a result, similar methods are acceptable for the ethical problems in genomics and precision medicine. Clinical genetics has offered suggestions on how to handle incidental results, that are more appropriately referred to as supplementary or secondary findings.[46] Additional findings are those identified during testing for unrelated issues that may have an impact on a person's health or ability to reproduce. Although there have been disagreements regarding which discoveries to communicate and whether this practise should be required or optional, it is now generally accepted to report medically relevant extra information in genetic testing. The American Society of Human Genetics (ASHG) recently released a policy statement on following up with research participants with updated genetic information. Data profiles can be used to identify people in anonymous databanks, which raises serious privacy concerns in databanks used for precision medicine. How can data access be restricted to preserve privacy without jeopardizing support for precision medicine? And under what conditions should this be permitted? In this area, we are still in the early phases of determining the appropriate standards and stakeholder ratio.[47] Individuals must have a negligible information risk, or no appreciable additional risk, as a result of having their data processed in the databanks. Fairness for all people without discrimination is the foundation of justice.[48,49] The key concern is how to deliver the benefits and advancements of precision medicine while maintaining equal access to healthcare. Precision medicine requires significant clinical and research work. Given the disparities in genetic make-up, environments and lifestyles, research data are typically generated from wealthy communities and results might not be relevant to other less fortunate people.[50] Clinical testing on individuals will actually be costly, even though greater precision medicine effectiveness may occasionally result in cost savings. In this context, individual rights present one challenging ethical conundrum. Can the state mandate that people adopt precision healthy lives in exchange for providing equitable access to precision medicine?[51]

Personalized Medicine: Motivation, Challenges and Progress

Personalized Medicine requires new framework that meets the necessary needs of precision medicine that is capable of incorporating the strength and ideas arising from more recent data, such as assessments of the impact of genome-wide genetic diversity. Undoubtedly, an active public debate will be necessary to develop any such new structure. The following criteria could potentially be used as an initial basis for debate to determine whether a method qualifies as a PM strategy.[52]

The processes connecting a potential cause to a clinically apparent condition are well understood and necessary.

The hypothesized disease mechanisms ought to be quantifiable at the level of essential and sufficient components in the pathophysiology of the disease.

The understanding of fundamental mechanisms should serve as a justifiable foundation for the precision treatment plan.

The plan should result in better clinical outcomes and provide the necessary mechanistic degree of evidence that the hypothesized pathology has been addressed or remedied.

The hypothesized disease mechanisms should be used to explain why a precision therapy failed.

The advancement of precision medicine faces obstacles due to the uncharted regions of the human genome

The human genome currently has a significant quantity of "dark matter," such as areas that cannot be examined.[53] The genetic

code is made up of the roughly 3 billion base pairs that make up the human genome. It is crucial to comprehend the complete code before using it to treat diseases. The genomic sequence responsible for encoding in humans spans approximately 100 million base pairs, constituting a mere 2% of the entirety of the genome. Non-coding sequences can make up to 90% of eukaryotic genomes.[54] Only a tiny percentage of the genes that are crucial for chromosomal regulation or that are involved in cellular development have recognized activities; the majority of these genes further uses are unknown, 90% of human genes are unknown.[55]

The procurement and scrutiny of extensive omics data for precision medicine is fraught with challenges

Since precision medicine is a macroscopic idea, genetic testing is not its only application. Genes cannot fully explain all phenomena due to the complexity of illness etiology. Consequently, multilevel and synthetic omics studies are essential for modern medicine.[56] Large-scale omics data is the foundation of precision medicine.[57] It is crucial and vital to get the appropriate quality control requirements for omics technology. For instance, establishing microarray quality control standards will support the development of large-scale, standardized biological data collecting for precision medicine.[58] The progression of precision medicine will be propelled and refined through revelations emerging from the comprehensive analysis of clinical trial data, phenotype data and the establishment of connections between phenotypic information and omics data obtained from substantial clinical samples.[59] Massive volumes of data will be generated by these clinical trials, particularly omics investigations. Currently, analysis can only be done manually, which is next to impossible. As a result, the gradual use of supercomputers to the study of massive data sets in bioinformatics may offer a useful technique for the rapid elucidation of omics data.[60,61]

Creation of a repository of biological specimens and the extensive analysis of this data for precision medicine-challenges encountered

