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**R E V I E W A R T I C L E**

# Review on Current trends in personalized medicines

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**A B S T R A C T**

Personalized medicine sometimes referred to as precision or individualized medicine is an emerging field of medicine that uses diagnostic tools to identify specific biological markers, often genetic, to help assess which medical treatments and procedures will be best for each patient. Personalized medicine does not mean creating medicines or medical devices unique to a patient, but rather the consideration of patient characteristics to optimize pharmaceutical treatment and overall care. This includes the ability to segment individuals into subpopulations that differ in their susceptibility to a particular disease, their response to a specific treatment, or the nature or origin of their disease. Personalized medicine allows preventive or therapeutic interventions to be focused on those most likely to benefit, sparing expense and side effects for those who are not. Personalized medicine combines patients genomic information with their family history, Lifestyle and environmental factors to make better prediction about their risk for disease or response to prescription drugs and tailor treatments for improved health.

**Keywords:** Personalized medicine, Precision, Individualized medicine, Treatment, Disease, Therapeutic interventions

**A R T I C L E I N F O**

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## 1. Introduction

Personalized medicine is fundamentally transforming the way we view disease from a catalog of clinical symptoms to a category defined by its underlying cause. Over the past century, medical care has generally focused on selecting medicines that are "standard of care" based on clinical signs/symptoms and that are successful in the "average" patient. However, we now know that complex diseases, such as diabetes, cancer, and Alzheimer's, are usually caused by a combination of genetic and environmental factors, not by a single gene or event. The personalized medicine approach allows physicians to profile genetic variation as a basis for understanding disease drivers in

each patient, while considering other factors, such as treatment history and environmental factors, in order to select the medicine or treatment that will potentially ensure a more successful outcome with a more favorable safety profile [1]. The development of tests to guide dose selection, or to help predict which patients are likely to respond to treatment or have high risk for adverse events, have allowed products that treat cardiovascular disease, HIV/AIDS, cancer, multiple sclerosis, and other diseases to be marketed and used more safely. In a growing number of cases, a test is developed together with a medicine in order to support the safe and effective use of the medicine. Such a test is called a companion diagnostic because it provides essential information for determining whether a patient is eligible to receive the associated therapy [2].

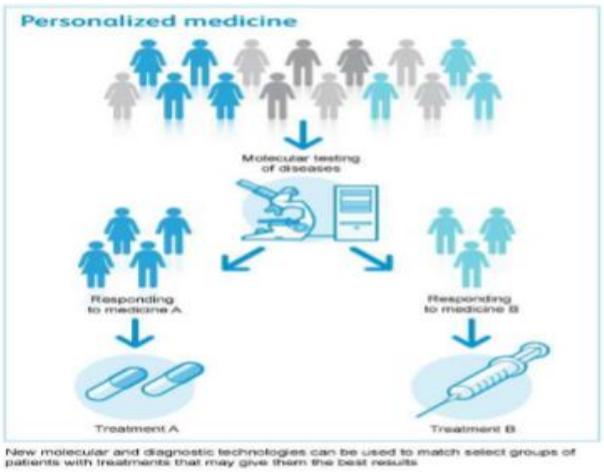


**Figure 1**

## 2. Systems Biology

One of the great challenges for 21st century medicine is to deliver effective therapies that are tailored to the exact biology or biological state of an individual to enable socalled 'personalized healthcare solutions'. Ideally, before the therapy started, this would involve a patient evaluating system that provide clinicians about the individual's correct drug and dose, or intervention. This evaluation concept approached on patient stratification, commonly according to some genetic features, be sub-classified to bio-features modeled in relation to the outcome. This stratification will be applied for personal therapy with a drug safety and efficacy model, as well as general healthcare involving optimized nutrition and lifestyle management[3].

Systems biology provides us with a common language for both describing and modeling the integrated action of regulatory networks at many levels of biological organization from the sub cellular through cell, tissue and organ right up to the whole organism. The relatively new science of molecular epidemiology concerns the measurement of the fundamental biochemical factors that underlie population disease demography and understanding 'the health of nations' and this subject naturally lends it to systems biology approaches. Thus, personalized medicine and molecular epidemiological studies are certain to have a major role in future development of systems biology. Genetic variants predicted to severely disrupt protein coding genes, collectively known as loss-of-function (LoF) variants, are of considerable scientific and clinical interest. Proteins form the structural fabric of cells and underpin all metabolic processes and regulatory mechanisms. Protein properties, including abundance levels, protein-protein interactions, post-translational modifications subcellular localization patterns and protein synthesis and degradation rates, are all highly dynamic and can change rapidly during the course of biological processes, such as cell proliferation, cell migration, endocytosis and development. Therefore, understanding protein structure function relationships in cell biology not only requires the identification of proteins but also the detailed analysis of the protein properties that constitute the dimensions of the proteome [4].

