Precision Medicine and It's Ethical and Social Implications: Public Health and Gobal Persepctives

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Duquesne University
PRECISION MEDICINE AND ITS ETHICAL AND SOCIAL IMPLICATIONS: PUBLIC HEALTH AND GLOBAL PERSPECTIVES

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By

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PRECISION MEDICINE AND ITS ETHICAL AND SOCIAL IMPLICATIONS: PUBLIC HEALTH AND GLOBAL PERSPECTIVES

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ABSTRACT

PRECISION MEDICINE AND ITS ETHICAL AND SOCIAL IMPLICATIONS: PUBLIC HEALTH AND GLOBAL PERSPECTIVES

By
Evangel Sarwar
May 2019

Dissertation supervised by Professor Henk ten Have

Ever since President Obama's launch of the Precision Medicine Initiative (PMI) in 2015, precision medicine (PM) has been anticipated as the new paradigm for healthcare with the capacity to “empower patients, researchers, and providers to work together toward the development of individualized care,” through research, technologies, and policies (President Obama, 2015). Precision Medicine (PM), in the form of genomics, offers unprecedented promise of providing new tools for improving health and reducing the burden of diseases, not just for the U.S. - but also globally. According to World Health Organization, genomics research and precision medicine will play a major part in the prevention, diagnosis and management of many difficult or impossible to control diseases. Genomics research is progressing at an extraordinary speed and soon the application will be important for clinical application to benefit healthcare, in the U.S. and globally. In order for PM to be implemented in the everyday primary care setting,
many considerable ethical and social implications of PM for families, researchers and policymakers need to be addressed, that will ensure the protection and fair treatment of patients and participants. The medical impact of PM will be less than revolutionary if proper implementation and translation processes are not in place, taking into consideration the social and ethical implications, and addressing the challenges involving public trust and participation, and adequately preparing the healthcare workforce to administer or give advice on the applications of PM. Recent studies that compare trends in the genetic curricula in the US and Canadian medical schools have identified that there is a need for health provider education and competency rich in genomics and ethics. Despite the barriers, it is evident that the precision medicine initiative is at the forefront of clinical practice and will impact the quality, safety, and cost of healthcare.

The primary focus of this dissertation is to analyze the clinical significance and social and ethical implications of PM in healthcare in order to critically explore how PM can be ethically implemented in the time of genomics and personalized medicine.

The dissertation is elaborated in nine chapters, with Chapter One being the introduction. Chapter two will give an overview of PM as the new paradigm of healthcare. Chapter three will focus into genomics and pharmacogenomics and PM’s clinical significance. Chapter four will look at the relevance of PM in infectious and non-communicable diseases, while Chapter five will look at the relevance of PM in Public Health Genomics and Global Health Genomics. Chapter Six will elaborately focus on the social and ethical implications of integrating Precision Medicine into healthcare. Chapter Seven will expand into laying the ethical foundation for the implementation of PM in healthcare organizations by looking at the organizational ethical issues that may arise, and how healthcare organizations can prepare themselves to address these
challenges. Chapter Eight will look at the competency of healthcare workforce in the era of PM.

Lastly, Chapter Nine will present the concluding thoughts.
DEDICATION

To my loving husband, Sohel, and our two children, Iris and Rayan: thank you for the unconditional love and support.
ACKNOWLEDGEMENT

By the will of the Almighty - all work is begun, and completed.

Yesterday I was clever so I wanted to change the world. Today I am wise so I want to change myself. ~ Rumi

This dissertation was made possible with the help of many, who I owe much gratitude:

I would like to thank all of my Professors: Dr. ten Have, Dr. Magill and Dr. Gielen for giving me the education that has made me the Bioethicist that I am today.

I owe my deepest gratitude to my advisor, Dr. ten Have for believing in me and giving me the support and mentorship that has made it possible for me to finish writing my dissertation and to see this day.

I would like to thank the Center for Healthcare Ethics for making me feel comfortable and at home during my time as a student and as a graduate assistant at the Center.

I would also like to acknowledge with my sincere gratitude the support and love of my family: my husband, my children and my parents.
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<td>American Board of Medical Genetics and Genomics</td>
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<td>ACCME</td>
<td>African Collaborative Center for Microbiome and Genomics Research</td>
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<td>ADE</td>
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Chapter 1: Introduction

Background

Ever since President Obama's launch of the Precision Medicine Initiative (PMI) in 2015, precision medicine (PM) has been anticipated as the new paradigm for healthcare with the capacity to “empower patients, researchers, and providers to work together toward the development of individualized care,” through research, technologies, and policies. \(^1\) PM, in the form of genomics, offers an unprecedented promise of providing new tools for improving health and reducing the burden of diseases, not just for the U.S. - but also globally. The World Health Organization (WHO), in its 2002 report, “Genomics and World Health: Report of the Advisory Committee on Health Research”, stated that genomics research and precision medicine will play a major part in the prevention, diagnosis, and management of many diseases which have been difficult or impossible to control. According to the WHO (2002), genomics research is progressing at a remarkable speed, and soon the application will be important for the clinical application to benefit healthcare, in the U.S. and globally. The expectation is that PM will shift medical practices from being “reactive” treatment, to being “proactive” healthcare management that includes screening, early treatment, and prevention; and is expected to change the healthcare delivery system and the therapeutics business models, including roles of patients and physicians.

The National Institutes of Health (NIH) has defined Precision Medicine as: “an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person.” According to the NIH, PM is anticipated to replace the traditional "one-size-fits-all" approach - enabling physicians, and scientists “to predict more accurately which treatment and prevention strategies for a particular disease will work” effectively, and in which specific groups of people. \(^2\)
Although the term “Precision Medicine” is new, the NIH states that the concept has been used in healthcare for a while, in a relatively limited role, such as blood transfusion. As scholars like Colleen M McBride point out, that the idea of PM has been dramatically improved by the development of large-scale biologic databases (such as the human genome sequence), robust methods for characterizing patients (such as “proteomics, metabolomics, genomics”), and computational tools for analyzing large sets of data. McBride also adds that PM is being considered as the emerging, cutting-edge healthcare delivery service of the future for the targeted prevention and treatment of chronic, noncommunicable diseases such as cancer, cardiovascular diseases (CVDs), diabetes, and other infectious diseases; and in the control of pandemics. The approach has advanced so rapidly that PM is anticipated to become part of the regular healthcare services in the future. As scholars like Favalli et al. (2017) note, pharmacogenomics (PGx), a new area in PM that studies the effects of genes on the response to drugs – is an integral part of PM's approach to developing effective, safe medication and doses that will be tailored to the variations in a person's genes. Wang et al. (2016) is optimistic that the deep understanding of patient's genetic and genomic information will enable in disease prediction, leading to the development of effective prevention, diagnosis, and treatment - empowering doctors to select the most appropriate drug with the optimal dose for the individual, and with the least side effects from the medication.

The Precision Medicine Initiative (PMI), as announced by President Obama seeks to move the field of precision medicine more rapidly into clinical care. According to scholars like Shah et al. (2016), the PMI is structured to fund efforts in cancer genomics with longer-term goals of advancing PM to all areas of health and will be supported through the creation of a ‘1 million person cohort study’ across the United States. It has been anticipated by WHO (2002)
that the PMI will provide an unprecedented opportunity for researchers and clinicians in cardiovascular disease, and other conditions, to galvanize the collective resources and wisdom and unite to establish and disseminate the knowledge required to translate discoveries to reduce the global burden of such diseases. PM holds promise for improving many aspects of health and healthcare—individual, community, public health, and global health priorities. The World Health Organization reported that genomics research and PM would play a significant role in the management of noncommunicable illnesses, such as chronic illnesses, as well as in the control of infectious diseases and epidemics, which are among the top global public health burdens. Studies have noted that genetic information about immune response could inform vaccine development and distribution, and disease treatment strategies; and that ongoing research on vaccine use has already provided more details about the critical role of genetics in vaccine safety and efficacy. In order to facilitate the creative approaches of PM, the PMI will provide the base for the broad research program; and also help in the testing process, and help build the evidence-base needed to guide clinical practice.

However, a myriad of scholarly articles also notes that the PMI with its enormous potential and promises raise significant ethical and social issues, many of which arise from the need for technological infrastructures that are either in the early stages of development or have not yet been developed. Data security have been pointed out as a critical issue that results from health data on such a large number of people, and emphasis has been put on the need to find ways to protect participants’ privacy and the confidentiality of their health information. Participants will also need to be educated on the risks and benefits of participating in PM research in order to build trust and increase participation, which is a critical component for the PMI. Currently, there are fears regarding the potential for misuse of genetic information - giving
rise to issues of confidentiality, discrimination, stigmatization, access, and equity. Scholars fear that there will be a creation of a genetic underclass that may be denied medical insurance, due to genetic testing and screening. Some of the fears also reflect past misuses of genetic science in the interest of advancing a national or international eugenic agenda.

A rise of equity in the provision of health services to disadvantaged groups, in both economically developed and developing countries have been cited as concerns by many studies. Scholars like Aicardi et al. (2016), Prince (2015) and McClellan et al. (2013) all point out the many harmful and beneficial consequences related to genetic information, which often discloses information not only about the person who donated the data but also about the biologically related (or even unrelated) others, resulting in issues of incidental findings (IFs) and reporting of these, and the right to not know. Such findings create the need for an appropriate balance and relationship between rights and duties. Studies have also cited particular challenges concerning clinicians' ethical and professional responsibilities. Cost is also an issue that is anticipated with PM since new technology and infrastructures will cost a hefty amount; and so will the drugs - resulting in problems in access and reimbursement from private insurance companies - also raising fears of exacerbating health disparities.

Understanding the ethical, legal, and social implications (ELSIs) is essential to provide patients, families, and communities with competent, safe, adequate health care - and there has been a lot of discussion and research in favor of ELSI scholarship and research. Genomic research is advancing rapidly, and soon this approach is expected to be utilized in the benefiting of globally. The World Health Organization (2002) has stated that profound inequities exist in the health status and disease burden of populations in low, middle, and high-income countries – where low-to-middle income countries account for 85% of the world’s population and 92% of
the global burden of disease. Even though PM promises to address the global burden of health, questions arise about the equitability of such an approach. Opponents argue that PM will only increase the 10/90 gap. However, genome-related technologies are anticipated to contribute to improving global health equity. The WHO (2002) states that it is imperative that developing countries pick up in the race of genomics and work towards forming genomics research with a more comprehensive, integrated strategy to address the determinants of ill health specific to their needs.

Scholars like Hawkins and Doherty (2010) point out that addressing people's fears through informed public discourse is essential not only for benefiting people but also in building public trust to ensure public participation, which is the most critical component of PM. Scholars like Andrew Faucet also points that healthcare provider, have a social and professional responsibility to provide fairness and equity to patients, families, and communities. According to Roy C Ziegelstein (2015); genetics differ from medicine in that it involves families, rather than only individuals. Healthy patients are curious about the future risk of developing or transmitting a disorder. The patient's perceptions of risk and their attitude towards genetic testing depend on factors such as cultural beliefs, ethnicity and personal experiences of disease in the family. Accurate information for one family member usually relies on sharing of information from other family members, and the lack of ownership in genetic information becomes ethically problematic, which will be an added dilemma on primary providers. Education in ethics will be a significant contributor to address such dilemmas. Moreover, scholars like Laurie Badzek et al. emphasizes the need for healthcare professionals to bridge the gap between physician knowledge and training, and interpretation of genetic test results through reformed education curriculum in order to be ready for this technology. Recent studies that compare trends in the genetic
curricula in the US and Canadian medical schools have identified that there is a need for health provider education and competency rich in genomics and ethics. Despite the barriers, it is evident that the precision medicine initiative is at the forefront of clinical practice and will impact the quality, safety, and cost of health care. It is critical that the various ESLIs be taken into consideration and addressed to implement PM into the healthcare setting in the future successfully.

**Outline of the dissertation**

The dissertation will be elaborated in nine chapters – with Chapter 1 being the introduction. Chapter 2 will give an overview of PM as the new paradigm of healthcare - starting with the concept of PM and how PM came into the limelight with the Precision Medicine Initiative. Advances in PM have already led to improvements in therapies in certain cancers, and cystic fibrosis cited as a critical example by President Obama in his State of the Union Address (2015), where targeted therapies based on genetic mutations can treat the underlying cause of the disease. Genomic studies also hold promise for the identification of novel therapeutic targets that could fuel the development of new pharmacological agents for prevention and treatment of disease, through the involvement of public participation of about at least 1 million volunteers from around the United States. PM is expected to allow not only individual diseases to be correctly diagnosed, but also allow future conditions to be predicted in advance for each before any symptoms from patterns of genomic variation. Although, knowledge of genomics continues to expand rapidly, promising numerous opportunities for improving health; it will not be of any importance without public understanding and acceptance. Against this backdrop, Chapter 2 will highlight the importance of Biobanks and Big Data integration in the successful implementation of PM, and the need for building public trust and public participation.
Chapter 3 will focus on the clinical significance of PM in healthcare for individuals. Prevention of premature deaths, reduction of related health care costs, preventing complications and catastrophic events, and improving the detection, and treatment of non-communicable diseases, will be the major goals of PM in clinical medicine. Pharmacogenomics (PGx) is a significant area in PM, with the responsibility of maximizing the potential benefits and minimizing the potential risks of medications, especially adverse drug reactions (ADRs). There are plenty of genetic tests that can help people make informed decisions about prevention and treatment of diseases. However, many social and ethical challenges also arise. Many of the social and ethical challenges that have been identified appear due to lack of knowledge, fears, and concerns about the application. Understanding public attitudes are part of the solution in addressing these issues. Chapter 3 will focus into genomics and pharmacogenomics - its potential in preventing, treatment, and management of diseases through genetic tests and screenings, and prevention of adverse drug reactions, and other areas that PM has the potential to impact. It will also discuss the importance of Family Health History (FHH) and Family History (FH) as a tool in clinical settings in the era of PM. Chapter 3 will also identify and briefly talk about the social and ethical challenges that need to be overcome in order to realize the full potential of PM in healthcare.

Chapter 4 and Chapter 5 will expand this focus on clinical significance initiated in Chapter 3 to look at the relevance of PM in infectious and non-communicable diseases (chronic diseases and epidemics and pandemics); and relevance of PM in Public Health Genomics and Global Health Genomics, while tying into the ethical and social issues anticipated to arise. Chapter 4 will focus on PM's role in the management of Noncommunicable Diseases (NCDs) such as cancer, diabetes and cardiovascular diseases (CVDs), and in the area of pandemics, while
identifying challenges and ways to overcome them. Chapter 4 will also focus on the ethical, legal and social implications (ELSIs) that may arise due to PM’s potential for tailored interventions for specific groups of the populations for public health and clinical practice. Public health plays a significant role in ensuring the success of genomic medicine, because of its focus on the population that has the most vulnerable segments. Chapter 5 will look at health-related benefits and harms between individuals and the broader community, including threats to individual privacy and autonomy, and warranting just distribution of scarce resources. This Chapter will also look at the relevance of PM and the benefits of this technology from a global perspective.

Since PM and genomics research is a new technology, it requires high capital investment, which according to the WHO, creates the fear of its potential to the widening of disparity in global spending ("10/90 gap") on health research between the developed and developing countries. To make the promises of PM a reality, it will only be wise to anticipate and address the potential for inequitable access to healthcare occurring from using genetic information, and ensuring that the health of individuals in less privileged countries are also taken care of. Against this backdrop Chapter 5 looks at the ethical issues that may arise due to the high expenditure in development and integration of genomic and personalized medicine into healthcare, and address how this technology can be distributed, and be effectively achieved by the developing countries, without incurring a significant increase in the expenditure on their healthcare.

