Perspective Article

Personalized Medicine: the Cure of the Future

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Reviewed on 2 May 2020; Accepted on 22 June 2020; Published on 26 October 2020

As the Human Genome Project came into completion, it became possible for the field of medicine to take drugs to the next level: of being able to base drug treatment from each patient's genetics. Personalized Medicine is a form of medical treatment that differs from the traditional medicine in that it is developed to suit each individual's genetic profile, instead of today's standard "One-Size-Fits-All" approach. Although it is a fairly new method of treatment, it gives the future the hope of utilizing preventative medicine, rather than reactive; of an overall higher effectiveness in treatments; and of cutting costs in medical treatments. This paper will address several aspects of this new methodology in the pharmaceutical branch. Firstly, it will discuss briefly about what personalized medicine is, and will give an overview of how this would work. It will also go into some details about the types of personalized medicine that have been successfully implemented into the present day's healthcare system. Furtheralong, the paper will discuss some ethical issues or concerns that may come up regarding the topic of personalized medicine and lastly, how this novel medical advancement would fit into the world in the future and some challenges that may be faced concerning this matter

Keywords: Personalized medicine, Ethics, Preventative medicine

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Understanding personalized medicine

The key understanding that led to the development of personalized medicine is the knowledge that different genetic sequences can cause different responses to drugs. For example, different genes create variations of the same type of enzyme that metabolize drugs. Thus, the process of "absorption, distribution, metabolism and excretion of drugs," (Vogenberg, Barash and Pursel 2010a), would also be different, due to this variation. This concept gave rise to a new scientific discipline called pharmacogenomics, which emerged in the early 1950s, and explores how the genome can influence a person's response to drugs. The application of this field into medicine is called personalized medicine, or PM (Vogenberg, Barash and Pursel 2010a).