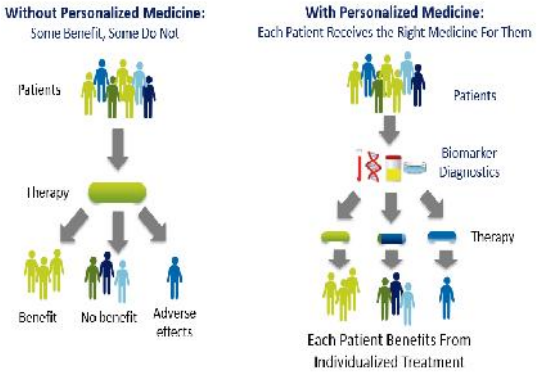


**Figure 2**

**Personalized medicine benefits to patients and Health care system**

**Get to optimal therapy more quickly:** The use of diagnostic tests can help the health care provider to select a treatment option with the greatest probability of success at the outset, helping to reduce inefficient "trial and error" prescribing.

**Use drugs more safely:** Screening tests can identify patients who have an elevated risk for an adverse reaction to specific medicines. Also, individuals with uncommon variants of drug metabolizing enzymes and transporters may need a different dose, or may not benefit sufficiently or at all from certain medicines.

**Increase patient compliance:** The failure of patients to adhere to prescribed treatment plans exacerbates their medical condition and increases medical costs resulting from nontreatment. When a therapy proves more effective or has a more favorable safety profile for a patient, the patient is more likely to adhere to the treatment.

**Leverage "precision medicine" principles to increase the probability of success in R&D:** Biopharmaceutical research and development focused on narrower, well-defined patient subpopulations has the potential to increase the speed of clinical trials and increase the probability of demonstrating clear clinical benefit.

**Reduce inefficiencies in health care:** Optimal practice of personalized medicine can help reduce many of the inefficiencies in the current health care system. Awareness of genetic risk factors encourages preventive care and early

diagnosis. Much of its value will come from the prevention of advanced disease states, reduction of ineffective treatment, and avoidance of additional care resulting from adverse drug reactions.

**Foundation of Pharmacogenomics in personalized medicine:** On January 30, 2015, US President, Obama, announced funding for an Initiative in Precision Medicine less than 3 years after a National Academy of Sciences committee report made clear just how such an initiative could accelerate progress in medical care and research. By understanding precisely, what the distinguishing features of specific subgroups of patients are, we can better individualize therapies. This led to rapid improvement in technology that drives genetic discovery in human disease. We now can monitor our personal health and environment easier than ever, just using wearable activity trackers to metagenomic sequencing and direct-to-consumer genetic testing [6,7].

As the cost and duration of genomic sequencing continues on a sharp downward curve, many scientists believe, with the help of private and public investment, that the widely available $1,000 genome will arrive within a few years. This price point is considered a critical benchmark because it is comparable to costs of existing medical tests and procedures, and could begin to attract a "consumer" market of patients (though the $1,000 price does not reflect the cost of interpreting genomic data). Costs have already fallen to the point that full genomic sequencing has been employed in an increasing number of cases to resolve difficult diagnoses, with insurers determining that the approach was cost-effective enough to be reimbursed. But advances are not confined to the realm of sequencing technology. There is a growing understanding of genomic changes that can alter the chemistry and structure of DNA without altering its sequence, through modifications such as adding singlecarbon methyl groups to the DNA chain. These "epigenetic" changes can occur in response to environments and lifestyles, and influence whether certain genes are turned "on" or "off." They represent an area of intense study and have already been linked to heart disease, diabetes, and cancer. The NIH Roadmap Epigenomics Program and the Epigenetics Consortium were set up to identify this supplemental "parts list" of the human genome. In addition, efforts by the National Cancer Institute (NCI) to standardize existing proteomic technologies such as mass spectrometry are leading to more robust identification of protein biomarkers, which indicate the presence or absence of disease apart from the risk prediction of genetic analysis. Entirely new approaches to protein biomarker detection are promising to make proteomics as "simple" as genetic analysis, ushering in an era when diseases can be diagnosed and treated in their earliest stages [8].

