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Personalized medicine could transform healthcare (Review)

SUNIL MATHUR and JOSEPH SUTTON

Molecular Drug Research Laboratory, Edinburgh Napier University, Edinburgh EH11 4BN, UK

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Abstract. Personalized medicine (PM) is about tailoring a treatment as individualized as the disease. The approach relies on identifying genetic, epigenomic, and clinical information that allows the breakthroughs in our understanding of how a person's unique genomic portfolio makes them vulnerable to certain diseases. PM approach is a complete extension of traditional approach (One-Size-Fits-All) to increasing our ability to predict which medical treatments will be safe and effective for individual patient, and which ones will not be, based on the patient's unique genetic profile. Implementation of PM has the potential to reduce financial and time expenditure, and increase quality of life and life extension of patients. Knowledge of PM facilitates earlier disease detection via enhanced use of existing biomarkers and detection of early genomic and epigenomic events in disease development, particularly carcinogenesis. The PM approach predominantly focuses on preventative medicine and favours taking pro-active actions rather than just reactive. This approach delays or prevents the need to apply more severe treatments which are usually less tolerated and with increased quality of life and financial considerations. Increasing healthcare costs have placed additional pressure on government funded healthcare systems globally, especially regarding end of life care. PM may increase the effectiveness of existing treatments and negate the inherent problems associated with non-PM approaches. PM is a young but rapidly expanding field of healthcare where a physician can select a treatment based on a patient's genetic profile that may not only minimize harmful side effects and guarantee a more successful result, but can be less cost effective compared with a 'trial-and-error' approach to disease treatment. The less efficient non-PM ('trial-and-error') approach, which can lead to drug toxicity, severe side effects, reactive treatment and misdiagnosis continue to contribute to increasing healthcare costs. Increased patient stratification will allow for the enhanced application of PM and pro-active treatment regimens, resulting in reduced costs and quality of life enhancement.

Correspondence to: Mr Sunil Mathur or Mr Joseph Sutton, Molecular Drug Research Laboratory, Sighthill Campus, Edinburgh Napier University, 9 Sighthill Court, Edinburgh EH11 4BN, UK
E-mail: s.mathur@napier.ac.uk
E-mail: joseph.sutton@napier.ac.uk

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1. Introduction

Personalized medicine (PM) is currently a particularly novel and exciting topic in the medicine and healthcare industries. It is a concept that has the potential to transform medical interventions by providing effective, tailored therapeutic strategies based on the genomic, epigenomic and proteomic profile of an individual, whilst also remaining mindful of a patient's personal situation. The power of PM lies not only in treatment, but in prevention. Increased utilisation of molecular stratification of patients, for example assessing for mutations that give rise to resistance to certain treatments, will provide medical professionals with clear evidence upon which to base treatment strategies for individual patients. With this development, there will no longer be a dependence on the adverse outcomes of trial and error prescribing methods (1,2). Currently, when prescribed medication is not effective, the patient may switch to a different medication. This trial and error approach leads to poorer outcomes for patients, in terms of adverse side effects, drug interaction, potential disease progression whilst effective treatment is delayed and patient dissatisfaction (3).

The 21st century vision of PM is to provide 'the right drug, with the right dose at the right time to the right patient' (4). Effective application of PM relies heavily on the availability of rigorous diagnostic tools which allow for the optimal selection of therapeutic product to improve patient outcomes. The products are fully regulated by manufacturers and Food and Drug Administration (FDA) bodies (5). According to the FDA, the aim of PM is to elevate benefits and reduce risks to patients by targeting prevention and treatment more effectively. PM does not seek to establish novel medication for patients, but to stratify individuals into subpopulations that vary in their response to a therapeutic agent for their specific disease. For

example, Herceptin is an extremely useful drug for around 20-30% of breast cancer patients who have elevated expression of HER2. However, some patients with elevated HER2 are inherently resistant to Herceptin due to mutations to the HER2 gene. Therefore, intelligent molecular characterisation of breast cancer patients at both a genetic and epigenetic level allows for the optimal use of Herceptin through stratification of patients (6).

The revolution of PM has created a lucrative opportunity for pharmaceutical companies developing molecular-targeted therapeutics, but also through the optimised use and repurposing of existing drugs and combination therapies. Adopting PM will alter the approach to diagnosis and treatment, and will lead to increased participation of the patient during and after treatment. For example, active surveillance in prostate cancer gives patients the choice on if they would like curative treatment immediately, with potential complications and discomfort, or wait until there is signs of disease progression (7). This aspect of PM incorporates the circumstances of the patient as an influence on the appropriate treatment strategy for them as a person, not just as a patient.

The advanced commercialization of molecular medicine has produced the novel concept of pharmacogenetics, the application of which is now acknowledged as PM. Molecular targeted therapies include monoclonal antibody (MAb) based therapeutics like herceptin which targets HER2 in breast cancer but MAb therapies are also used clinically to molecularly target therapies for rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and inflammatory bowel disease as well as several types of cancer (8). Currently, we are seeing the translation of immunotherapy research into clinical practice, including highly PM centric ex vivo modification of immune cells. These treatments, such as Sipuleucel (Provenge) extract dendritic cells from a patient's own blood, incubate and mature them in the presence of prostatic acid phosphatase (PAP), which is expressed on the surface of around 95% of prostate cancer cells. When these modified dendritic cells are re-infused to the patient, they are able to present PAP to the patient's immune system, directing the body to attack its own tumour (9). With the advent of CRISPR-Cas9, scientists now have even greater ability to engineer cells at a genetic level (10). *Ex vivo* modifications using CRISPR-Cas9 to gene edit specific oncogenes is already underway (11) and could be used to create treatments based on the unique tumour evolution path of each specific patient. Clinical trials using CRISPR-Cas9 gene editing have also begun in the USA (12).