Critical challenges exist to precision medicine's implementation in healthcare, especially in knowledge transfer of the genomic information from research into clinical care, and achieving greater patient and clinician engagement and trust. To move the genomic agenda forward, there needs to be a broad collaboration between health professionals, researchers and public health practitioners, and a supportive-base of well-informed public, to address the complex issues of
translation, utility and equity. Large numbers of samples and data need to be collected and analyzed to investigate gene-gene, gene-disease and gene-environment interactions over time. Only collaborative efforts in population studies can achieve such depth. It must also be emphasized that public participation is also crucial in PM and this is driven by trust, a shared belief in the common good and thoughtful engagement. Keeping these in mind PM must be implemented in healthcare settings. Chapter 6 will elaborately focus on the ethical and social implications; challenges and needs; the legal and equity issues; and public attitudes toward the need for screening and other tools for PM to be implemented - while recommending the demands for better regulatory standards, policy considerations and collaboration and education amongst various vital entities.

Chapter 7 will expand into laying the ethical foundation for the implementation of PM in healthcare organizations (HCOs). With all the recent promises of utilizing individual’s genetic information to tailor medical treatment decisions to optimize patient care, PM also raises questions about the upcoming changes in healthcare organizations, costs, and ethical obligations of HCOs. Overcoming challenges in these areas will require straightforward strategies that can provide clear solutions, and can drive systemic and cultural changes. With a clear understanding of the set of challenges and the best strategies for overcoming those challenges, a roadmap for healthcare systems to advance the precision medicine paradigm can be built. The purpose of Chapter 7 is to look at the organizational ethical issues that may arise in the era of PM, and how HCOs can prepare themselves to be ready to address these challenges while delivering healthcare services that meet the organization’s mission equipped with the tools needed.

Chapter 8 looks at the competency of the healthcare workforce. PM is anticipated to provide potential tailored interventions for particular individuals, populations or subpopulations,
which raises ethical, legal and social implications (ELSIs). In order to address the ELSIs and utilize this translation of genomic information into practice, healthcare providers will need to have proper knowledge and training of genetic tests and how to interpret the results. Recent studies that compare trends in the genetic curricula in the US and Canadian medical schools have demonstrated inadequate incorporation of genomics material into the curriculum, showing the need to adequately prepare the healthcare workforce to incorporate genomics into regular practice in the era of PM. Chapter 8 looks at the current education and competency level of the healthcare professionals and recommends the need for education and competency rich in genomics and ethics for healthcare professionals in the era of PM. It proposes potential solutions for educators to keep pace with this rapid advancement of PM while looking at existing educational gaps and challenges.

Finally, Chapter 9 will have the concluding thoughts based on the various arguments, insights and analyses made throughout the different chapters in the dissertation to offer the summary of the various arguments made so far in order to foster a good understanding for the topic that includes both the benefits of such a technology and also the concerns that might arise with such advancements in technology in healthcare.
Chapter 2: The Emerging Field of Precision Medicine – The New Paradigm for Healthcare

2.1. Introduction

The newly emerging field of ‘precision medicine’ (PM) has been anticipated as the new paradigm for healthcare. The Precision Medicine Initiative (PMI) launched by President Barack Obama in 2015, aimed at ‘enabling PM as the new era of medicine that can bring patients, researchers and providers together toward the development of individualized care through research, technology, and policies.’ Although PM is held at high esteem as the innovative technology in healthcare – scholars like Armstrong et al. argue that implementing PM into routine clinical setting will need to address considerable challenges that include addressing ethical issues, and the need for public engagement, and participation in trust building through informed public discourse. This Chapter aims to look at PM as the new paradigm of healthcare, and some of the essential challenges that need to be addressed to realize its potential; focusing on the imminent need of public education in developing trust and partnership. The Chapter starts with the concept of precision medicine (PM), and the Precision Medicine Initiative (PMI) created to bring this concept to reality.

2.1.1. Concept of Precision Medicine (PM)

Precision medicine, defined as an evidence-based approach, uses innovative tools and biological and data science to customize disease prevention, detection, and treatment; and improve the effectiveness and quality of patient care. According to Fradkin et al., PM aims to move away from the current "one-size-fits-all" treatment that is based for the average patient and does not work for all - to tailor treatment toward the individual, based on the individual’s variability in genes, environment, and lifestyle. The United States, along with countries including Canada, the United Kingdom, and Estonia is working towards a precision medicine
priority. Although research and clinical care considering genomic and other individual-level differences are not new, this broad research program, as Shah et al. notes, creates the opportunity to utilize technological advances in the development of new clinical approaches and also test them. All of these groups of goals united into the PMI will lead to the paradigm shift that the US government and the scientific community are envisioning for the future healthcare delivery. It has been argued that achievement of the broader reaching goals of the PMI will likely have significant implications across all medical disciplines.

The National Institutes of Health (NIH) also affirms that ‘Precision Medicine’ (PM) is an emerging approach for disease treatment and prevention that will allow doctors and researchers to predict more accurately the treatment and prevention strategies specifically for groups of people. PM’s goal is to focus on more specific disease treatment and prevention strategies, taking into consideration genetic variations, in contrast to the "one-size-fits-all" approach. It is evident from the various studies that PM requires large-scale biological samples, and extensive collaboration between multiple actors, to facilitate the collection and sharing of data. The anticipation, according to Wang et al., is that PM will make more effective prevention, diagnosis, and treatment, by developing a “deep understanding” of patients' genetic and genomic information – making it easier for doctors to select sensitive drugs, optimal dose and time for medication usage, and the least side effect.

As scholars from Genetics Home Reference highlight, the idea of precision medicine has always existed, however, the increasing cost of drug development led to the necessitation of newer innovative healthcare models that would be faster and cheaper. The slow drug development process, with the small amount of medications that actually worked for people, demanded for innovative technology for the development of efficacious drugs. As the scholars
argue, the discovery of genetic variants in the prevention, treatment and management of diseases – including better targeted medication with least amount of side effects was indeed a very appealing concept.  

Although the concept of PM is not new, the term ‘precision medicine’ as highlighted by the scholars is new, and researchers hope this approach will preferably expand into all areas of healthcare soon.

Godman et al. noted that multiple definitions has been assigned to PM, including ‘personalized medicine’ (commonly used in the past), ‘genomic medicine’ and ‘stratified medicine’ – essentially all of which include targeting of diagnostic or treatment approaches to improve the future care of patients.  

The ‘precision medicine’ term has recently become preferred over personalized medicine to avoid implying that novel treatments will be designed for each person. Rather, David J. Duffy highlighted that ‘precision medicine’ would be an approach focused on classifying individuals into subpopulations, with different susceptibility to disease.  

Although people still use the two terms ‘personalized medicine' and ‘precision medicine' interchangeably, there were always concerns that the word ‘personalized medicine' could be misinterpreted to apply for individuals only (per National Research Council). The National Research Council prefers the term ‘precision’ because of its focus on identifying approaches that are effective for patients based on their “genetic, environmental, and lifestyle factors.”  

Clayton Christensen from Harvard Business School coined the term ‘precision medicine’ and used it in his book, The Innovator’s Prescription (published in 2009), to describe how molecular diagnostics can allow physicians in precisely identifying the cause of a disease. The US National Research Council’s report, "Toward precision medicine, developing a framework for creating a new taxonomy of human disease," enabled the term to gain wider
acceptance in 2011. The next section looks at the creation of the Precision Medicine Initiative (PMI) and its goals.

2.1.2. Precision Medicine Initiative (PMI)

In 2015, President Obama launched the Precision Medicine Initiative (PMI) that proposed to implement several health activities including health research with one million volunteers. The two main components of the PMI are: a near-term focus and a longer-term focus. The near-term focus aimed at cancer, which was the most obvious choice; and the later aimed at generating knowledge to target the whole range of health and other conditions. As Francis S. Collins points out that we have both the components within our reach today through advanced research in molecular biology, genomics, and bioinformatics. This initiative also taps into other trends such as social media and mobile devices that are used by Americans in their persistent desire to be active partners in healthcare research, as noted by Collins. Collins adds that PMI also entails pursuing greater knowledge for better understanding and assessment of disease risk, disease mechanism, and prediction of therapy, with the goal of expanding PM into a myriad aspect of health and healthcare.

Per NIH, PMI’s significant components involve building a national research cohort of 1 million U.S. volunteers that “will reflect the broad diversity of the US population,” to provide the medical and other health-related data. Fradkin et al. note that the PMI will pioneer a new model of patient-powered research, with the promises to accelerate biomedical discoveries; and new tools, knowledge, and therapies, for clinicians to select the best treatment for the individual patient. They note that the NIH’s goal, by the end of 2016, was to enroll at a minimum 79,000 people; and by the end of 2019, the goal was to have at least 1 million people enrolled as volunteers. To eliminate disparities, Fradkin et al. also added that the NIH is also working
together with the Health Resources and Services Administration (HRSA) to begin collaboration with Federally Qualified Health Centers, with the goal of identifying approaches that will bring underserved populations into the Cohort Program - particularly those historically underrepresented in biomedical research. As studies suggest, the PMI can leverage these advances in genomics and the emerging technologies, while ensuring privacy, and equity, only through collaborative public and private efforts, with the purpose of generating information for the development of novel therapies and approaches to treat and prevent diseases only.

Although healthcare providers and patients in general, endorse the concept of PM, the practice of PM is currently not in routine use for disease management. President Obama’s initiative will hopefully accelerate the pace of these efforts, test these concepts, produce the necessary scientific evidence, and support implementation for PM in healthcare settings, across different diseases. Patient privacy has been emphasized repeatedly, and with that in mind the national cohort of volunteers will support the overall goals by initiating the foundation of a more open and responsible data sharing, that also puts patient participation at the center of the initiative. The initiative, as observed by Shah et al., will allow participants to be in control of the utilization and sharing of the information in research, with participants having access to their data for better decision-making about their health, which is contrary to other research cohorts. The next section looks at how PM works.

2.2. How PM works?

Although the concept of PM is not new, scholars like Samantha A. Adams and Carolyn Petersen note that the development of large-scale databases, the methods used to categorize or stratify patients, and the tools used for analyzing the data have all lead to PM’s enhanced opportunities for its widespread use in practice. PM relies heavily on genomic sequencing,
which is technically big data - built on information technologies and databases.\textsuperscript{24} Data in genomics are “representations” of an individual’s DNA, as pointed by Frizzo-Baker et al.\textsuperscript{25} Biobanks - or biorepositories - are collections of biological specimens and associated health data used for research purposes. Biobanks are valuable sources of data for PM, with the type and amount of specimen varying with the object, and scope of the biobank.\textsuperscript{26} According to scholars like Schwab et al. and Richard Tutton, the widespread use of biobanks in research - especially population-based biobanks - has only blossomed in the past two decades. Population-based biobanks were designed for analysis into genetic, environmental and lifestyle factors associated with common, complex diseases or the genetic basis of drug response.\textsuperscript{27, 28} The next two sections give a brief description of what biobanks are, such as the extent of their use, organization, and quality.

\textbf{2.2.1. Biobanks in PM}

Human biospecimens contain genetic material that can be used to analyze gene variations associated with human diseases and have become enormously valuable for medical researchers. As pointed by Karen J. Maschke, researchers can develop new diagnostic tests and targeted treatments for specific conditions, and investigate how genes interact with environmental factors by analyzing genes, opening up ways to treatments that are tailored to a person's genetic makeup – which is the approach used in PM.\textsuperscript{29} J.E. Olsen et al., states that biobanks are essentially, repositories that house collections of human biological material that comes in many different forms - depending on the type of stored samples, and the “medical-scientific” domain in which they are collected.\textsuperscript{30} Eric M. Meslin & Ibrahim Garba also note that PM requires large scales of research on genetics and “thousands of human studies,” to understand the influence of genetic variation on human health and disease.\textsuperscript{31} Biobanks are an important step towards the
improvement and development of PM and can provide critical research and infrastructure support. Gail H. Javitt notes that the collection and analysis of data available on health and disease - promise to enhance the quality and efficacy of healthcare, and to enhance the quality and longevity of life. The access to biospecimens, provided by human biobanks, has increased over the past decade both in the United States and internationally and, as noted by Javitt, is an essential component in the progress of PM.32

Biobanks, bio-repositories or tissue banks - as they are called - have been acknowledged as valuable tools in bio-molecular research, with the potential to providing improved techniques for predicting individual susceptibility to particular illnesses, as well as providing more targeted and innovative ways to treat many diseases. These repositories, according to Robin Bunton and Lesley Jones, seek to integrate collections of biospecimens with corresponding population data, such as genetic profiles, medical histories, and lifestyle information; and offer opportunities for better understanding of common, complex diseases - such as heart disease and cancers.33 Moreover, Bunton and Jones state that the type of specimen and amount of clinical information stored by biobanks depends on the purpose and scope of the biobank, and ultimately affect its shape. They add that biobanks can range from collections of specimens from a large number of individuals in different states of health to focused specimen banks that collect specific samples and data from individuals with a particular disease or disorder.34

Scholars like Michaela Mayrhofer portray biobanks as an organized collection of biological samples and associated data.35 Although biobanks have existed forever, they gained prominence only recently when some countries and health providers initiated large population-based studies to facilitate PM. The practices of collecting samples differ widely from institution to institution, and the coordination between different biobanks also varies. Herbert Gottweis and
Alan Petersen note that most of the biological specimens stored in biobanks occur as part of a medical intervention; during which tissues or fluids are already being sampled for diagnostic or treatment purposes - where patients agree to biobank these specimens as part of the surgical consent process. In addition to samples obtained through routine medical procedures, Schwab et al. add that biological specimens may also be obtained from individuals who consent either to participate in a research study or to donate to a biobank. They also note that many samples are gathered using procedures such as skin, swabs, oral swabs, that involve negligible physical risk. Samples once collected are preserved in biobanks, and an electronic coding of the sample's genome is stored (probably forever).

