

How to Cite:

Shivani, S. (2022). Genomics in precision medicine. *International Journal of Health Sciences*, 6(S3), 5791–5798. <https://doi.org/10.53730/ijhs.v6nS3.7234>

Genomics in precision medicine

Shivani S.

Department of Biotechnology, Kumaraguru College of Technology

*Corresponding author email: shivanisivakumar157@gmail.com

Abstract---The term Precision Medicine (PM) gained significant attention in the field of drug discovery. The roots of PM can be traced back even before the start of Human Genome Project (in the early 2000s) but came into existence only by 2010. PM is a preventative strategy that focuses on improved patient care by taking account on variability in genes, environment, and lifestyle for each individual. PM is a long-term endeavour, including the National Institute of Health (NIH) and multiple other research centres were pioneers in funding and conducting cutting edge research related to PM. Knowing the genetic makeup of an individual will help us better understand and predict the risk of disease, this will further aid in personalised diagnosis and treatment strategies. Although there has been significant number of research articles available on PM, however to the best of my knowledge they do not emphasise much on the reasons why PM has not been the choice for disease diagnosis and patient care. Therefore, this article will explain how PM will transform the future of health care as we know it today. In addition, this article also discusses on factors that will aid in the development of PM.

Keywords---precision medicine, genetic makeup, diseases, diagnosis.

Introduction

The current practices of medications are ineffective as they do not account for changes in individuals genetic makeup overtime and the symptoms associated with those genomic alterations [1]. Changes in genome such as mutations can pose a great variety of adverse effects on human health, and there are various studies that emphasizes on this issue. For instance, patients suffering from rheumatoid arthritis, are often prescribed with high dosage of naproxen, upon analysis of the effects of the drug, 4 out of 20 would show good prognosis the rest would be given initial dosage of another drug methotrexate for which few may react and others might develop ill effects such as erythema, stomach pain and oedema. Afore mentioned issues can be addressed by taking a precision medicine approach - where a physician/clinician would analyse the genetic profile and look into individual specific reactions for drugs such as methotrexate and prescribe custom made drugs that react effectively [2]. By understanding the complete

genetic makeup and the individual's variability of genes and the effects of various factors on gene expression reduce the complication involved in prognosis and stratification [2,3]. The research on precision medicine has been on road for a long time now, but have not met the expectations due to various ethical issues and due to few mishaps in the developmental methodologies like the challenges involved in identifying predictors of drug response, in general 1 out of 4 patients do not take drugs as prescribed and this in turn affects the genetic studies.[1]

Precision medicine initiative

The precision medicine initiative had various short term and long-term goals[5]. The major short term goal was to focus conspicuously in the area of Cancer research and to further expand it into more targeted therapies for various form of childhood illness such as Leukemea[6], Cystic fibrosis and Human Immunodeficiency Virus (HIV). The long term goals are aimed at making precision medicine a customary method for treatment in all areas of health and healthcare ranging from cancer to IPEX syndrome (i.e a genetic disease causing immune dysregulation)[7]. The prime goals of this initiative were to create a better methodology in predicting disease risk and to understand the underlying mechanism of disease occurrence, and finding improved diagnosis and treatment strategies [1,9].

Lab to clinical workflow

The ingress of a patients' genetic information would create wider options for doctors to access information as a part of routine medical care and improved ability to predict which treatment will work best for the specific disease in a particular patient [8].

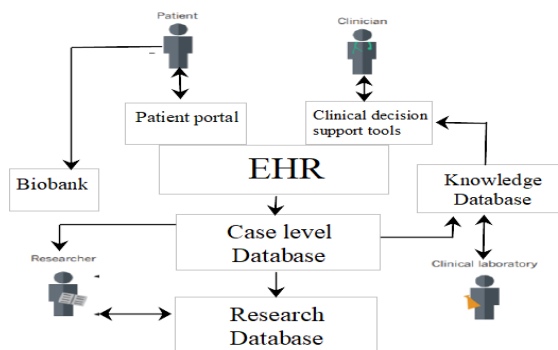


Figure 1. The Precision medicine Ecosystem. Image adapted from [1]

The basic workflow includes the collection of the sample data from the patients, storing them for access by Patients, Clinicians and Researchers as Electronic Health Records (EHR) is depicted in Fig1. The biobanks plays an the intermediary role to link samples with patient data to support discovery[6].Clinical knowledge sharing helps in refining data, and the research database on further research record those results as data. EHRs associated system helps in applying the results when patients' conditions are received and also to understand the

knowledge of evolving genetic variants, though they have few drawbacks in standardising the records [1][8].