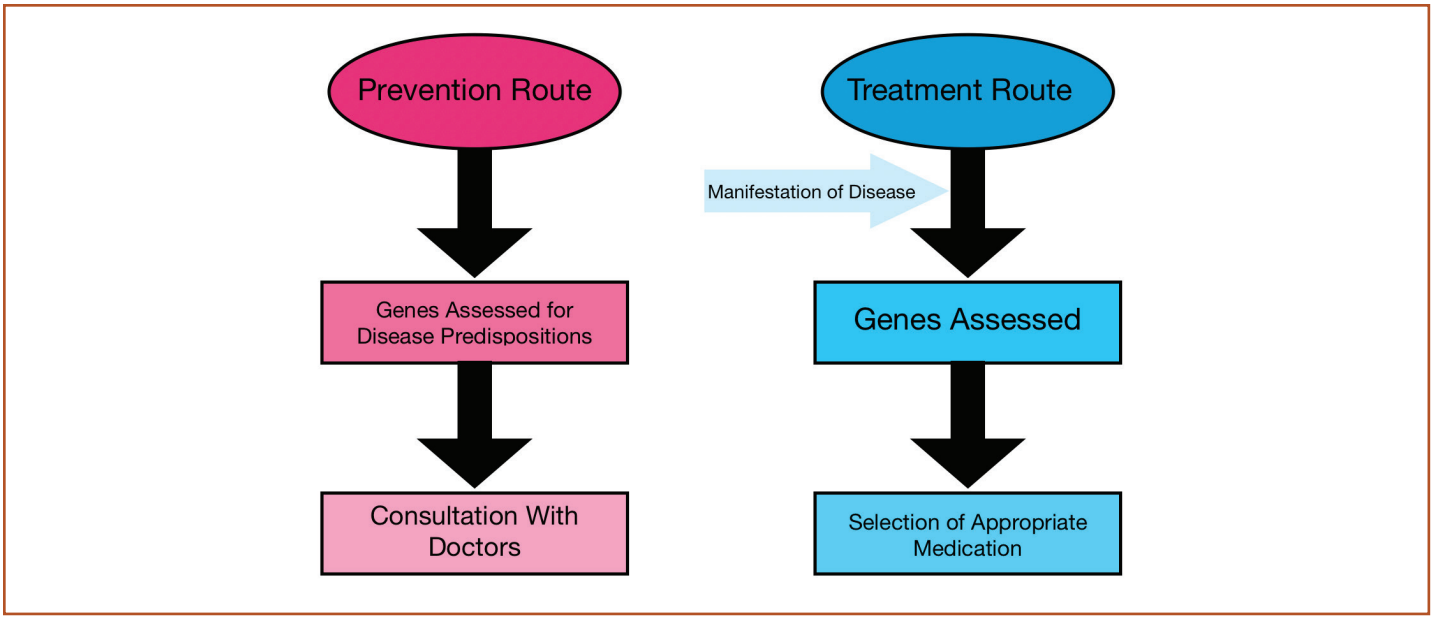

Figure 1: *This figure depicts the overview of the pathways of usage of personalized medicine (PM)*

A brief overview of the implementation of PM can be summarized within two pathways (Figure 1): the prevention route and the treatment route. Ultimately, the goal of PM is to be a preventative medicine, where the patient's genetic information is assessed to reveal certain predispositions to diseases. Consultations with doctors can further address the susceptibility to diseases that each patient has because of their genes, and methods of prevention can be utilized. The treatment route is similar to the prevention route and differs only in the fact that the disease has already manifested. When using PM treatment, the patient's genetic sequences are assessed and medications that best suit the patient are selected. That is, by taking their genetic profile into consideration (The Age of Personalized Medicine Date Unknown).

The aim of PM is to provide the "right drug, with the right dose at the right time to the right patient" (Sadée and Dai 2005). Implementing PM into the healthcare system will affect how medication is handled. The conventional medicine of the present day treats diseases with the "one-size-fits-all" approach, where one model that works for the majority of the population is given to every patient. This could cause adverse effects to some, since there is always the minority that reacts differently with the same medication. The people in the minority group may experience a toxic reaction towards the medication that works for other people due to the differences in their genes. PM, however, moves away from that approach towards a more "personalized" form of medication, where the patients' genes are assessed before they are given the medications, to best match their genetic profiles. This same method can be utilized in selecting the dosage of medicine for the patient. In the present day, dosages are often calculated by the patient's weight or age, however, these information are not sufficient in predicting the patient's reactions to the medication in some cases and therefore not sufficient to predict that safest dosage. Analyzing the patient's genes will be a better option, since the hope for this methodology is to reduce the adverse reactions of the medicine and the patient's body, which are primarily influenced by genetics (Vogenberg, Barash and Pursel 2010a). PM, however, does not seek to provide new medications for patients, but rather, to target effective medications to a group of individuals with certain genetic profiles that will respond appropriately to the medicine (Mathur and Sutton 2017).

The accelerated rate of growth for PM in the recent years has been possible due to the new tools that can decode the human genomes with greater accuracy and speed, the researches done about the relations between genetics and diseases and the availability of the health information technology (HIT) (Vogenberg, Barash and Pursel 2010a,b).

Personalized medicines in present day's healthcare system

Dako's Hercep genotyping test for trastuzumab

Following the treatment route of PM, one of the many successful PMs that has been implemented into today's society is Herceptin (also known by its chemical name,

Trastuzumab) (Breastcancer.org 2020). The treatment route utilizes PM so that it would be most effective with the patient's genes. In that sense, the treatment itself is the PM. Trastuzumab is a monoclonal antibody commonly used in the treatment of breast cancer. Before the treatment begins, the patient must be confirmed to have overexpressed HER2 gene in tumours or cancer cells, because the benefits of trastuzumab has only been proven with patients with overexpressed HER2 genes, and because there are risks concerning the treatment. Some risks include pulmonary toxicity, infusion reactions, and cardiomyopathy that can result in cardiac failure (Dean 2015). Thus, it is used to treat specific tumours from patients to contain the overexpressed HER2 genes (another name is ERBB2), which is overexpressed in 15-20% of breast tumours, known as "HER2 positive tumours" (Dean 2015). In the general population, the HER2 gene produces HER2 receptors, which act like antennas on the surface of the cell. These receptors detect growth-triggering signals, allowing the cells to grow. However, with the HER2 genes being overexpressed, the cells grow rapidly and out of control and may form cancerous cells (Breastcancer.org 2020).