Berthold Huppertz et al. note that specimens stored in biobanks require linking to pertinent medical data to be of value in clinical research; and are most often stored in a way that relates them directly or indirectly to identifiable personal health information - like diagnoses, prognosis, and treatments. Amy Fletcher notes that advances in information technology have enabled scientists and clinicians with a new and powerful set of research tools that directly link tissue, fluid, microbiome, and genetic samples with large compilations of medical data. As Fletcher points out, biobanks gain tangible social and economic value when data they contain potentially translate into progress toward PM. To provide the basis for the ranges and frequencies of expression used in the translation of the stored data sample most ‘omics' data depend on trusted, secure access to these collections. Richard Tutton notes that biobanks seek to gain legitimacy in the form of financial investment from the governmental and charitable sectors, through the willingness of individuals to volunteer their biological samples, medical records, and other personal data. Scholars like Bernice S. Elger and Arthur L.Caplan explain how data is utilized in biobanks. They state that biobanks utilize various data management
techniques for associating information about the donor and the donor's medical history or “disassociating the sample” from information about the donor. Samples may be stored as “anonymous, unlinked anonymized, linked anonymized, coded (de-identified), or identified samples.” Anonymized samples are those that are “stripped of the information” that would allow possible identification of donor. When samples are “delinked, the stripping is irreversible” – Elger & Caplan point out that there is no way to relink the sample and/or information to the donor. 42

According to scholars like Edward S. Dove, biobanks are a critical emerging research infrastructure, mainly because resources comprising biospecimens and data from many participants are viewed as particularly promising drivers of PM. 43 Huppertz et al. further describes biobanks as belonging to three categories: 1) Population-based biobanks that obtain biomarkers of susceptibility and population identity. 2) Disease-oriented biobanks that collect biomarkers of exposure, used for epidemiological purposes by using a substantial number of samples, following a healthy exposed cohort/case-control design. 3) General Biobanks, which are also disease-oriented (e.g., tumor banks), usually associated to clinical data, and sometimes to clinical trials, where it is essential that the amount of clinical data linked to the sample determine the availability and biological value of the sample. 44

Biobanks vary considerably in the data they store, the organization of information, and access to information. According to Scott et al., DNA, RNA, tissues, tumors, are all example of samples stored in biobanks. 45 Biobanks also differ in their organization and can serve as part of a value chain, moving samples from primary sources to researchers. Alternatively, storage schemes depend on the types, combinations, and volumes of stored samples and data, and the technical requirements for storage and access. Fabricio F. Costa moreover add that geography
plays a role in the way samples are exchanged, and also the way the infrastructure is developed for managing and maintaining the bank, and the recovery strategies in the event of disasters. They also state that the organization and access of biobanks dictates the conditions of privacy (such as descriptors of source individuals), procedures for anonymizing data, and the regulatory environment.\textsuperscript{46}

Publicly funded biobanks set up to promote the public interest, have expanded across the globe in recent years. Research suggests that biobanks exist on every continent, and enable large-scale genomic analyses, as well as the validation of findings through samples of large cohorts; thereby, promoting translational science and PM. Biobanks also advance genomic research in various other ways for the betterment of society. Researchers can begin to develop meaningful answers only by linking data from multiple resources. Huppertz et al. add that although the costs of whole-genome sequencing (WGS) are increasingly declining, it is critical to have reliable data to foster public trust - and clinically reliable data will be the key to drive this field past research to clinical utility successfully.\textsuperscript{47}

Huppertz et al. recommend the collaboration between academic, nonprofit and managed care researchers, stating that this will produce better progress in PM. Linking biological data to electronic medical records (EMR) is the essential role that biobanks play in the transition of precision medicine. However, biobanks face many challenges in identifying meaningful links between the many factors. Pharmaceutical and diagnostics researchers should be involved in the biomarker studies to develop better screening and diagnostic approaches to providing the data. As Huppertz et al. point out that the data shared must be useful to clinicians and integrated into the healthcare system for PM to work. However, Huppertz et al. also note that data sharing complicates the obligations and expectations of all stakeholders, and therefore, ensuring that the
data is reliable is crucial for biobank collaboration, especially for fostering public trust in biobanks.\textsuperscript{48} The next section talks about big data and data integration.

\subsection*{2.2.2. Big Data and Data Integration}

According to Frizzo-Barker et al., data mining is the process that discovers the patterns and the meanings from the large datasets - that involves gathering different types of data from users and consumers, with or (sometimes) without consents - and translates this information to achieve different organizational and institutional goals.\textsuperscript{49} According to scholars like Marinka Twilt, cancer research is one field where PM through pharmacogenomics (PGx) is expanding rapidly. However, the scholar adds that other chronic diseases, such as diabetes and neurodegenerative diseases are not further behind in their research initiatives.\textsuperscript{50}

According to Stoeklé et al., the practice and development of PM require the four essential elements connecting patients and doctors: “biobanks, databases, bioinformatics platforms, and genomic platforms.” Medicine, mainly used in cancer treatment and interventions, require large amounts of data, which are primarily electronic.\textsuperscript{51} The success of PM relies heavily on biobanks - and recruitment of participants across all age, sex, and racial groups have become a major goal of researchers, governments, private corporations, and advocacy groups.\textsuperscript{52} As highlighted by the \textit{Precision Medicine Initiative (PMI) Working Group Report to the Advisory Committee to the Director}, biobanking is essentially the collection of biological specimens - such as (but not limited to) DNA, RNA, plasma, and also blood specimens from participants - is essential to the mission of the PMI.\textsuperscript{53} The \textit{Report} emphasizes the need for a large volume of accurate data, stating that it will be critical for the PMI’s cohort mission to have a large number of participants.\textsuperscript{54}
The *PMI Working Group Report* also point out challenges that are related to insurers and payers and the data that will be derived from the EHRs, stating that there will be a need to address these issues given the anticipated large number of participants from different organizations with EHR systems. The *Report* emphasizes in need for proper technology, data security and organizational policies to address the anticipated challenges, which they suspect may also increase given the number of organizations that will be involved in the data collection and translation process. In order to address these challenges, the *Report* highlights the need for the establishment of a central biorepository early in the formation of the PMI cohort. According to the *Report*, the scope of the PMI biobank would cover all aspects, from specimen collection to analysis, as well as translation and communication between the recruitment centers, and approved vendors with the purpose of establishing “in-house high-throughput analysis platforms.” Moreover, the *Report* encourages establishing procedures that will guide in the maintenance of the accuracy of the specimen coding and linking, utilizing Clinical Laboratory Improvement Amendments (CLIA) standards. The *Report* also emphasizes the need for the PMI biobank to maintain security at all times.

Data sharing has been emphasized as the key element to realize the potential of PM. However, opponents have voiced concerns over sharing of data due to issues of ownership, proprietary knowledge, and commercialization. As Stevens Hallam notes, the issues were mostly related to technical problems due to the lack of infrastructure capabilities to meet the sizeable, growing volume of sequence data produced by genome projects. However, Hallam adds that bringing data into a *standard and consistent format* for sharing, and collaboration through data sharing of different kinds of information could mitigate these issues. Although the EHR data have been argued as beneficial for clinical and genomic research associated with
diseases, and drug response; the Report however, points out that the issues mentioned earlier must be addressed in order for the EHR data to be useable.\(^6^2\)

A fundamental truth that has been highlighted by the PMI Working Group Report is about the issues of incompatible formats currently used by the EHR systems that use no specific standard naming and coding conventions. The Report explains that this creates for additional steps to normalize the data, and therefore data curation process is essential to maintain the heterogeneity of the data quality. The Report recommends knowledge of local conventions and coding to ensure the proper flow of data.\(^6^3\) The PMI Report further points out the technical and policy challenges that exist in aggregating the narrative text present in clinical EHRs from clinical observations, that has the potential to reveal participant identity inadvertently, and computational methods that are not in place to ensure anonymity when applied to unstructured data sources. Ongoing collaboration between healthcare provider organizations (HPOs), have been highlighted in the Report, to ensure with data security, quality and address any questions that may arise.\(^6^4\) Biorepositories and data sharing raise ethical challenges and concerns and needs to be addressed. These issues will be discussed further later on in a different chapter.

The trend towards PM has resulted in an explosion in the amount of generated biomedical datasets – in particular, ‘omics' data (e.g., from genomics, proteomics, microbiomics).\(^6^5\) According to Edward S. Dove, validation requires analyses of large numbers of familial cases and controls, ideally from multiple populations; hence, international collaboration is a requirement for progress of PM. Dove adds that ‘unduly’ restricting data sharing across national borders or the matching of biospecimens with medical registries, and patient records limit the possibility of validating biological findings in larger cohorts. The results are less powerful, diminished medical breakthroughs, and lack of tangible improvements in healthcare.\(^6^6\) There are
challenges with the collaboration of different biobanks. As scholars like F Martin-Sanchez & K. Verspoor point out, success depends on the quality of specimens and data used to identify or validate biomarkers, but a lack of quality control for samples and data is only distorting the scientific data since flawed information will only take longer to sort. Because data linkage and sharing is an integral part of integrating disparate data sources in order to enable biomedical research and is pivotal to the advances in chronic diseases and infectious disease surveillance – they add that it is critical to use standards in Big Data sharing in genomics. The next section looks at the challenges and ethical and social issues that are associated with biobanks, and PM.

2.3. Challenges & Ethical and Social Considerations

The translation of genomics in big data technologies from research labs to the clinical setting can increase the risk to individual privacy, while being a benefit to PM. Addressing social and ethical considerations is crucial to adopt PM in regular clinical settings. As Chow-White et al. point out that there is a need to better address issues such as risks of re-identification, informational harms, and data security vulnerabilities in the clinical environment - to reconcile the unpredictable pathway of research and practice in the networked information society. According to many scholars, the increased use of genome-wide association studies (GWAS), and the increased ability to share data in PM leads to new issues of consent, feedback of results, privacy, and the governance of research. The next section looks at the ethical and social issues that are frequently raised in biobanking and genomics - such as, challenges in the areas of biobanking and informed consent, privacy, and confidentiality, genetic discrimination and equity.
2.3.1. Ethical and Social Considerations

**Issues with informed consent** - Biobanks contain both samples and data resulting in the legal and ethical controversy that relates to privacy and informed consent. As Ma’n H. Zawati point out, the expansive collection of samples in population biobanks that looks at sample data collected on a large population scale, and over an extended period makes it challenging to inform participants as to the use of their samples as resources for future research in health and genomics. Moreover, scholars like Stoeklé et al., point out that although population biobanks are limited regarding what information they can provide to research participants during the consent process, broad consent can be detrimental, since informed consent means more than a simple communication form between the different entities involved. With the increasing numbers of retrospective cancer studies, they add there is a need to consider the kind of informed consent, not just the contents, that should be provided at all academic medical centers with close ties to care and research. After all, *the informed consent is an essential form of communication* between patients, clinicians, researchers, and industry. William Wei Lim et al. noted that although biospecimen research reported on consent and approval, they did not do it in a meaningful way, even though *they stress* that non-meaningful ethics reporting does not imply inadequate consent and approval processes. Yann et al. noticed that informed consent is increasingly challenging because of the sheer volume of information. Given that PM requires a significant amount of patient participation, giving patients more access to their data is both empowering and leads to more informed choices and better quality of consent. From research, it is evident that the *consent information* for PM is not possible to be given *all at once*, and has to be an ongoing process, which provides more time for researchers to translate information, as well as for patients to absorb the given information. One of the most pressing challenges found for
clinical genomics revolves around the process of gathering informed consent. Frizzo-Baker et al. point out that the Internet plays a significant role as a barrier to the development of PM due to increasing individual privacy risk and creating challenges in the management of patient health information. Despite these issues, most stakeholder discussions fail to address the role of the Internet and information technologies with patients.\textsuperscript{75}

**Privacy and confidentiality** – PM raises concern for potential consequences of privacy breaches. Even though the PMI includes focusing on responsible data sharing and privacy protection, there is little information on how to accomplish these goals.\textsuperscript{76} According to data from research, participants voiced high levels of privacy concerns over the privacy of genetic information that prevented them even from supporting or participating in genetic research. Participants were concerned about the access to data (i.e., insurance companies), and its protection.\textsuperscript{77} According to Holly et al., participants were concerned about privacy and its effect on the individual when it was a matter of the *common good*.\textsuperscript{78} Scholars like Maya Sabatello and Paul S. Appelbaum add that the issue of genomic privacy has generated considerable public debate since genetic information is uniquely sensitive and personal, as it may reveal attributes of individuals and family members that are beyond anyone’s control; and also because knowledge of individuals’ genetic disposition to disorders may lead to stigma and discrimination.\textsuperscript{79} Branković et al. adds that the protection of data from patients with serious infections is of particular importance due to the potential for discrimination which can result from current interpretation as well as from future research in genomic technologies.\textsuperscript{80} Other issues according to Sabatello and Applebaum are related to genomic data sharing by professionals, especially in the context of new informational technologies - resulting in intense debates about the benefits of optimized care versus the harms from risk of privacy breaches and misuses of genomic data.\textsuperscript{81}
The significance of data protection cannot be underestimated, especially in the handling of samples taken from individuals who are afflicted with serious infections, since genome-based information can lead to risks of stigmatization and discrimination.\textsuperscript{82} Even though scholars like Frizzo-barker et al. note that anonymization and informed consent are both treated with equal weight by the traditional bioethics model for privacy, it is however nearly impossible to outline and attain informed consent with clinical genomics data for numerous unforeseen reasons.\textsuperscript{83}

**Genetic discrimination and equity**- Yann et al. highlight that concerns related to genetic discrimination in PM leading to genetically at-risk individuals being excluded from critical socioeconomic goods and services have convinced policymakers of many countries to adopt broad legislative solutions to prevent anticipated abuses. However, they also point out that the actual extent and impact of genetic discrimination have never been established. The current U.S. legislative framework, Genetic Information Nondiscrimination Act (GINA), enacted in 2008, was designed to prohibit insurers and employers from discriminating based on genetic information. Yann et al. add that the Act includes prohibitions on denying coverage or charging higher premiums to a healthy individual based solely on genetic predisposition to a condition and similarly bars employers from using this information when making decisions about hiring, firing, and promotions.\textsuperscript{84} Nicholas Rose also points out that identifying how a population may react to a particular drug could also result in the denied access to treatment for an individual on the basis of probability of poor response, or risk for adverse effects (identified for similar genetic variants of that population), even if there were no other drugs available for the treatment. Probability is not a certainty, and someone excluded from even the slim chance of benefit may well feel injustice. On the other hand, Rose adds that the development of drugs whose efficacy is specific to particular population groups would only provide incentives to pharmaceutical companies with
lowering their costs in trials and investing in products with most valuable markets, but would not ensure incentives to the medical needs of those who suffer from more prevalent diseases; thus, creating a fear of a new kind of racial segmentation of medicine. Moreover, Rose highlights that the promise of personalization via PGx may be more problematic than its advocates often suggest.\textsuperscript{85}

As scholars like Samantha A. Adams and Carolyn Petersen noted, with the establishment of PM and the availability of diagnostic tools and treatments, equity is feared to be a significant issue at both the individual and population levels.\textsuperscript{86} Scholars are afraid that if the numbers of patients seeking precision based medicine increase with the right-to-try laws, equity may become a more significant problem than it currently is. They point that such legislation allows patients to request any compound included in Phase 1 testing directly from the manufacturer and will enable patients with higher socioeconomic status (such as higher education, insurance or greater personal wealth) be able to access these compounds more than patients with lower socioeconomic status. Adams and Petersen add that another pressing concern is the degree to which various groups of patients will benefit most from PM. Although PM is anticipated to focus on common diseases such as diabetes, this can potentially widen the gap between patients with prevalent diseases and other patients groups (such as rare diseases).\textsuperscript{87} Concerns about patient autonomy in PM have also become prominent, which will be discussed later in this chapter. The next section looks at issues of data harnessing, knowledge transfer and citizen trust.

2.3.2. Data Harnessing, Knowledge Transfer and Citizen Trust in Data Sharing

According to scholars like Ipek Demir and Madeleine J. Murtagh, the generation of large volumes of data, in combination with the medical data associated with the sample – also known as “big data”- opens new avenues in “personalized and stratified” medicine.\textsuperscript{88} However, at the
same time, this is also one of the major challenges of these technologies. Demir and Murtagh added that the data analysis has not been able to follow the speed of technological achievements, producing large data sets that cannot be analyzed properly, making it impossible to utilize the important information generated by biomarker identification and stratification of diseases. Biobanks provide a platform for knowledge creation, rather than themselves creating scientific knowledge. No single biobank can provide a sufficiently large sample - data from several biobanks must be shared. This need for data sharing per Demir and Murtagh further focuses on biobanking science, on the specific challenges of using potentially disparate data sources. The technical challenges of sharing data, with the stated goal of translating biobank science into diagnostic and therapeutic interventions, are significant and well recognized. 89

Differences in how to collect and store bio information can create problems when it comes to sharing data from across biobanks, as they incorporate different kinds and types of data, depending on the priorities and the population base of that biobank.90 As scholars like Herbert Gottweis, and Demir and Murtagh point out, these are thorny issues when it comes to sharing, and is usually because two biobanks may use the same variable, but the usability of the data depends on the way the variables were collected and recorded. They further add that in data sharing - taxonomical and conceptual disparities, different styles of processing and grouping samples and associated data, different categorization and recording techniques – raise comparison, adjudication, as well as data sharing problems. The scholars point out that there is also the added risk that many times, such differences go unrecognized and lead to the sharing of incommensurable data - and hence flawed science. One way out of this issue might be to prospectively standardize - develop and apply uniform rules and procedures that can govern data collection, storage, and recording across all the biobanks. 91,92
Even though standardization of specific rules/procedures may be desirable, Jennifer R Harris et al. suggest that it is not possible to impose identical rules and procedures across all biobanks for numerous reasons. First, it would be difficult to impose uniform rules within a given country, never mind globally. Second, biobanks differ in the biobank’s population sample and/or its focus or scope. Third, even during the lifetime of one biobank, Standard of Operations (SOPs) may change as new techniques of data collection come into use. Fourth, there is the problem of imposing rules retrospectively on existing biobanks, long after the data were originally collected. Demir and Murtagh also add that standardization can only be done prospectively. They stress that harmonization of operational procedures and adopting best practices in biobanking operational procedures is critical for the success of global biobanking. They state that harmonization is critical for two main objectives. First, it increases the amount of usable data and numbers of biospecimens to achieve the statistical power needed to detect effects underlying the disease etiology. Second, translational science will rely on fundamental biological data to (re)classify human disease based on causality and to identify relevant drug targets and biomarkers. Yann et al. also comments that harmonization is not an easy task; it is time consuming, resource intensive and requires very high levels of accuracy and consistency.