Translational genomics

Precision medicine through translational genomics is done by achieving various translational milestones such as accelerated treatment, novel therapeutic approaches, early intervention/ prevention and personalised medicines [9]. The process starts by accelerating or targeting treatments using existing drugs and analyse the biomarkers and then move ahead with target discovery - identify prime genetic associations and their underlying mechanisms. The bullseye of tailored intervention - Polygenic Risk Scores (PRS) is constructed to understand the individual's genetic liability to that disease; their power is determined mainly on few factors: the number of variants involved in the score, frequency in the population, contribution of the environmental risks, so on. For example: compare two people with high polygenic risk scores for coronary heart disease. They are helpful in interpreting a person's risk score when compared with others with different genetic makeup. In prognosis the biomarkers[6]. For example biomarkers like rheumatoid factors(RF) and Anti Citrullinated Peptide Antibodies (ACPA) for rheumatoid arthritis [2] are discovered and the response to the treatment is studied through the pharmacogenomic markers (Biomarkers that are located in the genes encoding the drug metabolizing enzymes[10]. The final process of developing personalised medicine is done after stratification of patients to clusters based on their molecular profile [5].

Cancer genomics to precision medicine

Advances in genomic medicine is paving way for a new era of individualised cancer care and prevention treatments. Many genomics based tests are now being marketed to various physicians and some are even marketed directly to the consumers.

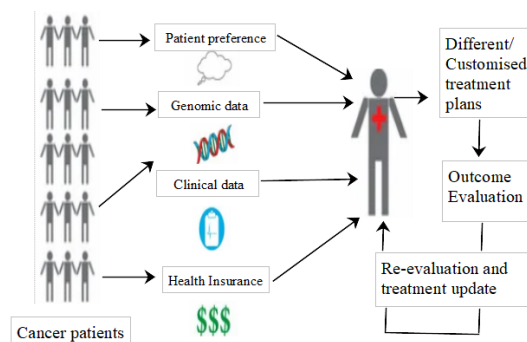


Figure 2. Networking of PM in oncology. Image adapted from [11]

Cancer patients have their clinical and genetic information evaluated by their physician and are provided with precise treatment plans. The outcomes are re-evaluated and further updated for betterment [12], [13]. The networking map of PM treatment is shown in Fig 2. The broad availability of genetic information

provided by various technologies like Next Generation Sequencing (NGS), and integration of Artificial intelligence (AI) approaches like machine learning, deep learning have paved way to transform big data not only related to cancer but also encompassing wide data sets of various chronic diseases to clinically actionable knowledge. Through application of machine learning and deep learning AI has outperformed various pathologists and dermatologists in diagnosing metastatic breast cancer, melanoma, liver cancer and several eye diseases [14], with increased advancements in precision medicine and genomics, patients approaches for risk prediction, disease diagnosis and development of targeted therapies have escalated [15].

Big data and pm for chronic diseases

PM application is developed and made available for various chronic diseases like Hypertension, multiple sclerosis, asthma, chronic obstructive pulmonary disease (COPD) and cardiovascular diseases[16]. The diverse complexity and heterogeneity in the chronic diseases explain the need of precision medicine. PM is a paradigm for combining new types of metrics with big datasets. Integrating PM into the clinical practices involves restructuring the health care infrastructure. Various needs are to be incorporated like the provisions and tools for collecting and sampling the data, interpreting the results and facilitating treatment choices based on the new biological understandings [18][17].