**Pharmacogenomics**

The study of variations of DNA and RNA characteristics as related to drug responsive is a critically important area of personalized medicine is a convergence of advances in pharmacology and genomics. To seek that understand how differences in genes and their expression affect the body's response to medications [9]. It uses genetic information (such as DNA sequence, gene expression, and copy number) for purposes of explaining inter individual differences in drug metabolism (pharmacokinetics) and physiological drug response (pharmacodynamics).

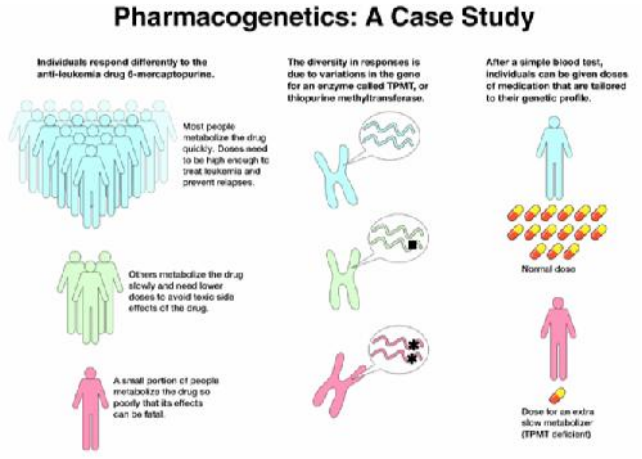


**Figure 3**

## 3. Biomarkers in Precision Medicine

Phenotypes are better described by the specific biochemical composition of each patient. These metabolites act as biomarkers to assess the health of an individual. Thus, the study of patient metabolomics promises to yield valuable information and help in clinical decisions. For this purpose, detailed information related to various biomarkers associated with diseased conditions is required, which demands a technical map of molecular underpinnings of human health. Such a precise molecular map specific to each patient can help to detect the deviations from this molecular blueprint. Hence, the metabolite analysis seems to be the connecting link between genomic data and the related phenotype. Measurement of metabolites such as glucose and cholesterol are regularly used to assess diabetes and cardiovascular diseases. The importance of metabolomics in precision medicine is established by the correlation of identified metaboliteswith genomic sequence associations with specific genotypes. Such a correlation has been studied by damaging mutations and early diagnostic markers by combining metabolomics with whole exome sequencing [10]. Metabolomics has also been beneficial to assess large molecule disorders via quantification of their component small molecules, known to be deviated under specific genetic abnormalities. In addition, metabolomics can estimate the variation in biomarkers under medical intervention.

**Personalized medicines impact on patient care in many diseases**

**In Breast Cancer:** One of the earliest and most common examples of personalized medicine came in trastuzumab. About 30% of patients with breast cancer have a form that over-expresses a protein called HER2, which is not responsive to standard therapy. Trastuzumab was approved for patients with HER2 positive tumors in 1998 and further research in 2005 showed that it reduced recurrence by 52% in combination with chemotherapy [11].

**In Melanoma:** BRAF is the human gene responsible for the production of a protein called B-Raf, which is involved in sending signals inside cells to direct cell growth, and shown to be mutated in cancers. In 2011, a drug called vemurafenib, a B-Raf protein inhibitor, and the companion BRAF V600E Mutation Test were approved for the treatment of late stage melanoma. Vemurafenib only works in the treatment of patients whose cancer tests positive for the V600E BRAF mutation. Around 60% of patients with melanoma have a BRAF mutation, and approximately 90% of those are the BRAF V600E mutation.

**In Cardiovascular Disease:**

Prior to the development of a gene expression profiling test to identify heart transplant recipients' probability of rejecting a transplanted organ, the primary method for managing heart transplant rejection was the invasive technique of endomyocardial biopsy – a heart biopsy. Today, a genetic diagnostic test is performed on a blood sample, providing a non-invasive test to help manage the care of patients post-transplant. New research suggests that ongoing testing may be useful in longer-term patient management by predicting risk of rejection and guiding more tailored immunosuppressive drug regimes.