Aronson & Rehm thinks highly of PM as a ‘patient empowerment tool,’ and recommends PM as a patient-centered approach that could be advantageous in the clinical setting, and they believe will act as a catalyst in the shifting of the nature of the physician-patient relationship. However, they recommend more public engagement and new collaborating processes. As suggested by the PMI Report, improved decision-making based on access to more up-to-date, real-time knowledge/evaluation techniques, has the potential to healthcare costs by reducing unnecessary or ineffective care. Open data-sharing resources due to partnering of academic
medical centers with commercial activities, will be instrumental in reducing cost of genomic research and limiting the scope of conflict-of-interest problems, setting precedence for data sharing rather than keeping its propriety, ensuring that commercial relationships are based on open principles.\textsuperscript{97}

According to the \textit{PMI Report}, it will be important for the PMI cohort to enable a centralized and bidirectional, user friendly participant portal for information sharing. This would empower participants to participate in an informed and voluntary and ongoing manner, and would also provide PMI cohort with the volume of participants that it needs. The \textit{PMI Report} also recommends providing participants with adequate information, in a language that is easy to understand.\textsuperscript{98} As Mirnezami et al. note, building partnership and trust are one of the goals of the PMI cohort, which can be accomplished by allowing active discussions by healthcare communities and the public about the ways to build shared responsibilities for health knowledge. They think that this can be a good way to empower individuals, families, and communities to make informed decisions, which are helpful in overcoming the challenges of lack of communication, and lack of public trust.\textsuperscript{99} The \textit{PMI Report} also highlights the importance of successful participation engagement by viewing patients as central participants, with the power to shape and develop the research with the right opportunities and access in the PM community, instead of being perceived as subjects only.\textsuperscript{100} Moreover, the \textit{PMI Report} also emphasizes collaboration between organizations with the same goals to generate better knowledge about the Cohort and its goals, stating that this will be essential in keeping participants informed and motivated.\textsuperscript{101}

The alignment of incentives for both individuals and organizations will guide the success of building a PMI cohort data resource that will contribute to the greater community good of a
According to scholars like Francis S Collins and Harold Varmus, it was identified that participants believed that education in genomics would enable the public to better balance the anticipated benefits, limitations, and potential harms of genomic information. They believe this would minimize the current fears or misperceptions about genomics, and also lead to empowering individuals to be more informed and involved in their healthcare decisions. They also noted that education was critical since it would create more trust in PM and increase public participation, which is critical for PM. A. K Hawkins and K. O'Doherty also noted that patient resources that are accessible to healthcare consumers will be critical for people to make informed decision-making in the era of PM. These will provide the basic knowledge about genetics and how the genetic tests work. However, according to studies it was noted that a substantial portion of the population does not have this understanding. Therefore, it will be important for both clinicians and patients to have access to required trusted online resources that will provide easy to read/understand information about genetics, and their roles in diseases and PGx to promote informed decision-making and support patient engagement in PM. Scholars like Holly et al., further point out that governance mechanisms were also viewed necessary to address the complex issues inherent in biobank research in many ways that include, “ensuring accountability, providing oversight, enforcing rules and regulations, and ensuring public values, opinions and viewpoints were taken into account.” Additionally, appropriate biobank governance was also considered as a trustworthy framework to counter the shortcomings of the informed consent process - particularly as it pertains to unknown, future research on stored biospecimens. Educational campaigns, as well as informed consent documents related to genetics research, as pointed out by Ma'n H. Zawati - should explicitly state what safeguards will be in place to protect participant data, and also report the limitations of that protection. The
informational elements, noted by the scholars, should be tailored to the local context, taking into account data protection laws, as well as resident concerns.\textsuperscript{106} The next section looks at the recommendations that focus on developing partnerships that unite the expertise of researchers and clinicians with the goals and perspective of the participants to create a thriving PMI cohort.

2.4. Recommendations

Scholars like Ma'n H. Zawati notes that critical challenges, especially in knowledge transfer of the genomic information into clinical care and research exist to PM’s broad implementation in healthcare; which also affects achieving greater patient and clinician engagement and trust. To move the genomic agenda forward, the scholars recommend that there needs to be collaboration between enthusiastic health professionals, forward-thinking public health practitioners, and a supportive and well-informed public, to address the complex issues of equity, utility, and translation. Zawati further adds that large numbers of samples and data need to be collected and analyzed to investigate “gene-gene, gene-disease and gene-environment” interactions over time. However, in their opinion, this can be achieved in such breadth only through collaborative efforts in population studies.\textsuperscript{107} Scholars like Erik Parens also views public role as central in PM, which he states is driven by trust, shared belief in the common good and thoughtful engagement. It is critical that these are taken into careful consideration in the implementation of PM into healthcare settings.\textsuperscript{108} The next two sections look at addressing concerns about patient autonomy and building trust, which are critical in implementing PM into the healthcare setting.

2.4.1. Retaining Autonomy

The data generated for applications in PM raises concerns about patient autonomy and the trust connecting all - patients, clinicians, researchers and industry in real time. Even though
there are more research on PM, patients still remain less knowledgeable about PM and its applications, and this creates a fundamental ethical challenge that needs to be addressed before PM can be implemented. According to scholars like Jane Kaye et al., retaining autonomy is vital in the physician-patient communication and the decision-making process in PM, and informed consent and its conception are critical components in addressing the ethical issues related to participant abuse in research ethics and PM. Kaye et al. note that PM raises issues of abuse in the form of infringements of privacy and the misuse of information. They explain that the process of obtaining informed consent was partly meant to ensure that individuals were not coerced into decisions. They also add that information may have different meaning for different people, thereby affecting individuals differently.\textsuperscript{109} Zawati adds that PM is complex since the precise specifications of future use of data cannot be provided at the time of research initiation, and therefore, creates greater concern of (maybe not) “adequately” informing patients. Furthermore, traditional notion of informed consent focuses on the individual, which in genomics research, presents pressing issues also for the family, community, and population groups in addition to the individual.\textsuperscript{110}

While traditional autonomy strives to provide direct benefit to the patient, human genetic research aims at benefiting the future generations as well. As Zawati points out that although individual autonomy's sole focus is on the participant, population studies destabilize the balance created by the various stakeholders involved - with the ultimate goal of better health for the population, which in turn, increases public trust in these endeavors.\textsuperscript{111} According to scholars like Alessandro Blasimme and Effy Vayena, population biobanks are limited in what information they can divulge. They highlight that with such large volumes of data, usually involving more than 10,000 individual, it can be tiring or even impossible for these projects to re-consent
individuals every time a researcher's request for access is received. Therefore, they add that the nature of consent and its specificity are limiting in fields of innovative technology that generate vast amounts of non-interpretable data.\textsuperscript{112}

However, Blasimme and Vayena argue that PM not only promises to change our understanding of a disease and the way health care is delivered to patients - but also controls how research participants and patients are considered in its developmental process, and their entitlement of information in the treatment decision-making.\textsuperscript{113} They add that this initiates the stage for bioethical debates and public discussion about novel issues such as rights and interests of those who participate, and this leads to the trust building that is necessary for PM's cohort to take shape. They further emphasize that participants should be offered meaningful ways to become a part of the precision medicine community.\textsuperscript{114} Sabatello and Appelbaum also agree that participants should be offered options to become members of such a community and have access to those freedoms. They suggest offering a detailed description of the cohort’s governance structure and the opportunities that are associated with the cohort. They add that public participation will also help balance relations of power and control between research participants and scientific experts, and ultimately build public trust.\textsuperscript{115}

\textbf{2.4.2. Building Trust}

According to Stoeklé et al., PM faces a crucial ethical challenge in maintaining and improving the trust of patients, clinicians, researchers and industry in academic medical centers. Indeed, the Presidential PMI rests on an appeal for citizens’ sharing of genetic, environmental, and lifestyle data in exchange for partnership and engagement to further advance individual, community, and population health.\textsuperscript{116} Research suggests that engaging participants in the design and conduct of the PMI cohort can lead to increased public trust initiative.\textsuperscript{117} Kaufman et al.
suggest the need for appropriate modern digital communication networks to maintain the trust and to improve the organization and effectiveness of the system. They also add that there is an inherent need to reconsider the form and content of informed consent (IC) documents at all academic medical centers, and a dynamic and electronic informed consent (e-IC) need to be introduced.\textsuperscript{118} Kaufman et al. point out that participation informs people about the initiative. Information sharing will be critical for PMI, as it will not only foster trust but will create willingness within the people to participate.\textsuperscript{119} As Stoeklé et al. noted from a study conducted by NIH, participants were interested in "governance-related tasks," and they highlighted that it would be beneficial to give participants the feeling they were "equal partners" in the initiative. They also noted that participants trusted the NIH researchers with their data; however, they were not comfortable sharing it with international entities. Therefore, they suggest addressing the negative attitudes about sharing of data with participants and clarifying how sharing would benefit all.\textsuperscript{120}

The PMI Report highlights the importance of building and retaining trust through collaboration amongst researchers and the communities for the success of the PMI. According to the Report, studies has shown trust to be based on communication – leading researchers to believe that open and safe communication, anywhere, at any time would allow participants to trust the system and share their personal samples and data.\textsuperscript{121} Educational efforts and comprehensive safeguards put in place for the protection of participant data have been viewed as critical in building and maintaining trust. According to scholars these goals also form the basis for recommendations regarding data access.\textsuperscript{122} According to Joseph D. McInerney, education that prepares the public for a genetically based revolution in medicine will require two things: the central message should be about the variations and individuality; and increased educational
emphasis should be put on the nature of genes in species and population. Additionally, Hawkins and O'Doherty add that education should also prepare the public for the transformation of medicine based on genetic perceptions of diseases. They also add that deliberative democracy can be used to enhance informed and widely representative views of the public interests. They add that deliberative forums that allow bi-directional exchange of information can be influential communication between policymakers and the public. Holly et al. also agree that deliberative forums offer a possible solution of bringing together a diverse group of lay citizens in the effective formulation of recommendations for policymakers. This can greatly add to the issues of social and ethical implications of biobanks and create an opportunity for an informed debate.

Furthermore, Holly et al. highlight that literature reviews reveal that understanding the public perception about genetics and genomics research, public concerns, and public attitudes towards using genetic and genomic information in making health decisions is critical in the planning and provision of genetic services, and policy and ethical decision-making. They add that diverse community engagement methods such as Focus groups, surveys, and interviews can be instrumental to engage community stakeholders in PM research initiatives. In the era of PM, transparency and accountability will be vital to foster trust and participation in genetics research; in turn, it will also help provide information to general practitioners who are faced with increasing numbers of patients curious about their predisposition to illnesses. According to a survey, a large number of respondents responded positively to the use of genetic information in health-related decision-making, which is consistent with positive attitude toward the application of genetic advances. Kaufmann et al. highlight that although the aim of the PMI, launched by President Obama in 2015, was to speed up the implementation process of PM in all areas of
healthcare; the speed has not picked up yet. Kaufman et al. point out that by providing consumer-friendly educational resources to the public can speed up the implementation process by helping people understand PM’s approach in determining the genetic predispositions to diseases, and identification of disease risks; and how effective treatment (through PGx) are generated. 129

Conclusion

Scholars have defined PM as a predictive, preventive, personalized, and participatory healthcare service delivery model. 130 The national cohort study of PMI aims “to foster open, responsible data sharing, maintain participant privacy, and build on strong partnerships between researchers and participants,” as noted by André J Sheen. Through this initiative, participants will have access to findings from the research, as well as personal research results. 131 The medical impact of PM will be less than revolutionary if proper implementation and translation processes are not in place, and that involves public trust and participation, through education. 132 There are considerable challenges for families, researchers, and policymakers that need to be addressed in order to ensure the protection and fair treatment of patients and participants if PM is to be implemented in the primary care setting. In order for PM to be successful, addressing people's fears through informed public discourse is essential. Scholars like Hawkins and O'Doherty argue that public discourse that involves deliberative civic engagement to explore the public values, concerns, and interests underlying recommendations about biobank governance to achieve trust in biobanks through accountability, transparency, and control - is essential. 133 Genetic variation can have significant impact on patients’ response to different drugs, even causing serious side effects and death. 134 PGx gives the new definition to drug development, and selection of the drugs to the patient based on their genetic make-up, greatly reducing ADRs. 135 As scholars like Dua et al., and Beery & Smith highlight that the ultimate aim of PGx research
will be to provide the knowledge of individual variation in genes controlling drug dose, and drug response, to improve efficacy, to avoid toxicity, and treatment failures.\textsuperscript{136,137} The next Chapter looks at PGx in response and toxicity to drugs
Chapter 3: Clinical Significance of Precision Medicine – Genomics and Pharmacogenomics (PGx)

3.1. Introduction

Despite the advances made by modern medicine, life spans are still lower in the U.S. than comparable countries due to lack of access to care, unattainable cost containment for research, and development, and clinical use - especially for new technologies such as precision medicine (PM). The Agency for Health Care Research and Quality (AHRQ) made the observations that unsafe and ineffective drugs cause avoidable deaths; adverse reactions (ADRs) resulting in costly hospitalizations; and wastage resulting from discontinued medications. They also noted that the efficacy of prescribed medicine was around 50% to 60% for most common ailments and only 20% for cancer therapies - with ADRs resulting in more than 770,000 injuries and deaths each year, resulting in costs up to $5.6 million per hospital, depending on the size. According to Vogenberg et al., a report published in 2009 by the National Academy of Sciences emphasized the need to monitor and treat any malfunction according to the individual patient.¹ Scholars like He et al. are optimistic about the potential of PM, especially in improving the practice of medicine and its outcome, by increasing accuracy and efficiency of drugs through the use of Pharmacogenomics (PGx).² Brian Godman et al. also asserts that PGx studies are anticipated to tailor treatments based on the variation of individual's genetic variation, thereby effectively enhancing drug effectiveness, and reducing toxicity, and resulting in the improved management of conditions from prevention to treatment - depending on the availability of targeted therapies.³ However, Fradkin et al. adds that the lack of infrastructure and mechanisms for data collection, storage, and sharing will create impediments in the implementation of PM.⁴ Scholars have also pointed out that physicians would be critical players in the implementation process and eventual
success of PGx, and must be taken into the implementation equation. This Chapter looks at PM and the area of PGx, and its clinical significance; while looking at the essential challenges that include ethical and social challenges that need to be identified and addressed in order to realize its potential in the clinical realm fully.