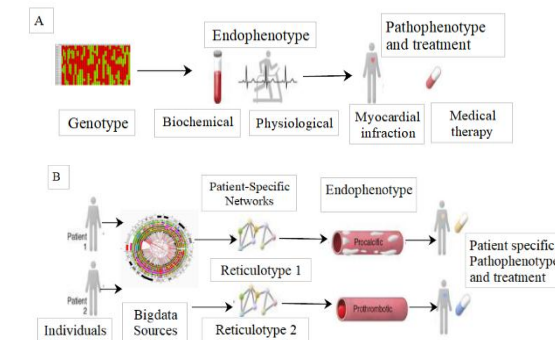


Figure 3. Treatment approaches in cardio vascular diseases. Image adapted from[18]

Current approach for cardio vascular diseases is shown in Fig 3A and be 3B is a representation of network medicine that ensures precision phenotyping and endo phenotyping. Using bigdata and patient specific integrated data(eg: protein-protein interaction) variations owing to an individual's genetic makeup called reticulotype can be studied, which in turn provides the patient-specific phenotype that would help in precision treatment which was not possible earlier. Similar approaches can be used for various other chronic diseases for eg: diseases like hypertension [18]. Family studies suggest that monozygotic twins shows a greater correlation of blood pressure phenotype than dizygotic twins, it also states that parental and grandparental history of hypertension tend to have an increased risk of hypertension in an individual. Thus, bringing in the need for precision medicine and genomics.

Public health and awareness

Genomics play an eminent role in clinical and public health research as they are helpful in developing various methods for treatment like precision medicine to improve public health, to be more precise Genomics in Medicine (GIM), has made important contributions towards integrating genomics into clinical practice and disease prevention. Developing awareness among the public regarding the usage of various tools (sequencing methods and precision medicine) involved in improvising public health also plays a role of equal importance just like the methods used[19], [20]. Various programs and awareness talks are being conducted on the same, for eg: Precision public health - A public health programme organised in 2016 raised awareness about next generation health that use tools like genomics and precision medicine in public health surveillance and interventions moreover, the evidentiary foundation for public health genomics lays a strong foundation for big data storage and proofs, the National Institute of Health Genetic Testing Registry, currently contains information on more than 50,000 genetic tests conducted in nearly 500 labs, for more than 10,000 disease conditions[16].

Potential benefits and bottlenecks

Precision medicine provides various benefits to the health care community in understanding how diseases occur [8], [21]. Custom made medicines for each individual will reduce the development of adverse effects of the drugs such as leleaxafor, methotrexate, and ibuprofen [2]. This method also plays a vital role in deflating the risks involved in the conventional method of medications - like, delay in switching to alternate treatments that might achieve benefit or development of adverse effects owing to overdose of particular gene[8]. For instance, overdose of ibuprofen can cause renal failure and methotrexate can cause abnormality in liver functioning [2], [7]. There are various limiting factors that stand as reason for the shortcomings in the development of precision medicine, most important being that the treatment response and progression are analysed from clinical endpoints(months) that is relatively slower compared to biomarkers (days or weeks)[1], [5]. Based on the results from a research conducted to understand the benefits and barriers of Precision medicine on African American and Hispanic, it was observed that the major concerns of achieving effective end result revolved around bioethical and discrimination issues [5], [6], [22].

Endeavours of precision medicine

The concept of precision medicine has attracted significant attention in the past few decades. This field aims to encompass as many unique and relevant aspects of a patient and their disease[23]. This field seems to be highly appealing, however far from the current reality in clinical aspects[17]. Regardless, it is likely to show huge impact by integrating huge data to predictive models with the use of deep learning, machine learning and artificial intelligence. Advancement of fluorescent chemical probe and design clears a bright path for precision medicine in disease diagnosis. Introduction of various types of probes like fluorescent probes or enzyme-substrate probes promote the options for non-invasive optical imaging in animal models, further advancements in probe based diagnosis and treatment