Trastuzumab works by targeting the HER2 receptors, and binding itself to the extracellular domain of the cancer cell, making the receptors unable to pick up signals that stimulate growth (Dean 2015). Trastuzumab therapy is used in both neoadjuvant (treatments before the primary treatments) and adjuvant treatments (treatments after the primary treatments). The most common sequence for adjuvant treatments containing trastuzumab is specifically in the order of "AC→TH", (Adriamycin, Cytoxan, then Taxol and Herceptin); a chemotherapy treatment regime. (Dean 2015). Trastuzumab can also be used alongside other drugs such as Taxol, Taxotere, and with hormone therapies called aromatase inhibitors. Trastuzumab is injected directly into a patient's bloodstreams via plastic tubes. The first treatment lasts approximately 90 minutes, and depending on the patient's reaction to the drug, the follow-up treatments are usually 30 minutes. (Cancer Research UK 2018)

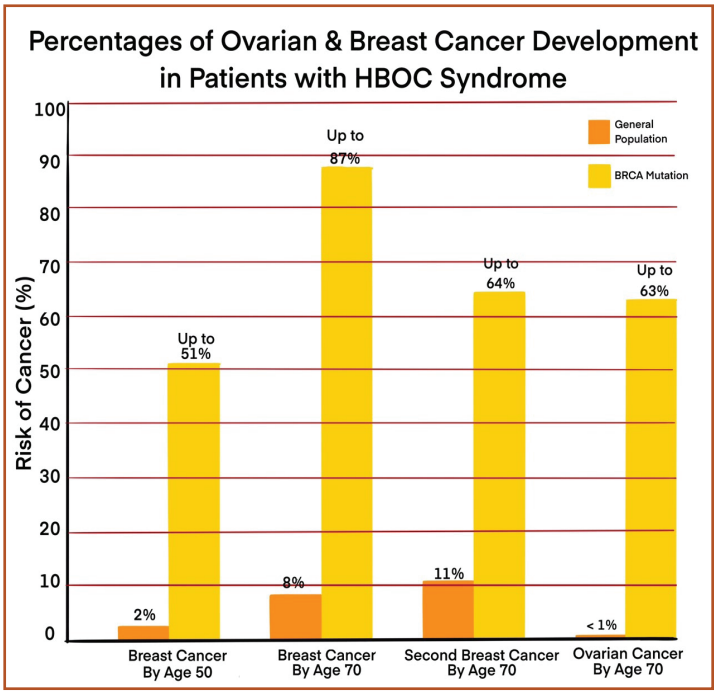

Figure 2: *The graph depicts percentage of ovarian and breast cancer development in patients with and without the HBOC syndrome. (Myriad Team, Data Unknown)*

Myriad's BRCA1/BRCA2 test to determine breast and ovarian cancer risk

In contrast to Trastuzumab, which acts in the treatment route after the disease has already manifested, PM also can follow the prevention route. This route highlights the idea that assessing the patients' genetic information, which reveals each patient's predispositions to different diseases, will make it possible for doctors to derive methods of disease prevention in accordance to each patient's genetic information. By determining certain genes in a patient's body, it is possible to prevent certain diseases.