3.1.1. Clinical Significance - Impact on Healthcare

According to Nicholas Rose, PM through the use of PGx is anticipated to potentially enable tailored treatment on the basis of genomics of an individual’s disease-pharmacogenomics, with greater accuracy and efficiency. Rose adds that it is expected to not only allow diseases to be correctly diagnosed, but also predict the correct disease in advance prior to symptoms, and also improve the efficiency of medication with the correct dosage, and prevent administration of drugs, which will be ineffective or cause toxicity, and ADRs - all based on the patterns of genetic variations. Although, PGx was initially focused at being, “personalized, predictive and preventive medicine,” that has however, shifted to disease susceptibility. As noted by David J. Duffy, advances in PM have already led to improvements in therapies in certain cancers and cystic fibrosis, as cited by President Obama, where targeted therapies based on genetic mutations now can treat the underlying cause of the disease. Duffy also adds that PGx holds the promise for the identification of novel therapeutic targets that could “fuel the development of new pharmacological agents” for the prevention and treatment of disease. Duffy insists that these extremely ambitious goals of PM may bring numerous rewards such as reducing the ever-increasing healthcare costs, and more importantly, improving the welfare of citizens and patient outcomes.

Cancer is a potential area of focus for PM. According to Raymond Bingham, BRCA testing for breast cancer has a large financial and public health impact due to its high cost, and
the high volume of tests ordered, as well as the cancer detection and prevention measures subsequently chosen by those tested. Breast and ovarian cancer remain among the most significant causes of morbidity and mortality among U.S. women; and have a dramatic impact on the quality of life for millions of patients, survivors, and their families. Bingham notes that roughly 5 to 10 percent of breast or ovarian cancers in the U.S. have a genetic, or hereditary, component. He highlights that the risk for hereditary breast and ovarian cancer (HBOC), based on family history, can be of high concern for any woman if cancer occurred in her birth mother or another female family member closely related by blood - such as a grandmother, aunt, or sister; if the diagnosis was made in the affected person before age 50; or if it occurred in a male family member. Bingham insists that the prevention and early detection of these cancers are highly desirable and can save lives. He is very optimistic that the advances made through HGP will make it possible to identify women with HBOC. According to Bingham, the highest lifetime breast and ovarian cancer risk known for these women: 50–80 % for breast cancer and 11–65 % for ovarian cancer; and these women are also more likely to develop cancers at younger ages compared with the general population.

Scholars like Elvira D'Andrea et al., note the options that are available for women with HBOC. Some of these options include managing essential and difficult decisions that are better/effective to start early in young adulthood, such as cancer screening, chemoprevention, and/or preventive surgeries. It has been demonstrated from research that early detection of BRCA1 and BRCA2 genes have resulted in effective cancer diagnosis and early detection, and increased overall cancer-specific survival. They point out that an estimated up to 1 million people in the U.S. carry a BRCA1 or BRCA2 gene (BRCA) mutation, and more than 100,000 people undergo BRCA testing annually, and moreover, BRCA testing is usually covered through
private insurances, making it available, and accessible.\textsuperscript{12} Karen Lisa Smith and Claudine Isaacs also note the clinical significance for genetic testing for common conditions (e.g., cancer) and their use in PM for several reasons: 1) BRCA testing is clinically proven, being used for more than 15 years; 2) there is evidence for its clinical utility, and 3) published guidelines are widely available for its appropriate use. They assert that such testing allows for early detection, thereby, often resulting in prevention, and treatment. However, Smith and Isaacs also note, despite the advances in BRCA testing, personalized cancer medicine due to its young age still needs more information regarding the management of \textit{BRCA} mutation-associated breast cancer; and this issue exists for other genetic tests which are being introduced into clinical care for a range of other health conditions.\textsuperscript{13}

PM is widely used in PGx to indicate the safety and efficacy of drugs for patients. However, the ultimate goal of PM as Duffy points out is the prevention, and control of infectious and chronic diseases, both nationally and globally. Duffy adds that PM approaches are being developed to improve the outcome and quality of life of patients with such conditions, both at the “disease-specific and the co-morbidity level.”\textsuperscript{14} Scholars like Rose points that the genomic information generated through genome sequencing technologies allows for the stratification of the population into groups with different probabilities of responding, to particular types of medication or developing an ADR. Rose is hopeful that this stratification will ensure efficacy, compliance, the accuracy of dosage; and thereby minimize ADRs, which will eliminate waste. Rose explains that the reality of PGx is misconstrued and is not about providing individually tailored drugs, but to utilize the information generated in the stratification of population into groups with different probabilities of responding to particular types of medications or developing ADRs.\textsuperscript{15}
Scholars like Semiz et al. are optimistic about the benefits of PGx in the improved treatment management of chronic diseases such as Type 2 diabetes mellitus (T2DM), and in the effective prescribing of oral antidiabetic drugs (OAD). T2DM is a known worldwide epidemic. Patients are afflicted with considerable health and economic burdens. Semiz et al. add that more than one drug is often used to treat T2DM patients that include OAD, and drugs to treat diabetic complications, such as “dyslipidemia and hypertension.” Per Semiz et al., significant pharmacogenetic evidence has demonstrated several variants related to “drug-metabolizing enzymes, drug transporters, drug target, and diabetes risk genes,” to be linked to inter-individual differences in the OAD therapeutic and side effects. PGx identification of drug-genotype interactions of the OAD treatment might have clinical implications soon resulting in the selection of more specific personalized therapy in T2DM. They note that although benefits are anticipated for patients with certain monogenic forms of diabetes, there is anticipation for individualized treatment options in the more common polygenic forms of diabetes as well. However, Semiz et al. add that epigenomic research will also be needed to address potential barriers to the translation of pharmacogenetic findings, in order to expand the scope of PGx towards optimized drug therapy.

According to Robert N. Schuck et al., PGx is also essential in the labeling of drugs, which provides clinicians with information about its safety and efficacy and aids in preventing ADRs, which is critical in influencing regulatory decision-making and clinical uptake of the resultant prescribing recommendations. These are incorporated into drug development programs and included in indication statements during the initial approval of many drug products. The scholars add that although many kinds of pharmacogenetic information have been included in drug labeling, the most important change has been the approval of targeted drug therapies for
genetic subsets, widely adopted in the oncology community. The advent of targeted therapies has been “lauded as a major medical breakthrough;” however, they add that research activity is increasing in other fields as well. ¹⁹ According to Johnson et al., clinical pharmacology is inclined in uncovering and using the information that causes the “interpatient variability” in drug response to benefit the patient. Although “pharmacogenetics” was coined in the 1950s, it was not until recently (past decade), that it was extensively used in research for discovering drug efficacy, toxicity and dosage based on the genetic variants. They also add that PGx research on cardiovascular drugs, although young, holds much potential and has already led to understanding of the metabolism and pharmacological mechanism of many commonly used cardiovascular drugs such as Warfarin. ²⁰ The next section looks more thoroughly at genomics and PGx.

3.1.2. Genomics and Pharmacogenomics (PGx)

Genomics is the foundation for PM, which aims to individualize care by understanding differences in genetics, lifestyle, and environment. ²¹ Substantial information demonstrates that individuals vary on a genetic basis in their response to drugs - and PGx is promising because of its potential to direct drug prescribing to increase safety and effectiveness. ²² According to scholars like Andrzej Śliwczynski and Ewa Orlewska, a growing number of drugs are present today whose efficacy is tied to the presence of one or more molecular alterations - especially used in oncology, with FDA-approved drugs targeting mutated genes. They note that off-label prescription of the drug targeting the alteration is possible whenever such actionable mutations unexpectedly occur. ²³ They also add that PM promises to accelerate the ability to recognize disease heterogeneity and create new distinctions using large numbers of measurements, to create prediction models in chronic diseases on large populations of patients. ²⁴ Additionally, scholars like Andrea Sboner and Olivier Elemento assert that PM strategies in chronic diseases,
such as diabetes and CVDs show that the addition of big datasets to the course of individually profiling diseases and patients will be the key to developing PM.\textsuperscript{25}

According to Dickmann and Ware, PM aims: “to offer the right treatment to the right person at the right dose, thus maximizing efficacy and minimizing toxicity for each individual patient.” They note that ‘pharmacogenetics’ and ‘pharmacogenomics’ are broad terms that tend to be used interchangeably, and there remains debate as to the most appropriate definition and use of each term. However, the aim of this Chapter is not to differentiate between the two terms, but rather highlight that the terms both refer to the ability of genetic-based testing, to give the correct drug at the correct dose to the correct patient, thus maximizing efficacy, and minimizing toxicity.\textsuperscript{26} Dickmann and Ware also add that the ultimate goal behind PGx approaches in drug discovery and development is to treat the appropriate classified group of patients “to maximize efficacy and minimize toxicity.” \textsuperscript{27}

As pointed by Zhi-Wei Zhou et al., PGx studies the effects of genetic factors on an individual's response to pharmacotherapy, especially to the risk of ADRs – which are a significant public health concern and cause considerable patient morbidity and mortality.\textsuperscript{28} Zhou et al. add that in the past 60 years, PGx has been applied to identify the genetic determinants of a drug’s effect to maximize drug efficacy, reduce and minimize the ADRs, and select responsive patients.\textsuperscript{29} Godman et al. also note that adverse drug event can be greatly increased by individual genetic variability, thereby reducing effectiveness of drugs and leading to poor quality care increasing costs. The scholars suggest that recognizing the complexity of the various biological systems involved in different diseases can help explain the high number of non-responders to certain drugs; adding that this increased knowledge can also impact drug development policies.\textsuperscript{30}
Genetic tests have the ability to identify the patients who would potentially benefit from the drug therapy of interest, as noted by scholars like Hiroyuki Morita and Issei Komuro. They add that adding PGx data to the variables for pre-specification in the clinical studies will allow more accurate comparisons of the responders and non-responders, and thus improve the quality of clinical studies. Additionally, Godman et al. observed that an estimated 20% to 95% of the variation in drug disposition is attributed to genomes, translating into differences in clinical outcomes including benefit and side-effects – resulting to the need for different dosing regimens. Even then they add that current treatment regimens still tend to use ‘general or average’ doses.

Godman et al. add that PGx, through the inclusion of the identification of host genetic factors such as biomarkers, that influence drug absorption, metabolism, and action at the receptor level, could reduce the trial size, as well as minimize the toxicity. They point out that the use of biomarkers with existing drugs has improved patient management, and can additionally increase the number of drugs that can be more rationally prescribed and dosed.

Scholars like Antonio Aceti looks at the potential of PM in infectious diseases and other noncommunicable diseases, and asserts that PM through PGx has great potential to revolutionize the prevention, diagnosis, and treatment of infectious diseases, and other noncommunicable diseases. Aceti highlights that antibiotic resistance has become a predominant challenge in the therapeutic management of infectious diseases, mainly due to the improper prescription and use of antimicrobials. The ability to determine the antimicrobial resistance of different pathogens using whole genome sequencing holds great promise. Mary S Hayney notes, through the use of comparative genomics (using bioinformatics and microarray technology), “virulence determinants, antimicrobial drug targets, vaccine targets and new markers for diagnostics” can be identified. Hayney adds that human genomics also assists in the informed disease management.
by adding to our understanding how individual genomic variation affects response to the pathogen, and to vaccine or drug used to prevent or treat infections. Hayney is optimistic that this new understanding of the genome of the pathogen and the human genome will likely yield multiple targets for drug development.36

Robert N. Schuck points out that genomics and PGx play a vital role in predicting response to therapy and vaccines, and ADRs. PGx testing strategies have been recognized as a valuable tool by the FDA, resulting in FDA to proactively incorporating PGx information into labeling of new and drugs already on the market. However, they add that despite the readily translated examples in routine clinical care, utilization of this information is still limited.37 Hayney add that PGx approaches to drug therapy have the potential to improve patient outcomes by allowing clinicians to preemptively adjust dosages or choose alternative agents based on the expected response associated with a given genotype, potentially resulting in greater effectiveness, or fewer adverse events, or both. They further add that much knowledge needs to be acquired and many obstacles overcome before the information can be translated into proper interventions.38 All in all, Hayney asserts that PM will offer multiple rapid diagnostic for identifying susceptibility patterns to infectious diseases over time that will provide clinicians with real-time, crucial clinical information that should greatly improve the prevention, treatment, and management of diseases - saving lives, improving the quality of life of infected patients, and reducing healthcare costs.39
3.2. Role of PGx in Toxicity and ADRS

Substantial studies show the potential of PGx in avoiding toxicity from use of drugs in patients, and greatly reducing ADRS. As noted by Aceti, serious ADRs classed as idiosyncratic reactions (IDRs), not directly related to drug concentration but may be due to an unusual patient phenotype, are a significant cause of death and serious illness in patients. Aceti also states that IDRs are an important cause of drug attrition in the pharmaceutical industry, both during drug development and after licensing. Daily asserts that PGx gives the new definition to drug development, and selection of the drugs to the patient based on their genetic make-up, greatly reducing ADRs. Moreover, J. Dua et al. insists that knowing the individual variation in genes controlling drug response would allow clinicians to personalize medicine and select the appropriate drug at the appropriate dose. Scholars like Theresa Alice Beery and Carolyn R. Smith also argue that the ultimate aim of PGx research is to provide information for PM, by providing accurate medicine with the appropriate dosage to the patient, to improve efficacy, to avoid toxicity, and treatment failures. They add that PGx research has the potential to a better understanding of “drug-drug response and drug-organism response.” The next section looks at PGx in response and toxicity to drugs.

3.2.1. Response and Toxicity to Drugs

Primary care is changing rapidly with the use of electronic medical records (EMRs), which according to Dua et al., is redefining the way we approach disease management by reducing risk and optimizing quality. With the advance of PM, a complete understanding of DNA sequence variation is needed to modulate drug response. Although traditional non-genetic factors, such as age, organ function, other medications, and disease status, can affect drug response - there is substantial evidence, according to Sonny Dandonna, that shows genetic
variations to play a causal role in the alteration of drug response and drug clearance - especially in “drug absorption, disposition, metabolism, and excretion, and drug action in patients.” 46

According to the WHO, people differ in their response to medication due to differences in genetic make-up that interferes in drug processing and metabolism, and results to a medicine's effectiveness and possible side effects. Therefore, Zhou et al. emphasizes, a better understanding of how the genetic variations work in drug response is necessary and can have important implications in the efficacy of drugs in patients. They add that the PGx research aims to investigate the association of inherited genetic variants with response to drug therapy, including drug efficacy or adverse effects, utilizing this search throughout the entire genome. 47

The Nuffield Council on Bioethics points out individuals varies significantly in their response to drugs due to genetic variations. They add that most drugs are effective in only 25%–60% of patients, making it a challenge to optimize a dosage regimen. According to a study it was noted that various genetic factors contribute approximately 20% – 95% to determine the interindividual variability in drug responses. PGx enables scientists to assess specific genetic variants that may be responsible for an individual's particular drug response by identifying the specific genetic loci involved. 48 Today, on an average, 30-60% of drugs work effectively in patients' illness. Chunmei Huang and Jose C. Florez argue that the application of PGx will bring the success of drugs to 100%. They add that in many cases of chronic diseases, patients were/are mistreated or misdiagnosed due to a lack of exact symptoms and medications. The scholars are hopeful that PGx will help with chronic disease diagnosis and treatment, and increase patient longevity. 49

Shabbir Ahmed et al. also argue in favor of PGx stating that PGx has been able to achieve great accomplishments in achieving PM, specifically in cost-effectiveness. They cite Single
Nucleotide Polymerase (SNP) screenings as an example of PGx, which allows pharmaceutical companies to exclude people who would not benefit/or be harmed from testing certain drugs in clinical trials; thereby, facilitating smaller, less expensive and safer clinical trials. They add this ability of excluding people who will not benefit, will increase both physician's confidence in prescribing drugs, and also the patient's confidence in taking the drug. This will in turn, make it cost-effective, safe and precise, and is estimated to eradicate the likelihood of any ADRs – reducing more or less 100,000 deaths, and two million hospitalizations in the United States every year. Ahmed et al. also add that PGx studies can be used at various stages of drug development, and can be used for stratification of patients based on genotype - resulting in a better selection of effective therapy and eliminating treatments from ADRS.