can also lead to a new dimension of PM[24]. The methods like auger effect of using low emission electron from an atom to damage cancer cells also provides a promising future scope in targeted radiotherapy[25]. The growth of PM is expected to bring in breakthrough in the treatment of epilepsy, if a particular epilepsy is shown due to the pathogenic variants in the gene coding ion-channels, instead of going through the traditional method of just finding whether the phenotype is due to loss or gain of function that encoded the mutant protein and then proceeding with the treatment and medications, Precision analysis and treatments are now being preferred as the mutations need not evidently prove the cause for patient's epilepsy and additional information like analyzing the segregation of variations might be necessary[26], [27]. Thus, the growth and development of PM in various fields of disease diagnosis and treatment is looked upon. As Sir William Gowers said: "Strive by every method you can think of to gain the utmost certainty attainable....whether the diagnosis of a disease or the action of a drug; or at least, relentlessly expose, and candidly admit to yourselves, the degree of uncertainty." [26]

Conclusion

In recent times, consumers reach out to the internet for the information on diseases. However, in the near future (i.e Precision medicine era), people would search for their genetic profiles in the internet rather than a generalised approach. Expanding beyond the traditional "Bench to Bedside" model would play an inevitable role in bridging the gaps in designing customized medications and narrow down not only the adverse effects on health resources but also the risks involved in traditional method of medication. Introducing the practice of using specific biomarkers as the means to analyse the outcomes and improvising methods like individual monitoring to ensure drug adherence is a proof that genomics will play a predominant role in transforming the healthcare community.

References

1. S. J. Aronson and H. L. Rehm, "Building the foundation for genomics in precision medicine," *Nature*, vol. 526, no. 7573. Nature Publishing Group, pp. 336–342, Oct. 14, 2015. doi: 10.1038/nature15816.
2. J. Bluett and A. Barton, "Precision Medicine in Rheumatoid Arthritis," *Rheumatic Disease Clinics of North America*, vol. 43, no. 3, pp. 377–387, Aug. 2017, doi: 10.1016/j.rdc.2017.04.008.
3. H. Collins, S. Calvo, K. Greenberg, L. Forman Neall, and S. Morrison, "Information Needs in the Precision Medicine Era: How Genetics Home Reference Can Help," *interactive Journal of Medical Research*, vol. 5, no. 2, p. e13, Apr. 2016, doi: 10.2196/ijmr.5199.
4. H. R. Warren et al., "Genome-wide association analysis identifies novel blood pressure loci and offers biological insights into cardiovascular risk," *Nature Genetics*, vol. 49, no. 3, pp. 403–415, Mar. 2017, doi: 10.1038/ng.3768.
5. E. Zeggini, A. L. Gloyn, A. C. Barton, and L. v. Wain, "Translational genomics and precision medicine: Moving from the lab to the clinic," *Science* (1979), vol. 365, no. 6460, pp. 1409–1413, Sep. 2019, doi: 10.1126/science.aax4588.