This is true for the Myraid's BRCA1/BRCA2 test used to determine the risk of breast and ovarian cancer. Mutations in the BRCA1/BRCA2 genes account for approximately 7% of breast cancer cases (Myriad Team 2020) and around 1 in 500 Americans have mutations in genes BRCA1 or BRCA2 (Lindor, Lindor, Apicella, et al. 2007). Furthermore, the BRCA1/BRCA2 gene mutations also account for approximately 15% of ovarian cancers as well. Although mutations in other genes such as PTEN, TP53, STK11, CDH1 and PALB2, have been discovered to increase the risk of breast cancer, BRCA1 and BRCA2 have proven to be most contributing (Lynch, Venne and Berse 2015). People with mutations in either one of these genes have a condition called Hereditary Breast and Ovarian Cancer (HBOC) syndrome (MySupport360Team 2020) and have up to 87% chance for developing breast cancer by the age of 70 and 63% chance for developing ovarian cancer by the age of 70 (Myriad Team 2020). Figure 2 depicts other percentages of ovarian and breast cancer development in patients with the HBOC syndrome.

Myriad's test to determine BRCA1/BRCA2 gene mutations in patients is one way to find out whether they have a predisposition to breast or ovarian cancer. Myriad Genetics Inc. described themselves as the "trusted advisors to patients and physicians" (Myriad Team 2020) and the company has been offering these tests since the late 1990s (Lynch, Venne and Berse 2015). As of the present, these tests are also offered at other academic and commercial reference laboratories such as Baylor College of Medicine and Ambry Genetics respectively. Test

results can be positive, negative, or a variant of uncertain significance (VUS). A positive result means that mutation is detected in one of the genes, negative meaning that no mutation is detected, and the latter meaning that a mutation is identified but it is uncertain whether this variant may affect the person's risk of cancer or not. Patients then use these results to consult their doctors about their genetic predisposition to breast or ovarian cancer and the possible treatments available (Lynch, Venne and Berse, 2015).

Many factors contribute to the consideration of whether a testing for mutations of BRCA1/BRCA2 gene mutations is recommended or not. It is recommended that an individual take the test if the individual has had breast cancer at the age of 50 or younger, if the individual ever has had ovarian cancer, if someone in the individual's family is diagnosed with breast cancer before the age of 50, etc. (Myriad Team 2020). For these genetic information may help assist the doctors in their process of analyzing the patient's genetic information to allow for a specific prevention route.

Roche's AmpliChip CYP450 test to predict patient's responses to different therapies

Similarly to the Myriad's test to determine the BRCA1/BRCA2 genes mutations, the Roche's AmpliChip CYP450 Test is also used to predict a patient's response to various therapies, thus also following the prevention route of the utilization of PM. In short, a patient's response to therapies can be determined by how fast (or slow) the individual metabolizes certain drugs (Rebsamen, Desmeules, Daali, et al. 2008) and several other types of enzymes each person have (Juran, Egan, Lazaridis 2006). Specifically, the CYP450 gene super family encodes for enzymes that are largely responsible for the metabolism of drugs, with two genes from the superfamily, CYP2D6 and CYP2C19, that the AmpliChip CYP450 Test is able to detect. This is linked to the bioavailability of drugs and adverse drug reactions some patients may exhibit (Juran, Egan and Lazaridis 2006). Being able to identify the genotype for these genes also allows for the individual's CYP2D6 DNA sequence to be determined at high accuracy. Based on the alleles identified, it is possible to predict a phenotype (Rebsamen, Desmeules, Daali, et al. Rossier 2008).