Another primary goal of clinical PGx according to Dua et al. is to establish “phenotype-genotype associations” through genetic tests that reveal genetic predispositions to disease and drug toxicity. They add that the practical purpose is to “identify patients who are drug responders and patients who are prone to drug toxicity.” They also add that this is a very challenging task due to the complexity of human genome and diseases, and only limited success has been achieved in recent years. Per Dua et al., genotyping in the area of CVDs may be applied to predict risk for drug toxicity, such as risk for myopathy with statins, with the possibility of its application “on a broader scale to choose the best combination of drugs to treat complex diseases, such as heart failure.” Currently, the scholars highlight that PGx data are being used to guide treatment in the clinical setting.

It is evident that PGx is increasingly influencing medicine and biomedical research in many areas, including clinical medicine, drug development, drug regulation, pharmacology, and toxicology. Dua et al. highlight that routine screening and prediction of drug response is
currently the focus of ongoing PGx research for the rapid determination and validation of individual genotype that would result in the prediction of drug response and avoidance of toxicity.\textsuperscript{56} Currently, there is an increasing demand for the application of PGx to predict unwanted ADRs associated with genetic variants in clinical practice. Scholars like Qiang Ma and Anthony Y. H. Lu add that there are a growing number of genetic variations “in genes encoding drug metabolizing enzymes (DMEs), drug transporters, and drug targets that have been identified” – that show an association with ADRs with varying strengths of evidence. However, they add that there are many challenges and hurdles along the way to fully understand, and elucidate the contribution of genetic variations to ADRs, and to translate it into clinical practice.\textsuperscript{57} The next section looks at ADRs.

\textbf{3.2.2. Adverse Drug Reactions (ADRS) and Costs}

According to Dr. Edgard, more than 2.4 million people suffer a serious adverse drug reaction, and more than 100,000 die every year in the United States alone. Johnson and Cavallari add that this is usually due to inappropriate drug or incorrect dosage or because of the person's genetic make-up which metabolizes medication to rendering it as ineffective, or deadly with side effects. The application of PGx allows for the best drug and dosage to be determined for the patient. They also add that many of the FDA-approved drug labels mention available genetic tests today; and FDA-approved genotyping kits can also be used to evaluate the metabolism of multiple medications.\textsuperscript{58} Steven R Kayser adds that the tests are, however, still not affordable for all - ranging from $400 to a couple of thousands, and aren't routinely covered by insurance.\textsuperscript{59} As Qiang Ma and Anthony Y. H. Lu note, ADRs are a significant concern in both clinical practice and the pharmaceutical industry that owes to substantial morbidity and mortality in patients. Data from PharmGKB, a web-based pharmacogenomics resource, have identified at least 244
pharmacogenes associated with ADRs of 176 clinically used drugs. Moreover, 28 genes with potential pharmacogenomic biomarkers associated with ADRs have been listed by FDA. The scholars assert that the availability and affordability of PGx testing tools is allowing PGx to be a feasible tool for the prediction, reduction, and minimization of ADRS in selected populations. 0.32% out of 6.7% of the hospitalized patients in the U.S. experience from fatal ADRs, ranking ADRs between the fourth and sixth leading causes of death.\textsuperscript{60}

An estimation of the annual cost for ADRs is over $136 billion. As Zhou et al. point out, multiple factors can cause ADRs, including drug co-administration, lifestyle, age, and diet. However, increasing evidence shows that “inter-individual” genetic differences are a significant contributing factor to ADRs. Zhou et al. note that genetic variations in drug-metabolizing enzymes (DMEs), drug transporters, and drug targets substantially contribute to the alteration of pharmacokinetics and pharmacodynamics. A lot of research has been done to understand these differences in order to find an association between these variations and ADRs. As the scholars point out, many genetic mutations that result in cancer have been found to have associations with ADRs. The drugs that can cause increased ADRs in patients with genetic mutations, as highlighted by the scholars, mainly include anticancer drugs, cardiovascular drugs and antipsychotic drugs (for the central nervous system).\textsuperscript{61}

According to Dr. Edgard, the FDA has listed at least 50 genes as clinical pharmacogenomic biomarkers that are significantly associated with “altered drug response, clearance, and/or risk” of ADRs of more than 145 drugs. While looking at chronic heart failure (HF), it was identified that the individual patient responses to HF pharmacotherapies are highly variable due to genetic variations. Even though pharmacogenomics has proven successful in other therapeutic areas, Dr. Edgard suggests more research is needed to prove the success of
pharmacogenomics on HF. Dr. Edgard also adds that HF pharmacogenetics associations may be race-specific, dose-specific, sex-specific, and drug-specific. According to Zhou et al., it is unethical to assign patients the ‘regular’ dose or even the medication if it is not even beneficial to the patient.

As noted by Zhou et al, and Jasmine A. Talameh and David E Lanfear, genetic variations in drug transporters are important factors in determining ADRs and drug response, since they lead to alteration in the activity and/or protein expression level causing altered drug response. Talameh and Lanfear note that about 50% of drugs interact with membrane receptors; therefore genetic variation will cause significant alterations in drug response. Talameh and Lanfear further add that applications of Genome-Wide Association Studies (GWAS) have increased the identification of genetic mutations associated with ADRs. Although this approach is still limited, many common and rare genetic mutations associated with ADRs have been identified. Many PGx tests have been approved so far which will minimize ADRs induced by genetic variations. However, the scholars add that there is still need for more clinical trials to validate the genetic variation-ADR association, and determine the cost-effectiveness and benefits of PGx in clinical therapy.

ADRs are common, associated with morbidity and mortality, and costly to healthcare systems worldwide. Caudle et al. point out, even though genetic variations are factors in predicting ADRs, there are other factors that can also affect drug responses such as the type of drug, the patient, and the disease. The scholars assert that genomic testing can be potential in diagnosing and monitoring those at risk in order to provide vital future improvements in the benefit-risk ratio of drugs. As Caudle et al. note, this genomic information if integrated can develop a comprehensive and integrated approach to better drug responses in patients in the era
Zhou et al. argue that it is imperative to prevent ADRs today, not only to reduce morbidity and mortality, but also to improve compliance with medications. They add that discontinuation of effective treatment due to ADRs is also detrimental either in the short-term or long-term. An example the scholars cite is cardiovascular medications – stating that withdrawal can increase the risk of cardiovascular events and death. They further highlight that an estimated 20-30% of ADRs can be prevented by using PGx testing – which is a pretty significant benefit associated with PGx.  

Even with the advancement of pharmacogenomics, patients still receive the same old-fashioned treatment, often leading to different drug responses and unexpected therapeutic outcomes. Zhou et al. point out that pharmacogenomic-guided personalized therapy can assist in maximizing drug efficacy, thereby, reducing the risk of ADRs according to the recommended clinical dosing guidelines which are a promising therapeutic approach with great clinical significance. They add that PGx brings with it a new set of promises as well as ethical concerns. The possibility of improved drug safety and efficacy and cheaper, faster, and smaller clinical trials would represent a big boon for the pharmaceutical industry and the public as a whole. However, ethical, legal and social concerns that arise due to lack of knowledge, fears and concerns about the application must also be addressed to facilitate the development of this new technology while minimizing negative social consequences.

3.3. Identifying and Addressing Challenges

Studies demonstrate that the rapid advances in PGx research will continue to lead to improvements in the pharmacologic management of disease processes. As is, most of the PGx drugs are already FDA-approved; therefore, adoption of PGx in the clinical setting is dependent on the implementation of the appropriate technical infrastructure. Scholars like Karczewski et al.
have pointed out, that PGx applications will likely be helpful to not only physicians in the clinical setting; but can also provide better drug development tools to pharmaceutical companies, and in the design of cheaper and faster trials.\(^\text{72}\) However, advancements in technology will also present ethical and social concerns that will need to be addressed.\(^\text{73}\) It will be critical to identify and address the anticipated challenges in order to usher in the era of personalized drug treatment in PM. This section looks at the ethical and social concerns and other challenges that yet remain in the implementation of the PGx from the *bench to bedside*.

### 3.3.1. Social and Ethical Concerns and Other Challenges

As Andrea Maluso demonstrates, the use of PGx testing has implications that are similar to genetic testing, especially in regards to PGx surrounding privacy, and possible genetic discrimination that could result in loss of insurance, denial of treatment, or employment. Maluso notes that patient and physician attitudes are important factors that need to be considered in the implementation of PGx into the clinical setting. Maluso points to findings from a survey that demonstrated that 63%–75% of patients felt positively about the benefits of PGx tests in helping them choose the most effective drug, the apt dosage, as well as the lowest side effects. However, Maluso also points out that 69% of the patients feared test results could lead to discrimination from employers, and 71% of physicians expressed similar concerns. It was observed from the findings that both patients and physicians were concerned about health insurance discrimination.\(^\text{74}\)

Studies have highlighted that the application of PGx could lead to the stratification of patients according to their response to medicine, or according to the diseases. However, there are concerns that this stratification can create fear for discrimination and denial of treatment. Race as a proxy, if used in the stratification purposes, can be problematic and lead to inaccurate results.
As research suggests, denying treatment to a particular racial group by using race as a proxy for genetic profiling would be problematic, since different people in a specific race may have genetic variations, this could lead healthcare professionals to use race as a proxy in determining and eventually denying treatment if the correct PGx test was not available.\textsuperscript{75} Moreover, it has been feared that this type of stratification would result in serious social and ethical problems, if it were used to deny treatment to \textit{already socially and medically disadvantaged population}.\textsuperscript{76} Better monitoring of such stratification approaches would be wise in order to avoid future issues. Moreover, studies have emphasized that psychosocial effects of PGx testing be taken into consideration to avert ethical and social issues in the future due to them. Given the nature of PGx tests, the tests may reveal the patient's susceptibility to illness for which there are no effective treatments available – maybe because the medication available for that condition, for that person, has been identified as ineffective or cause toxicity/side effects. Such information, instead of being helpful, could be as distressing as the knowledge that one already has the disease. Other issues may be of the knowledge of limited options available. Consent has been identified as another serious ethical issue, since PGx may reveal (more) information to issues that are not the topic of query for which no consent was asked. Therefore, consent regarding return of result may be difficult, and also raise ethical issues.\textsuperscript{77}

Scholars have highlighted that with increasing possibilities come increased demands and rising costs. It is feared that with the advances in PM and its innovations allowing for more personalized diagnosis and cures, it will lead to a highly stratified patient population. As Gronde et al. point out the negatives of smaller population qualifying for better outcomes, which they say means a lower volume of sales for pharmaceutical companies, resulting in increased drug pricing to generate revenues. They add that although, this shift will allow for many untreatable diseases
to be treatable, it will also make healthcare unaffordable - even in high-income countries. Olvey and Bootman assert that the high prices of drugs maybe equating to unaffordable healthcare even in developed countries. Out-of-pocket costs, although not uncommon in the U.S., are also feared as a possibility for (willing) patients if insurance companies will not cover PGx testing, or cover for some, and not all – may make healthcare less affordable for some. The scholars suggest that patients may be willing to pay out-of-pocket if they perceive the test to inform clinicians about the appropriate therapies. However, Olvey and Bootman argue that if insurance companies are willing to provide some coverage then PGx may be more widely utilized. However, the scholars highlight that the degrees to which costs and other economic factors will impact patient uptake of PGx tests remain uncertain. Moreover, they note that increased costs may affect certain disadvantaged populations (without insurance or with less coverage, or those who cannot afford the additional costs) more.

Studies have identified lack of education in genomics as a challenge that must be overcome to implement PGx successfully. Scholars like Leslie J. Dickmann and Joseph A. Ware note that physicians will play a critical role in implementing PGx in the clinical setting. However, recent studies indicate that healthcare professionals do not feel adequately prepared for this application. They highlight results from a survey on U.S. PCPs, cardiologists, and psychiatrists that show only 12.6% of the respondents being extremely or very familiar with PGx, and only 11% had any formal training in PGx, with only 37% either strongly or somewhat agreed that they were self-reliant on their understanding on PGx. Scholars highlight that many professional associations and academic institutions are working diligently to incorporate PGx education and training in pharmacy and medical schools currently. They are hopeful that this
implementation in the early phases of healthcare professionals’ career will increase their comfort in utilizing PGx approach in their routine care process.\(^8\)

Scholars have also related various data related to informatics and PGx into the EHR, to guide drug selection and dosing. According to Hicks et al., clinical decision support (CDS) has been identified as a critical tool for the implementation of PGx into routine patient care. They cite that the large volume of evolving PGx knowledge presents challenges in integrating PGx into clinical care.\(^8\) W. Francis Lam also state that the clinical implementation of PGx biomarkers can raise social issues. Lam notes that there is a fear that patient’s socioeconomic status (inability to pay for insurance/ or copayment) could prevent them from accessing the potential benefits of PGx testing, and exacerbate the existing health disparities. Moreover, Lam adds that the identification of a person as a nonresponders, or being at high risk for ADR, may lead to incidents where PGx test can be used as a “gatekeeper” of accessibility to drug treatment. And this might pose a problem, especially if there is no suitable alternative drug available, and the patient is willing to take the chances. Lam also points out another potential concern, the liability for the healthcare provider in the case if a PGx test is used to guide therapy, and a different medication is prescribed which also affects the gene previously tested. Lam highlights the need for some point-of-care mechanism that will make the clinician aware of the genetic test results relevant to the prescribed drug, and guide in the treatment process. Lam also emphasizes that the immediate implications with the availability of PGx should not be ignored for clinical, ethical, and legal reasons.\(^8\)

Although at least 10\% of drug labels in the EU and USA contain information on genetic factors determining drug response, studies have noted that very few genetic tests are currently used in the clinical practice. Scholars like Ana Alfrevic and Munir Pirmohamed suggests that
many reasons can be attributable to this slow implementation process of PGx. They highlight the clear need for evidence that reflect the benefits of implementing PGx. Among other areas that deserve priority, they highlight: lack of knowledge and training in using PGx testing, interpreting results among healthcare providers; and the lack of computerized decision support with appropriate information for clinicians.  

3.3.2. Recommendations

As highlighted by scholars, PGx will play a role as one of the first clinical applications of PM, in drug dosage and preventing ADRs. Many challenges were identified in the previous sections. However, infrastructure and regulatory hurdles remain to be discussed, especially as scholars like Karczewski et al. and Toon van der Gronde et al. point out that developing ways to continually update findings, delivering the knowledge to physicians, and integrating PGx into medicine will be critical. Well-designed infrastructure that allows the flow of validated information from one end to the other to enable accurate use of the information in regulatory submissions will be crucial in the era of PM. Patrice M Milos and Albert B Seymour explains that the challenges lie in the ability to effectively mine the data sets with the clinical data, and requires a comprehensive information technology solution. However, this will have to be addressed to enable maximum return on investments in pharmacogenomics.