6. F. Carrasco-Ramiro, R. Peiró-Pastor, and B. Aguado, "Human genomics projects and precision medicine," *Gene Therapy*, vol. 24, no. 9. Nature Publishing Group, pp. 551–561, Sep. 01, 2017. doi: 10.1038/gt.2017.77.
7. M. Dixit, T. Doan, R. Kirschner, and N. Dixit, "Significant acute kidney injury due to non-steroidal antiinflammatory drugs: Inpatient setting," *Pharmaceuticals*, vol. 3, no. 4, pp. 1279–1285, 2010, doi: 10.3390/ph3041279.
8. L. R. Cardon and T. Harris, "Precision medicine, genomics and drug discovery," *Human Molecular Genetics*, vol. 25, no. R2. Oxford University Press, pp. R166–R172, Oct. 01, 2016. doi: 10.1093/hmg/ddw246.
9. P.-A. Gourraud et al., "Precision medicine in chronic disease management: The multiple sclerosis BioScreen," *Annals of Neurology*, vol. 76, no. 5, pp. 633–642, Nov. 2014, doi: 10.1002/ana.24282.
10. Z. Ahmed, S. Zeeshan, D. Mendhe, and X. Dong, "Human gene and disease associations for clinical-genomics and precision medicine research," *Clinical and Translational Medicine*, vol. 10, no. 1, pp. 297–318, Mar. 2020, doi: 10.1002/ctm2.28.
11. "Role of NGS in Precision medicine".
12. M. Gwinn et al., "Horizon scanning for new genomic tests," *Genetics in Medicine*, vol. 13, no. 2, pp. 161–165, Feb. 2011, doi: 10.1097/GIM.0b013e3182011661.
13. T. A. Beery, "Genetic and genomic testing in clinical practice: What you need to know," *Rehabilitation Nursing*, vol. 39, no. 2, pp. 70–75, Mar. 2014, doi: 10.1002/rnj.126.
14. J. Xu et al., "Translating cancer genomics into precision medicine with artificial intelligence: applications, challenges and future perspectives," *Human Genetics*, vol. 138, no. 2. Springer Verlag, pp. 109–124, Feb. 08, 2019. doi: 10.1007/s00439-019-01970-5.
15. N. I. Simonds et al., "Comparative effectiveness research in cancer genomics and precision medicine: Current landscape and future prospects," *Journal of the National Cancer Institute*, vol. 105, no. 13. pp. 929–936, Jul. 03, 2013. doi: 10.1093/jnci/djt108.
16. M. H. Harris et al., "Multicenter feasibility study of tumor molecular profiling to inform therapeutic decisions in advanced pediatric solid tumors," *JAMA Oncology*, vol. 2, no. 5, pp. 608–615, May 2016, doi: 10.1001/jamaoncol.2015.5689.
17. A. Śliwczyński and E. Orlewska, "Precision medicine for managing chronic diseases," *Polskie Archiwum Medycyny Wewnętrznej*, vol. 126, no. 9. *Medycyna Praktyczna*, pp. 681–687, 2016. doi: 10.20452/pamw.3503.
18. J. A. Leopold, B. A. Maron, and J. Loscalzo, "The application of big data to cardiovascular disease: Paths to precision medicine," *Journal of Clinical Investigation*, vol. 130, no. 1, pp. 29–38, Jan. 2020, doi: 10.1172/JCI129203.
19. A. Sivadas and V. Scaria, "Population-scale genomics—Enabling precision public health," 2019, pp. 119–161. doi: 10.1016/bs.adgen.2018.09.001.
20. M. J. Khoury et al., "From public health genomics to precision public health: A 20-year journey," *Genetics in Medicine*, vol. 20, no. 6. Nature Publishing Group, pp. 574–582, Jun. 01, 2018. doi: 10.1038/gim.2017.211.
21. Y. Xue et al., "Precision Medicine: What Challenges Are We Facing?," *Genomics, Proteomics and Bioinformatics*, vol. 14, no. 5. Beijing Genomics Institute, pp. 253–261, Oct. 01, 2016. doi: 10.1016/j.gpb.2016.10.001.

22. V. M. Yeh et al., "Can precision medicine actually help people like me? African American and Hispanic perspectives on the benefits and barriers of precision medicine," *Ethnicity and Disease*, vol. 30. Ethnicity and Disease, Inc., pp. 149–158, 2020. doi: 10.18865/ed.30.S1.149.
23. M. J. Khoury and K. E. Holt, "The impact of genomics on precision public health: beyond the pandemic," *Genome Medicine*, vol. 13, no. 1. BioMed Central Ltd, Dec. 01, 2021. doi: 10.1186/s13073-021-00886-y.
24. M. Garland, J. J. Yim, and M. Bogyo, "A Bright Future for Precision Medicine: Advances in Fluorescent Chemical Probe Design and Their Clinical Application," *Cell Chemical Biology*, vol. 23, no. 1. Elsevier Ltd, pp. 122–136, Jan. 21, 2016. doi: 10.1016/j.chembiol.2015.12.003.
25. G. Pirovano, T. C. Wilson, and T. Reiner, "Auger: The future of precision medicine," *Nuclear Medicine and Biology*, vol. 96–97, pp. 50–53, May 2021, doi: 10.1016/j.nucmedbio.2021.03.002.
26. S. M. Sisodiya, "Precision medicine and therapies of the future," *Epilepsia*, vol. 62, no. S2, pp. S90–S105, Mar. 2021, doi: 10.1111/epi.16539.
27. "Epilepsy in Multiple Sclerosis".