AmpliChip CYP450 Test is a clinical test from Roche Molecular Diagnostics that aims to determine the genotype of individuals by detecting polymorphisms and mutations of 2 genes, CYP2D6 and CYP2C19 (Jain 2005). The test uses microarray technology to classify individuals into phenotypes of these two genes. By testing 3 alleles, CYP2C19 gene can be classified into two phenotypes (extensive metabolizers and poor metabolizers), while CYP2D6 can be classified into four phenotypes (ultrarapid metabolizers, extensive metabolizers, intermediate metabolizers, and poor metabolizers) by testing 27 alleles, including seven duplications (de Leon, Susce and Murray-Carmichael 2006). CYP2C19 is largely responsible for the metabolism of many proton pump inhibitors (PPIs), tricyclic antidepressants, and antiepileptics, while CYP2D6 is very polymorphic (has many genetic variations), meaning that it plays a large role in variety of activities in humans (Juran, Egan and Lazaridis 2006). One can say that the AmpliChip CYP450 Test is the "first successful pharmacogenetic test in the clinical environment" because it is approved by the US-FDA and is the FDA definition of a "valid biomarker"(de Leon, Susce and Murray-Carmichael 2006). The test should be used alongside pharmacotherapy as a guide for doctors to best utilize medicines in accordance with each patient's genetic information for the greatest benefits (Jain 2005).

Ethical issues behind personalised medicine

Health information centers and databases such as the electronic health records (EHRs) and the Human Genome Project provide PM with large amounts of intensive information to further aid both doctors and patients in decision making. However, because of the excess information that these databases provide, moral and ethical issues further consider if PM is truly a considerable option. The main issues that this section will discuss are such topics as of the patient's privacy and rights, discrimination and liability within PM which accounts for dissimilarity between people groups as well as the potential balance of future drugs.

As personal health information from EHRs become crucial for the use of PM, the individual's privacy and ethical rights often come into question. In regards to the patient's emotions, this may lead to emotions of discrimination or embarrasment. As the entirety of the healthcare industry heavily relies on the aspects of confidentiality and both proper mental and physical healthcare services, every patient's individual emotions and rights should be taken highly into perspective. With the increase of PM, this would increasingly risk the proper amount of healthcare services that is provided. Not only in this manner, but directly through healthcare workers as well. This may lead to a larger impact of prejudice or bias, which could possibly lead to the decline of practices and proper quality of healthcare from the healthcare worker's biases. With the ethical issue in mind, the escalated introduction of the PM may simply put the healthcare service and industry into question, rather than benefiting from the now vast information from the EHRs.(Vogenberg, Barash and Pursel 2010a,b)

As the EHR can be viewed by healthcare insurers and anyone who has the access to the database, the availability of an individual's entire health information becomes strikingly accessible. This raises a significant ethical question, of whether it is morally acceptable for a health provider or patient to acquire vital knowledge of an individual's potential future well being, along with the malicious uncertainty of the insurer's future actions towards it. (Silverman 2004) Furthermore, the privacy of an individual may be easily violated when accessing the unlimited genetic information of the patient and other blood related family members (Vogenberg, Barash and Pursel 2010a,b). This leaves an insufficient room for individuals to give consent in accessing health information, as well as with giving third parties a possible benefit in future life insurance programs (Silverman 2004).

On top of the matter, arguments such as the widespread of discrimination and liability also surface when considering the value of PM overall. Such examples of discrimination towards the functionality of PM are such things as "questionable stereotypes rather than assessment of individual merit, eligibility or ability; it results in the impermissible stratification of society and the denial of essential opportunities to members of a disfavored segment of the population" (Vogenberg, Barash and Pursel 2010b). Another possibility of how discrimination can occurr when considering information intensive testings of PM is genotype-based discrimination, and whether if the mattter is socially acceptable, legal or rational. Future insurances, employment and further activities could possibly be discriminated against by insurance companies, employers and future activities, if an individual does not comply with "clinical appropriateness" that should have been reached (Vogenberg, Barash and Pursel 2010b). Instinctively, discrimination within the area of PM also raises the issue of liability, with the added responsibilities due to more complicated genetic information and demanding procedures and standards. Mortality risks, as slight information could hint to possible medications for future illnesses or drugs that are passive for the patient would increase heavily with the introduction of more access to the EHR. Inaccuracy or the lack of formal experience of health insurers or physicians are also a potential threat to liability. Moreover, larger companies, laboratories, pharmacies and potential hospitals in the field are also equally unprotected from legal liability. (Vogenberg, Barash and Pursel 2010b)