Integration of PGx data, into the CDS in EHRs for clinician utilization will be critical. However, once integrated this will be an essential tool to address the other implementation challenges, such as the evolving PGx data, complexity of the tests and interpreting results. Hicks et al. point out that curating PGx data with all relevant clinical recommendation will be an essential role of the EHR with CDS, which will also distribute the information that is patient-centered at the point-of-care in clinical settings. Mary V. Relling and William E. Evans
suggest that the cost and complexity of the computational approaches should also be identified, and genetic variants that influence drug responses should be catalogued and prioritized for addressing barriers of uptake of PGx testing. They also add that substantial level of expertise and manual interpretation is still needed to apply PGx information in the clinic.89

Communication and collaboration between the various key players were also identified as essential challenges that need to be addressed. The FDA regulates drugs and drugs labels in the U.S. Karczewski et al. point out that it will be essential to develop a communication between researchers and the FDA for the adoption of PGx information on drug labels; with evaluations depending on the trial design, sample size, reproducibility, and effect size. As PGx research continues and more data are generated, bioinformatics will play an integral role in the extracting data and translating that into updated knowledge bases, such as PharmGKB, which will be integrated into a centralized EMR system that will be accessible to all. They also add that a curated and updated database with the FDA approved drug-gene interactions should be available for the clinicians in order to implement PGx in the clinical setting.90

Another important recommendation made by studies was for all stakeholders, including insurance companies, to be on board, and also beware of both the advantages and the disadvantages of the applications of PGx to dispel myths and ethical issues. Moreover, genetic testing facilities that meet the U.S. government's Clinical Laboratory Improvement Amendments (CLIA) certification requirements need to be established to provide patients with adequate genomic data for clinical use. The recent rise in drug prices is feared to create health disparities and need to be addressed through policy frameworks. As Gronde at al., noted, “striking a balance between rewarding investments in innovation, achieving reasonable drug pricing for governments and securing equitable access to medicines will be the challenge.” 91 Moreover
Gronde et al. state, access to medicines needs to be central to any policy intervention. Transnational cooperation between various entities like the European Union, African Union, World Bank or the WHO could create a collective negotiating power, by increasing their bargaining power and bringing the drug prices down. Such cooperation would also lower administrative costs, and also stimulate positive exchanging of trial data, and sharing of data, and result in improved evaluation methods. Such a global framework for cooperation among drug regulatory authorities would also increase the benefits even further by amplifying the WHO's existing framework that helps in reducing drug prices by utilizing the essential medical list which facilitates compulsory licensing.92

Better laws that address the concerns about the use or misuse of genetic information by insurers and employers must be in place to protect individuals. As Vogenberg et al. note, GINA signed into law in 2008 by President George W. Bush, explicitly prohibited employers and health insurers from discriminating against individuals on the basis of their genetic risk factors.93 However, Gina has limitations, such as life insurance and long-term care insurance companies are not prohibited from using genetic information, and GINA only protects patients who have a genetic predisposition, but not with a diagnosed disease. Despite these concerns, scholars argue that GINA enables people toward taking advantage of the predictive knowledge of genetic research.94 However, to prevent discrimination due to stratification, it has been recommended that those responsible for monitoring the access of different ethnic groups to treatments establish procedures for assessing whether critical problems emerge from the development and application of PGx.95

The public perceptions of PGx are important in part because resistance to PGx testing could lead to patients not receiving the best care. Patients might not be given the most beneficial
medicines if these are only prescribed with a genetic test which they refuse to take. Even more serious is the possibility that a medicine may be administered without an associated PGx test and result in a serious, predictable and avoidable ADR.\textsuperscript{96} Despite the benefits of PGx, D.C. Wertz fears that PGx will likely be more beneficial to those who are more affluent, causing inequalities between the developed and developing world. As with most expensive technologies, equality will be a major issue for PGx, which will warrant for regulations that safeguards the benefits of this revolution \textit{is accessible} by all.\textsuperscript{97} Public-private partnerships have been encouraged for providing the funding efforts and the support needed to provide PGx research on the most commonly used medicines to improve efficacy and safety.

Given the variation within racial groups, using genetic variants to categorize racial groups have caused considerable debates about whether it will be meaningful in the field of genetics. It has been observed that such categories are used in the development and marketing of medicine in different countries. This can be concerning because such drugs are advertised directly to consumers and there are serious risks if those medications are marketed using misleading or even wrong information.\textsuperscript{98} It has been recommended that PGx researchers should be aware that misunderstanding and prejudice may arise from racial stereotyping, and regulatory bodies should be vigilant about claims of racial specificity in the marketing of PGx tests and medicines.

\textbf{Conclusion}

As highlighted by Jesse J. Swen et al., PGx promises personalized medicine rather than the established "one size fits all" approach to drugs and dosages, and will be one of the first clinical applications of the PM. It has been expected that the reduction in trial and error as a result of PGx would lead to efficacious drugs. Although, the recently commercially available
PGx tests have been approved by FDA, their applications in patient care still remain limited. This demonstrates that the implementation of PGx in clinical setting still faces significant challenges. Scholars suggest that PGx will ultimately influence patient care by having an impact on optimal target selection, and by increasing efficacy in clinical developments by targeting patient populations based on genetically defined disease phenotypes - thereby providing a clear benefit to physicians' to deliver better care. Johnson and Cavallari, and Relling and William, both assert that there will be need for clear guidelines for translating genomic knowledge into the decision-making process, but regardless of the barriers, we must continue the research process of acquiring better understanding the genetic influences in drug response and treatment processes. Scholars also highlight the need for ethics in preventing inequities and injustices from occurring in the name of so-called ethnic-therapies, or race specific drugs; and enabling the advancement of a justified PM approach that will lead to the success of health and well-being for us all.
Chapter 4: Relevance of PM in Infectious and Non-communicable Chronic Diseases and Pandemics

4.1. Introduction

Research demonstrates that human genetic variants affect our risks for many of the major non-communicable diseases (NCDs) - also known as common chronic diseases - such as cardiovascular disease (CVD), diabetes, and cancer. Chronic diseases are concerning because they cause serious personal and economic challenges in people. It is hopeful that precision medicine can address these NCDs in the future and yield the most benefits for healthcare. So far, scholars have highlighted PGx as the first type of PM approach that will be instrumental in maximizing the potential benefits, and minimize potential risks of medications. Additionally, PM is also expected to play a critical role in addressing infectious diseases, which remain a challenge as of today - killing several millions of people each year due to the “emergence and reemergence” of new and more virulent pathogens. Genomics research is anticipated to be vital in mitigating pandemic threats - such as Ebola outbreaks (most recent), severe acute respiratory syndrome (SARS) and avian (H5N1), and pandemic H1N1 2009 influenza (commonly referred to as “swine flu”) - to name a few. Moreover, scholars have highlighted the successful application of genomic science in the design and development of vaccines, used in the successful treatment for certain infectious diseases. PM’s major future goals, as discussed by scholars, will include preventing premature deaths, reduction of healthcare cost, and better prevention and management of infectious, non-communicable diseases and management of pandemics. Despite all these advantages of incorporating PM into the clinical setting, it will be difficult to navigate through the challenges and the ethical and social issues that are anticipated to arise for the clinical practice, public health, as well as policy making in the era of PM. The focus of this
Chapter is to look at the importance of PM in infectious and non-communicable chronic diseases, and pandemics - while identifying and addressing some of the anticipated challenges.

4.1.1. Precision Medicine in the Management of NCDs - CVD, Diabetes and Cancer

PM has the potential to be the emerging healthcare technology of the future. PGx studies is expected to enhance the effectiveness and reduce toxicity of prescribed medicine based on the knowledge of biomarkers in patient subgroups – in order to enrich the management of diseases from prevention to treatment - depending on the availability of targeted therapies. Personalized treatment guided by PGx is one of the anticipated applications of ‘precision-personalized’ medicine that will be used in clinical practice. PGx holds promises of shifting the way medications are prescribed, and is anticipated to reduce ADRs and toxicities. DNA-based risk assessment has been recognized important in the determining of chronic diseases risk. Different scholars like McBride, Godman et al., Favalli et al. and Beery and Smith et al., all advocate for PM in the management of NCDs such as CVD, diabetes and cancer. It is not long until PM will play an active role in healthcare. This section looks at PM, and its clinical significance, particularly in the areas of CVD, Cancer, and Diabetes.

According to the WHO, NCDs have potential serious socioeconomic consequences. Each year, an estimated 9 million plus deaths are caused by NCDs throughout the world before the age of 60 years, with associated negative impacts on productivity and development, creating a significant burden on health systems, and on country economies (WHO, 2010). The WHO also lists the leading causes of NCD deaths in 2008: CVD (17 million deaths, or 48% of NCD deaths); cancers (7.6 million, or 21% of NCD deaths); and diabetes (1.3 million deaths). As Miller et al. point out, developments in genomics, including low-cost next generation sequencing (NGS) technologies; will hopefully usher in a more personalized approach to clinical care, with
improved risk stratification and treatment selection.\textsuperscript{17} Beery and Smith note that there are clinical genetic tests available for more than 1,500 diseases, with an additional 277 tests available for participants in research studies.\textsuperscript{18} PGx has already been highlighted by scholars as an instrumental application in the prediction of drug response and toxicity.\textsuperscript{19} Finally, de Denus et al. highlight that PM promises the use of diagnostic testing to provide the best clinical decisions based on a patient’s genetic profile, by analyzing the coding and structural variants in a patient’s genome to provide information about the causes of existing conditions, future risks for disease, and responsiveness to drug therapies.\textsuperscript{20}

**CVD:** Favalli et al. note that coronary heart disease remains a leading cause of death and disability worldwide. They point out that findings from decade-long genomics research in Iceland suggest coronary heart disease is related to multiple genes. They further add that a thorough understanding of the genetics of coronary heart disease would be helpful in understanding the molecular mechanisms that would aid in therapeutic or preventive interventions.\textsuperscript{21} Zaiou and Amri point out that cardiology has already taken the lead in applying newer tools of PM, such as sophisticated phenotyping, combined with machine learning to find patterns in diseases. Substantial evidence suggests that most of the burden of CVD is supposed to have complex genetic and environmental origins.\textsuperscript{22} According to Morita and Komuro, many successful stories show that Genome Wide Association Studies (GWAS) has been important in the discovery of novel genetic biomarkers such as single nucleotide polymorphism (SNPs), which have been effective in providing the knowledge of the likelihood of “disease onset, progression prediction, and management.”\textsuperscript{23} Zaiou and Amri point out that these genetic variations were also helpful in explaining observed “inter-individual” differences in cardiovascular protection from different classes of used medications.\textsuperscript{24} To add to all these
arguments, Wells et al. also agree that cardiac pharmacogenomics is a rapidly growing field that offers the potential for improved treatment outcomes, as well as the prevention of adverse drug reactions.\textsuperscript{25}

\textbf{Cancer:} Cancer is predicted as an increasingly important cause of morbidity, and mortality in the next few decades - in all regions of the world. The challenges of tackling cancer are enormous, with the forecast that the estimated incidence of 12.7 million new cancer cases reported in 2008, is expected to rise to 21.4 million by 2030. According to the WHO (2010), the leading causes of cancer deaths in high-income countries “are lung cancer among men and breast cancer among women.”\textsuperscript{26} The WHO states that cost-effective interventions are available across the four broad approaches to cancer (breast, cervical, colorectal, skin and oral cancers) prevention and control: through primary prevention (screenings), early detection, treatment, and palliative care.\textsuperscript{27} Nora M. Gerhards and Sven Rottenberg noted that despite the substantial advances in the treatment of various cancers, many patients still receive anti-cancer therapies that are not beneficial in eradicating tumor cells, and instead inflict adverse side effects injurious to the health of the patient. They added that a major goal of PGx is to identify predictive markers for a personalized therapeutic strategy.\textsuperscript{28} PGx is steadily advancing in the area of cancer genomics. Karczewski et al. add that the very nature of cancer is “personal,” since “each specific cancer is caused by the unique sum of individual somatic mutations” (mutations that are not inherited or passed and occur in the individual after birth). They add that currently, cancer drugs are utilized in a “guess and test” manner and as a result, have many toxic side effects.\textsuperscript{29} Karczewski et al. are optimistic that the ability to sequence cancer cells will enable researchers with better knowledge of cancer cells and somatic mutations. This knowledge will greatly empower physicians in the decision-making capacity and allow them to administer the best
treatment for a particular individual, without wasting time on treatments that would fail. Berm et al. note that it is important that the safest and most effective pharmacological treatment be selected (to avoid severe toxicity), that is based on the molecular characteristics of both the patient and the tumor. They add that providing the basis for the best-tailored treatment is not an easy task since “multiple genes, as well as pathophysiological and environmental factors,” must be taken into consideration. However, they add that PGx will be critical in establishing this relationship with drug outcomes and biomarkers in order to provide the basis for the best-tailored treatments – ultimately providing the optimized, cost-saving health outcomes by preventing hospitalization due to ADRs associated with inappropriate, expensive drug treatments.

Diabetes: Scholars like Elizabeta Topic, and Wang et al., pointed out that diabetes is a worldwide epidemic with significant health and economic consequences - with 366 million prevalent diabetes cases reported in 2011, and a projected 552 million cases expected by the year 2030 - becoming a leading public health challenge worldwide. According to the WHO (2010), diabetes is the seventh leading cause of death in the United States - two to three times the health-care resources are required for those afflicted with this condition, accounting for up to an increase of 15% of the national healthcare budget for diabetes care. According to Wang et al., an estimated ~285 million adults suffer from type 2 Diabetes Mellitus, and in the next 20 years this number has been projected to rise to 438 million – and additionally, it is important to point out that T2D etiology is known for having a considerable genetic component. According to twin studies, the heritability of T2D ranges from 26% to 73%. The rapid development of genotyping techniques has resulted in the identification of numerous T2D loci that has also been replicated by GWAS among the world's major ethnic populations. Therefore, Herder and Roden are optimistic that the identification of T2D-related genes could improve risk prediction, and lead to
better prevention, and management of diabetes. Studies from the WHO have also identified that the response to any antidiabetic medication may considerably vary between individuals due to genetic variations. Therefore Zhou et al. is optimistic, advancement of genomics will help to better understand the multifactorial etiology of type 2 diabetes mellitus (T2DM), as well as the multiple subtypes of monogenic diabetes mellitus. A variety of PGx treatments already exist for patients with T2D, in addition to dietary and physical activity. Läll et al. report that GWAS have been highlighted as having high prospects in T2D risk assessment through the identification of genetic risk score (GRS) - with the strongest association with T2D status in a population-based cohort. Although, the current knowledge is not sufficient for the prediction of diabetes risk or for decisions regarding specific prevention, or treatment measures using genomics – Herden and Roden suggest that a more complete understanding of the genetic role in T2D, in combination with lifestyle and environmental factors will be invaluable to the reassessment of the clinical relevance of genotype data.

4.1.2. Clinical Significance and Costs

Dandona and Roberts state that the availability of the GWAS in 2005 has substantially enabled the identification of genetic variants related to drug risk, and drug metabolism, which has been remarkable in identifying more than 1200 DNA common risk variants for more than 160 human diseases. The scholars are optimistic that PM will play a crucial role in avoiding ADRs and allergies, which are responsible for more than 100,000 annual deaths reported in the United States, with 2 million surviving after periods of hospitalization, costing over $4 billion in the U.S. alone. The FDA claims ADRs as the fourth most common cause of death in the United States. Dandona and Roberts furthermore, add that PGx in PM can be successful in prescribing “the right drug, in the right dose, to the right person.”
Bloss et al. also argue that PGx is the area of genomics that provides the clearest example of the targeted utilization of genomics in order to provide individualized treatments, and positively influence the clinical care. They cite the example of Warfarin, an anticoagulant medication, most commonly prescribed worldwide for the prevention of stroke, and venous thromboembolism. However, Warfarin metabolism can be affected by many factors, which complicates its dosing. Bloss et al. add that there is evidence for the importance of genetic variants in Warfarin metabolism which has led the FDA to update Warfarin's label to include a statement acknowledging the importance of “genotyping during the early phase of dosing.” They further add that as a result of this and PGx research efforts, there has been an increase in drug safety and efficacy, to the extent that PGx today symbolizes genomics' role in disease treatment and prevention of ADRs, and is a step forward in ushering in a new era of PM.  