**Personalized Medicine Tests:**

The emergence of personalized medicine tests informing clinical decision-making, along with tests to guide drug selection and dose, has led the FDA to publish guidance documents on the regulation of these products. Traditionally, diagnostic tests have fallen into two main categories, which include diagnostic kits and laboratory-developed tests (LDTs). The former are products containing all the reagents and materials needed to run the test, and are regulated by the FDA as medical devices. Very few personalized medicine diagnostics fall under this category; most are considered LDTs. Although the FDA has long regulated in vitro diagnostic products (IVDs) as medical devices—and has taken the position that it has the authority to regulate LDTs—the agency has exercised what it describes as "enforcement discretion" and has not actively regulated LDTs. The agency stated its intention to apply risk-based oversight of LDTs as medical devices under the Federal Food, Drug, and Cosmetic Act, although some question whether the FDA has jurisdiction and whether it is the appropriate regulatory authority to do so. The Centers for Medicare and Medicaid Services (CMS) also claim jurisdiction over LDTs. The laboratories that perform these tests are subject to the Clinical Laboratory Improvement Amendment (CLIA) rules, administered and implemented by CMS. Clinical labs can obtain CLIA certification directly from CMS, typically through state agencies that survey labs for compliance with CLIA requirements. In addition, Developments in personalized medicine, in particular the proliferation of complex new diagnostic tests and services linked to major health decisions and targeted directly to consumers, have prompted concerns in some sectors about their safety. The concept of test "safety" comes into play when one considers the consequences of misinterpretation. These consequences may include an ineffective therapy, an unnecessary preventive surgery, or any number of suboptimal, and sometimes irreversible, medical decisions. Some have argued that the FDA should assume a more active role in regulating certain molecular diagnostic tests used in the selection, dosing, or exclusion of treatments.

**Key Coverage and Payment Policy Challenges**

Emerging personalized medicine products and services often cause disruptive changes in health care. As a result, they require extra efforts to overcome payment policies grounded in traditional approaches to coverage and reimbursement. Challenges include cuts to Medicare payment for diagnostic tests, proposed cuts to Medicare reimbursement for tailored therapies, proposals for coverage and payment policy based on one-size-fits-all assessments, and expensive cost-sharing for tailored therapies and diagnostics that guide treatment decisions [12]. CMS( Case for personalized medicine and private payers are proposing new payment models that seek to drive improvements in care quality and efficiency, partially reacting to increasing demands to drive down health care costs. If properly implemented, these alternative payment models (APMs) can support the emergence of personalized medicine concepts and products; improperly constructed, they will create significant new barriers to its development and adoption.

**Adequate Reimbursement for Personalized Medicine Diagnostics and Tailored Therapy** Under pressure to address rising health care costs, policymakers and payers are increasingly pursuing policies that may result in across-the-board coverage and payment cuts, inadvertently discouraging continued developments in personalized medicine. Leaders in the cancer community, including PMC, have contended that in order "to stimulate the development of a more robust diagnostics pipeline and to harness the benefits of personalized medicine in patient-centered care delivery, policymakers and regulators must create an environment that encourages increased investment in diagnostics, enables new advances in patient care that are safe, accurate, and reliable, and establishes a viable pathway toward patient access [13]. Recent changes to payment and reimbursement policies for diagnostic tests demonstrate how poorly conceived policies can have a negative impact on personalized care. Until recently, payments for diagnostic and molecular tests, the backbone of personalized medicine, were predictable and standardized, relying on payments based on "stacked codes." However, payment and reimbursement policy changes have led to significant disruptions for laboratories and developers of personalized medicine products. CMS' decision, for example, to use "gapfill" methodology, which allowed regional contractors to set prices for laboratory and molecular diagnostic tests, coupled with other payment decisions, unfortunately caused a near complete cessation of federal payments for genomic tests in 2013[14].

**Payment and Delivery System Reform**

Traditionally, Medicare and private payers have paid for items and services on a feefor-service basis, in which doctors, hospitals, and other health care providers are paid for each unit of service provided. APMs are intended to pay providers for the value of the care that they provide, rather than the volume of services delivered. If implemented

appropriately, APMs, such as medical homes, ACOs, and pathway- or episode-based payments, improve health care by encouraging the adoption of personalized medicine, but only if they are designed in ways that support continued advancements in and adoption of personalized medicine products and services (as noted above). APMs should encourage physicians to tailor care based on an individual's genetics and other factors, and support the adoption of novel targeted therapies [15]. Accordingly, these models would include sufficient incentives to augment clinical care quality and not focus exclusively on cost control, ensure that patients have access to and are aware of all their diagnostic and treatment options, and encourage innovation that improves patient outcomes and quality of life. As APMs continue to be adopted, they should be aligned with the principles of personalized medicine and biomedical innovation so that, again, both patients and the health system benefit.

## 4. Conclusion

Personalized medicine offers significant short- and long-term benefits, especially for chronic and complex diseases. Personal genomic information and exome sequencing for individual genetic variants are paving novel therapeutic strategies for diagnostics and treatment of diseases. Payment and reimbursement policies should not discourage interventions that may raise short-term costs but improve clinical/ cost value over time. Innovators are responsible for developing the collective evidence to justify the contention that personalized medicine can improve outcomes while controlling costs.

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