Another large ethical issue is the overall disparities among racial groups and social status that affects PM actual use and effectiveness. The likelihood of the "over-representation of particular phenotypes in certain racial or ethnic groups may serve as an indicator of underlying genotype–phenotype associations, which might then allow for the development of targeted therapies" (Vogenberg, Barash and Pursel 2010b). The benefit of most PMs would likely be unevenly and targeted towards the majority, which defeats the overall purpose of PM, which is to allow for those with genetic mutations or those that contain variable genes to the majority to gain treatment suited for them. This is resulted from the severely over-represented basis that the actual studies behind PM, hence 75 percent of the "'inputs' for translated efforts" involved were of European descent (Vogenberg, Barash and Pursel 2010b).

Asides for the under-representation within PM, other factors such as the cultural and economical aspects of global disparities also contribute to its importance to the lack of representation, let alone the actual balance medicines that certain minorities gain access to (Vogenberg, Barash and Pursel 2010a,b). This highly suggests the ethical problems underlying the groundwork of PM. With the technological advancement of PM, the question of accessibility becomes a crucial ethical issue, where not every patient may receive the full benefits of PM, let alone any benefits to heal a patient's root cause. Although PM may benefit the majority of the population where PM itself is developed, social disparities such as certain minorities, people groups and their ability to access additional information relating to PM based on their background could either restrict or allow them in accessing its actual full benefit. Some factors that directly lead to the level of accessibility include things such as internet access and knowledge or access to transportation as well (Vogenberg, Barash and Pursel 2010a,b). Unfortunately, concerning aspects such as the financial factor of a population, such economic difficulty, may also only limit this option further. This is such as affordability, choosing not to take diagnostic tests for further research of one's PM because of its cost, or limited healthcare services, insurance and technology as well (Vogenberg, Barash and Pursel 2010a,b). The matter of accessibility and affordability as well as the sets of disparities might as well lower the importance of the actual desired outcome of PM for all its patients, only then displaying the true underlying issues. Considering the over effectiveness of PM, this disparity severely affects one's choice of selecting an appropriate medicine which increases the "potential for poor clinical outcomes when coverage decisions are made" (Silverman 2004).

Challenges and hopes for the future

Personal medicine guarantees improved healthcare, yet there certainly are challenges in its development. Currently, scientists are still lacking knowledge of some diseases to the molecular level, which are essential to the developmental process. Researchers are also faced with economic issues, hindering them from fully

exploring and experimenting in the field. Because of the economic issues, it is necessary to utilize technological systems that best serve their purposes and are efficient. In addition, there have been concerns regarding the privacy of research information that is crucial to further development (Mathur and Sutton 2017).

Despite the challenges mentioned above, PM does bring about great hopes in the healthcare field. Because they consider each patient's molecular information as the basis of treatment, PMs work more effectively than general medicines, eliminating side effects of medicines and increasing efficiency. The successful development PM will majorly shift the future of medicines to the prevention route, thus leaving a huge impact on the healthcare landscape (Mathur and Sutton 2017).

Acknowledgements

Our team would like to acknowledge Mr. Paul Muri for guiding, encouraging, and mentoring us through the writing process of this paper. With his contribution to our team through the topics of biology, the members were able to push to the limits of our knowledge and motivation towards the research paper. We would also like to sincerely express our gratitude to his passion for biology and teaching, as it was able to fuel more of our team's continual interest towards our teamwork, research, overall biology knowledge and engagement with the paper. With this, the completion of this paper will not have been possible without our co-authors, Kandharika Bamrungketudom, Praifa Muadthong, Ingfa Muadthong, and Nutthun Tulayathun. Lastly, we would also like to give thanks to our friends and teachers for the willing support and encouragement throughout the writing process.

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