To fully realise the potential of PM, pharmaceutical companies will need to invest in development of new diagnostic techniques, that will help to stratify patients at a higher resolution, allowing for optimised therapeutic selection and timing. PM requires coordinated adjustments to each aspect of the value chain, from discovery to development and from commercialization to lifecycle management (13).

2. Challenges

PM is considered to be an innovation in the healthcare system; it is preventive, synchronized and proven (1,2). In the current healthcare system, stakeholders and consumers do not yet fully recognise the benefits of PM. Recent studies demonstrate the following challenges to the development of PM: Scientific challenges (wherein genetic markers are the most clinically significant, with a poor understanding of the molecular mechanisms of certain diseases) (14); economic challenges; operational issues (difficulty identifying technology and operational systems that will save costs); and protection of private information during the investigation and development stages (3). Furthermore, there are policy challenges regarding the association between government research and regulatory agencies (15).

3. Benefits

PM has the potential to offer improved medication selection and targeted therapy, reduce adverse effects, increase patient compliance, shift the goal of medicine from reaction to prevention, improve cost effectiveness, and increase patient confidence post-marketing by approving novel therapeutic strategies and altering the perception of medicine in the healthcare system (15).

4. Strategy

For the development and rapid adoption of PM it is vital that pharmaceutical companies invest in these new technologies and show willingness to work collaboratively with academic research teams. Identification of more stringent biomarkers and are necessary to inform a pro-active approach to PM. One example is the recent development of liquid biopsies, which can be used to detect DNA circulating in the blood. This type of biopsy is non-invasive, much lower risk than traditional biopsy and has been used to detect disease extremely early. One of the first uses of liquid biopsy was a test for Down syndrome is pregnant mothers (16). Now studies such as TRACERx are using ctDNA (circulating tumour DNA) to analyse and predict the tumour evolution of lung cancer (17). Approaches like this will allow medical professionals to apply PM pro-actively by pre-empting the course of tumour evolution and switching patients onto different therapeutics as soon as signs of drug resistance are detected. This may be able to delay the onset of resistance For long-term purposes, pharmaceutical companies must educate themselves in order to be profitable using the novel diagnostic and treatment methods in markedly reduced volumes. Novel drug development is prohibitively expensive and pharmaceutical companies are increasingly keen to repurpose existing drugs. PM allows for optimisation of treatment regimens and therefore increases the utility of existing products.

All pharmaceutical companies implement PM according to their own methods as follows: i) Transitioning from traditional drug methods to PM is not an option, but a necessity. Accept that each molecule in the pipeline will be personalized to precise patient populations, rather than the mass market. ii) PM is an innovative approach towards delivering improved healthcare and reducing overall healthcare costs. This will be achieved by implementing the digitalization of healthcare, by improving the healthcare IT system and with innovative technologies, such as developing single-cell omics, which permits the investigation of different cells in a high throughput manner (18). iii) Embedding PM skills into the existing healthcare system. The implementation of PM

requires a united effort of a broad community of stakeholders, all working towards a primary goal of exploiting breakthrough in science to improve patient care (19,20). iv) Biomarkers (an indicator of biological state) are facilitating the support of research and design (R&D) in healthcare industries. R&D is improved by decreasing trial sizes and increasing the speed to market. Support smaller-market therapeutic agents that are more likely to succeed. v) Access novel capabilities by forming partnerships; for example, contact with world-class diagnostics by corporations with assay developers and different industries. vi) Intelligent sales forces with the most up-to-date expertise. Sales teams will be required to have knowledge of patient history, as well as diagnostic and treatment methods. Furthermore, sales teams must understand molecular analysis and disease pathways. vii) Post market surveillance is particularly important in PM to allow more focused clinical trials of pharmaceutical products (21).

In addition, in the coming decades, the demand for PM will increase, as consumers will become more educated about this novel treatment approach. This will encourage the shift from the current medicine module to the novel methods of diagnosis and treatment. Furthermore, currently, clinical trials are time-consuming and require significant manpower; however, in future the concept of clinical trials will be more advanced and easy to accommodate PM with the help of regulatory approval. The development of PM R&D map by improving public/private sector. Establish a simple method of identifying and prioritising the disease, which may benefit from the application of novel technology. Additionally, development of joint venture programmes for validation of study designs and biomarker standardisation (13).

5. Conclusion

PM has the potential to fulfil the requirement to improve health outcomes by reducing healthcare costs, drug-development costs and time. This revolution in the healthcare system will only be possible to achieve by equal contribution of patient and consumers in participating in clinical trials, entrepreneurs and innovators to develop smart tools and analyze the genetic information, regulators by educating consumers and providers, and support essential revolutions in policy and regulation, physicians to understand the disease at the molecular level, academic researchers by accompanying innovative research to uncover new insights at the molecular basis of disease and supporting target-based drug development, IT sector by creating unique electronic tools to collect and secure patient information, stakeholders, payer and policy makers by exploring new business models, novel diagnostics tools, target therapy and other personalized treatment protocols. PM has the potential to have a positive effect on the healthcare system. In future, with use of the personalized approach, each individual, on the day of their birth, will receive their full genomic information to place into an individual medical record. This information would allow physicians and clinicians to implement more effective healthcare approaches based on patient exposure to different diseases.

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