Benefits of genetic information for more accurate clinical diagnosis and treatment choice have been demonstrated. The outcome of a patient's treatment is not only influenced by genetics but also by the patient's lifestyle, upbringing, environment, cultural background, level of education and a variety of additional variables, contributing to application of PM more challenging and necessitating higher levels of individualization.[62,63] Precision medicine's ultimate objective is the development of accurate medical interventions that are based on personalized care and are tailored to the unique conditions of each patient.[64] Precision medicine is hampered by the difficulty of applying these basic medical research discoveries in actual clinical settings. The core elements of precision medicine are qualities, including genetic indicators, protein factors, or environmental cues, as well as how people respond to a given treatment. These attributes are identified in various populations.[65] The most extensive repository of biological samples, encompassing over 1 million data instances, inclusive of information pertaining to environment, genetics and social factors from diverse ethnicities, will be established as per the initiatives of American precision medicine programs.[66] According to one plan made public by the National Institutes of Health, experts from many fields will be hired to Utilize information from repositories of biological specimens, incorporating genomic, lifestyle and environmental aspects, as well as data gleaned from Electronic Medical Records (EMRs).[67] The establishment of a substantial and longitudinally extended database through the creation of the biological specimen repository would offer a valuable resource to numerous medical researchers, statisticians and mathematicians. This resource would facilitate deeper comprehension of the underlying processes governing disease and well-being.[68] Building a huge library of biological samples is likely to face a number of challenges, such as comparing data gathered from various sources and in various methods and varying levels of public support. Additionally, the rules of some nations may continue to impede the improvement of international cooperation in genomic research despite the regulatory framework at the national level, along with clear authorization and formal recognition by individual countries.[69] In the era of extensive data accumulation, cloud computing has the capacity to rapidly and economically store vast quantities of information.[70]

The issue of medical ethics and informed consent in precision medicine

The consent must be given voluntarily, without coercion or unlawful inducements.[71] Using gene sequences to predict diseases could lead to ethical issues.[72] Because precision medicine differs from conventional clinical testing, new, focused ethical review methodologies should be developed.[73] The advent of the era characterized by extensive datasets aligns with the inception of the novel precision medicine era, which is poised to revolutionize medical practitioners' methodologies in patient treatment and clinical decision-making. Precision medicine initiatives are anticipated to drive a substantial paradigm shift in clinical care within the medical domain. There will be significant advancements in the detection and management of numerous diseases.[74]

Progress and other problems

Despite the advantageous implications of precision medicine for patients, considerable efforts remain to be undertaken in this domain. The endeavor is in its initial stages and demands substantial resource allocation for its progression.[75] Effective implementation of precision medicine necessitates collaborative efforts at both the global and national levels. The progression

and evolution of precision medicine are presently attracting heightened focus from various countries and international entities. By engaging in substantial, in-depth international collaboration to build a sizable clinical database of sample data, the current hurdles facing precision medicine can be overcome. Such cooperation will encourage the alliances required for the eventual implementation of precision medicine. PM interventions have become more and more beneficial for the diagnosis, monitoring and treatment of numerous disorders. The cost-effectiveness of PM is still unknown because of the numerous factors that affect it and the various willingness-to-pay levels that are used. As a result, valuing precision medicine therapies may require a different strategy.[76,77] Considering the presence and ongoing recognition of substantial variations among individuals with clinical relevance, the imperative of personalized medicine arises. This approach involves the comprehensive profiling of individual patients across multiple dimensions (such as genetic, biochemical, behavioral, etc.) to glean insights into their response to interventions and subsequently tailoring their treatment accordingly.[78] The availability of advanced biological technologies such as DNA sequencing, proteomics and wireless monitoring devices has facilitated the detection of this variability, effectively exposing the necessity for some form of personalization in treatment.[79] Subsequent challenges stemming from this situation will involve optimizing the precision of individual characterization and devising and assessing personalized interventions to establish their effectiveness. This does not propose the dismissal of universally efficacious treatments (i.e., conventional singular agent "blockbuster" medications) if identified. Instead, it underscores the potential growing challenge of identifying such treatments in the future.[80,81] Several additional challenges associated with personalized medicine may prove challenging to address in the immediate future. As an example, the necessity for extensive data compilations to discern factors that may pose disparities among specific populations, yielding greater advantages from particular interventions, may give rise to concerns concerning privacy and the potential misuse of information pertaining to these individuals for unauthorized objectives.[82-84]

CONCLUSION

In order to address the requirements of diverse patient populations comprehensively, it is vital to innovate more efficient methodologies for the development of personalized therapeutics. This pertains particularly to strategies like cell replacement therapies or mutation-targeted medications, which exhibit utility in restricted patient subsets. Moreover, given the potential higher initial expenses associated with personalized medicine approaches, ensuring sustainable financial provisions for their implementation in the future may present challenges. Enhanced strategies for educating and equipping healthcare professionals in the realm of personalized medicine must be devised and implemented to garner acceptance from diverse stakeholders. Precision medicine is a jargon that raises both professional and patient expectations. Instead of being arrogant, the field should carefully manage expectations and avoid making promises that it cannot possibly keep.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

PM: Precision Medicine; **EGFR:** Epidermal Growth Factor Receptor; **CML:** Chronic Myeloid Leukemia; **Bcr-abl:** Breakpoint Cluster Region-Abelson; **BRCA:** Breast Cancer gene; **AAV8:** Adeno-Associated Virus Serotype 8; **ICD:** Implantable Cardioverter-Defibrillator; **ASHG:** American Society of Human Genetics; **EMRs:** Electronic Medical Records.

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