According to Blaus et al., safety is a major concern for the use of PM by researchers, drug developers, and regulatory agencies. They argue that amongst the many areas covered by PM, the most exciting one is the ability to identify the likely responders through “genetic, proteomic,” or other tests - so that only likely responders will be treated - reducing ADRs in response to drugs, and increasing the potential benefits of the drug. Thereby, PM through PGx has the potential to reduce the costs of treatment and at the same time, increase the efficiency of drugs for individual patients. Blaus et al. also argue that “genomic or pathophysiological markers” can aid in improving the efficiency of clinical trials, by identifying and enrolling only the population in whom the number of events is expected to be higher, and with larger effect size. Furthermore, they add that this will reduce the costs and the time needed to complete clinical trials, as well as improve the effectiveness of the clinical trial.
Scholars like Claude Lenfant noted that CVDs remain the dominant cause of death worldwide due to the limited clinical applications, due to limited knowledge of genetic risk and mechanism of action of genetic factors of prevalent CVDs. However, they also note that PGx research advances have widely opened the concept of PM in CVDs, and have become an active field today, providing clinically valuable information regarding individualized, personalized drug prescriptions, and contributing to the reversing of trends of expected CVDs. Fiona M Walters points out that cancer is another potential area for PGx. According to recent work undertaken by the European Commission funded Multicenter Collaborative Oncological Gene-environment Study (COGS) on genetic variation and breast cancer risk - testing for genetic variants can be an effective way to stratify the population. They argue that this will allow for earlier and more frequent screenings of those with a higher genetic predisposition to breast cancer; while those with lower risks can even opt out or be recommended to forgo the screening. Walters argue that this could effectively minimize the harms of mammography, while still detecting most women with breast cancer. Walters add that similar work is underway on CVDs, where risk scores through genetic testing would identify people with higher risks before they develop the “phenotypic markers of risk,” thus avoiding administration of statins to those who will not benefit.

Śliwczynski and Orlewska also looked at the role of PGx on diabetes. According to high-dimensional EMR data, and genotype data from 11,210 individuals from Mount Sinai Medical Center in New York, a tailored treatment plan of T2D using the characters of the diversity of the patient population, looked more appealing than the one-size-fits-all approach. Śliwczynski and Orlewska added that based on the findings, by using an accurate risk prediction tool and through better risk targeting - higher efficiency of lifestyle interventions and limited occurrence of the
side effects of metformin, for example, could be achieved. They argue that PM can be used to determine the exact subtype sensitivity to therapies. They also assert that PM can be more effective in a more proactive management of diseases and healthcare, that includes screening, early treatment, and prevention, and could change the roles of both physicians and patients by making them more involved in health care, and health research.

Scholars like Gilchrist et al. look at PM’s role in infectious diseases, and argue that PM has a potential role in the prediction, prevention, and management of infectious diseases, epidemics and pandemics – nationally and globally. PM, through the utilization of whole genome sequencing (WGS), can facilitate in the rapid and accurate identification of virulence factors, aiding in the identification of the path of the disease transmission within a population, and in providing information on the probable source. They add that the advance of inexpensive, ultra-high throughput DNA sequencing tools, have transformed the microbial WGS from a costly enterprise to a very accessible routine exercise in molecular biology. Gilchrist et al. note that through phylogenetic analysis, “evaluation of the evolution of strains during an outbreak is possible;” and it can be especially useful in comparing the “finished assembly and trace genetic changes,” not only about the current epidemic - but also in the broader global context. Moreover, Gilchrist et al. add that the advances in NGS have enabled the rapid WGS of the “causative microbe” during an outbreak. They emphasize the need for first responders to be well-informed about the capacity, as well as the limitations of WGS, so they know how “to collect appropriate samples” that will be useful for WGS, in the prediction, prevention, and management of infectious diseases, epidemics and pandemics - “to predict the course, or define the origin, of an epidemic.” The next sections look at PM in infectious diseases.
4.2. PM in Infectious Diseases

According to scholars like Geller et al., advances in the genetic sequencing technologies are contributing greatly to the development of more personalized approaches of prevention and treatment of infectious diseases. At the same time, these technologies are influencing future policies and procedures for infectious disease management, since we are better able to understand the interactions between human genomic and pathogen genomic factors, and their roles in the different immunologic responses to vaccines, infections, and drug therapies. Gupta et al. point out that discovering novel pathogens and elucidating the implications of genetic variation among existing pathogens, is critical for rapidly mitigating pandemic threats, as demonstrated recently with the severe acute respiratory syndrome (SARS), and avian (H5N1), and pandemic H1N1 2009 influenza (commonly referred to as “swine flu”). The next two sections will look at the use of genomics in infectious diseases, clinical significance and costs.

4.2.1. Genomics in Infectious Diseases

It is evident from studies that genomic information creates more opportunity for more personalized treatment, and prevention in clinical practice, and public health setting. According to scholars like Sintchenko V. et al., bacterial genomics in pathogen genotyping has improved our understanding of the different “molecular pathogenesis, host-pathogen interactions, and antibiotic-resistance mechanisms.” Sintchenko et al. noted, bacterial genomics has also facilitated the study of population structures, epidemics and outbreaks, and newly identified pathogens - which resulted in numerous opportunities for clinical pathologists to contribute to bacterial genomics - including the design of new diagnostic tests, therapeutic agents, and vaccines. Sintchenko et al. also add that the sharing of data on pathogen profiles creates a greater
understanding of the transmission patterns and processes, and is critical in the informed disease management and surveillance.\

Sintchenko et al. emphasizes that the accurate classification of pathogens with epidemic potential can optimize communicable disease control, and reduce associated costs. According to studies, analyzing the dynamics of infections that have epidemic potential relies on the “accurate demarcation and identification of individual strains or epidemic clones,” together with the identification of specific virulence factors and other validated markers. Together, the scholars add, this information can be consolidated into a pathogen profile. Sintchenko et al. also note that the systematic collection and construction of pathogen profiles from a combination of genomic or other markers in a manner that enables data to be integrated and shared - is essential for successful surveillance and disease management. For example, genetic markers are used to identify antibiotic-resistant strains of Mycobacterium tuberculosis. Similar monitoring is also utilized for HIV or hepatitis C virus (HCV) infections.\

Sintchenko et al. further suggest that there is a need for a larger volume of data relevant to microbial profiles to characterize the entire phenotype of a pathogen in an environmental or experimental context. The scholars note that linking annotated profiles systematically with clinical and research databases can lead to the identification of previously unrecognized genes. They moreover, note that although public electronic bacterial typing databases exist, data sharing is still difficult due to lack of conventional structures. Sintchenko et al. explains that microbial typing are important since they can confirm or refute the epidemiological links that might trigger public health investigations, and can also determine unrelated clusters to rule out further action. However, they add that pathogen profiling goes beyond the investigation of outbreaks, and can also be important in the monitoring of diseases; thereby, aiding in providing information for
organic-specific infection control policies, and predicting clinical outcome. According to Sintchenko et al., molecular profiling also facilitates the detection of chains and patterns of infection transmission and aids in the construction of epidemic trees that can guide appropriate control efforts. However, Sintchenko et al. also point out that microbial genotyping alone might not always be the best classification method, since outbreaks are occasionally caused by several different agents, rather than a single, virulent clone - for example, sewage contamination of water or food could cause an outbreak of diarrhea.

4.2.2. Impact of Genomics

As highlighted by scholars like Olsen et al., NGS platforms and bioinformatics tools are opening a new chapter in the history of infectious disease research and clinical pathology laboratory practice. In the past, it used to cost a lot ($one million) and take a long time (a year) to complete bacterial genome. Today, depending on the instrument, it is possible to sequence the complete genome of a bacterial strain in one day for much less than $1000. Similarly, a single instrument can generate 100 or more bacterial genome sequences in less than one week. Assuming this trend continues, Olsen et al. are hopeful that the cost will go down to only $10 soon. These low-cost, high-throughput sequencing platforms are readily available today, enabling the pursuit of new investigations and novel applications that were previously inaccessible. Olsen et al. argue that sequencing technologies provide pathologists with the opportunity to not only perform research on infectious diseases, but also develop laboratory tests applicable for clinical settings, and improve patient care.

Olsen et al. also point out the recent achievements in the decreased cost and increased DNA sequencing capacity in bacterial genomics, which have transformed our understanding of virulence factors, host-pathogen interactions, and population genetics – paving the way for
rational design of diagnostics, therapeutics, and vaccines that may significantly improve patient care. They add that this new knowledge can be used to design more effective vaccines and treatment regimens, and also aid in public health efforts to prevent vector-borne infectious diseases through preventative efforts. Moreover, Olsen et al. state that population genomics allows investigators to study origins and subsequent evolution, thereby leading to insights into how they are disseminated today.

Tang et al. add that bioinformatics algorithms along with the new sequencing technologies have given rise to the field of genomic epidemiology where WGS methods are integrated with epidemiologic investigations to yield the knowledge into communicable disease outbreaks. Tang et al. note that infectious diseases continue to be one of the leading causes of death worldwide, given the ability of the pathogens to evolve and spread rapidly which results in the emergence of novel human pathogens, more virulent forms of existing pathogens, and antibiotic-resistant organisms. They add that the knowledge of the entire genome allows for better identification and characterization of the pathogen responsible for the outbreak; allowing better risk estimation and thereby, not only allowing for the selection of the most appropriate interventions, but also a better understanding of the origins and dynamics of the outbreak. The advanced genotyping technology will be able to detect various outbreaks and factors involved in the transmission process, and can be applied in the informing and guiding of infection control and public health practices.

The prevention and containment of debilitating and often-lethal infectious diseases have had an enormous impact on world health. Seib et al. argue that the arrival of different sequencing and profiling tools in the genomics era has created a shift in the development of vaccines, and also in the development of antibiotics. They add that infectious diseases, however, create an
enormous burden on the global population – observed in the “classic pathogens, newly discovered causes of diseases and the emergence and reemergence of infectious diseases.” In addition to all that, Seib et al. note that antibiotic-resistant forms of microbes are a novel challenge to address. According to the WHO, at least one such new pathogen can be expected to appear every year. Therefore, Seib et al. suggest that it is essential that we be well equipped with adequate and effective vaccines and other therapeutics to limit infectious diseases from spreading. They also highlight that the traditional approaches for screening vaccines are time-consuming and ineffective in controlling many of the emerging or reemerging infectious diseases.\textsuperscript{67} 

Seib et al. have noted that vaccines can generate “self” immune reactions potentially leading to damage to the host tissue – this must, therefore, be taken into consideration when designing new vaccines. They add that studies have suggested that vaccine or drug targets should be screened for “homology or similarity” to human proteins, to identify “self” immune reactions using BLAST (Basic Local Alignment Search Tool) to query human genome database. They argue that PGx can determine the correct vaccine/drug and the dosage utilizing the genetic differences in the way individuals metabolize therapeutics.\textsuperscript{68} Although we are still not sure about the efficacy and protection of genome-based vaccines and therapeutics against infectious diseases due to lack of valid models to measure their efficacy, Seib et al. are optimistic that the increased understanding of microbial pathogenesis should greatly aid in this respect.\textsuperscript{69} 

According to Olsen et al. genome-wide investigations of larger strain collections, as generated by WGS and NGS technologies are needed to expand the scope of outbreak investigations and provide a genetic basis for designing diagnostic tests and antimicrobial therapies. Olsen et al. add that WGS sequencing of outbreak strains is similar to evolutionary
relationships inferred from genomic comparisons of geographically diverse strains, enabling the precise map of the dissemination and clonal evolution. Antibiotic-resistant strains are a major cause of concern among specialists in infectious disease worldwide. Olsen et al. add that NGS techniques have recently been used to identify the genetic basis of new antibiotic-resistance mechanisms; additionally, WGS is anticipated to become the standard tool in the diagnostic laboratory. Olsen et al. are positive that NGS tools are capable of economically generating tremendous amounts of bacterial genomics data, able to aid in the investigation, containment of present and future foodborne outbreaks. The next section looks at outbreaks and pandemics.

4.3. PM in Pandemics

Studies show that infectious diseases play a significant role in negatively affecting the public health and economic stability of the population worldwide. Infectious diseases have been identified as the leading causes of death, disability, and for impeding the growth of human progress for centuries. According to scholars like Nii-Trebi, the continued emergence of new, unrecognized and even old infectious disease epidemics persistently threatens our health and economic stability, with far reaching effect on the global population as well. An estimated 30 plus new infectious agents have emerged affecting humans over the past thirty-five years - showing a correlation with socioeconomic, environmental, and ecological factors – presenting a formidable challenge. Nii-Trebi further emphasizes the urgent need for constant awareness and pursuance of effective strategies for controlling infectious diseases and disease emergence. Nii-Trebi adds that studies demonstrate that microorganisms generally cause infectious diseases, and their importance is derived “from the type and extent of damage their causative agents inflict on organs and/or systems” upon entry into a host. Nii-Trebi further points out the enormous impact of the HGP on genomics and health - that plays a greater role in the prediction and
prevention of the next pandemic through their sequencing techniques. The next section looks at the clinical impact of genomics in pandemics.

### 4.3.1. Clinical Impact of Genomics in Pandemics

According to Nii-Trebi, infectious diseases can affect a person's psychological, emotional, and mental wellbeing, and can greatly “worsen the plight of people living with an infectious disease.” A notable example is leprosy. Nii-Trebi adds that in some communities, this particular infectious disease has been reported to bring shame to those affected, shunning and maltreating the afflicted ones – to the point where some even lose their freedom and worth. Infectious diseases are also known to cause loss of capacity to work, which in turn increases poverty in adults; this may consequently affect children's education, cognitive development, leading to various social vices - ultimately adding to the burden created by the disease, and worsening poverty. Bhutta et al. also add that infectious diseases of poverty (IDoP) affect the poorest population in the world disproportionately, contributing to a cycle of poverty due to decreased productivity ensuing from long-term illness, disability, social stigma, and even death. The scholars also note that an increase of 111,000 deaths globally was attributable to IDoP - for instance, neglected tropical diseases (NTDs) and malaria that have been reported in 2010 by a study from the *Global Burden of Disease*. They add that mortality from NTDs in 2010 was reported to have risen to 152,000, with an estimated more than 90% of the total impact as a result of death and disability caused by neglected diseases occurring in Sub-Saharan Africa. The scholars point out that the socioeconomic and physical conditions of those living in poverty create environments that facilitate the transmission of vectors and pathogens, consequently leading to a long-term illness that further exacerbates poverty by diminishing productivity. Unfortunately, Bhutta et al. add, NTDs have slipped into the “neglected” diseases and is not
given the attention needed to address them. As of 2010, NTDs only received 0.6% of the total international development assistance for health.\textsuperscript{75} However, much focus is on malaria.

Malaria is known as one of the leading causes of mortality.\textsuperscript{76} The WHO (2016) reported an estimated 216 million cases of malaria in 91 countries, which is an increase of over 5 million cases over 2015.\textsuperscript{77} Globally, over 200 million annual malaria infections result in up to 660,000 deaths, of which 77% occur in children under the age of five years. Preventive measures are crucial; however, prevention of most malaria deaths is by the use of antimalarial drugs. However, scholars like Winzeler and Manary note that the development of resistance to these malarial drugs threatens to increase morbidity and mortality by malaria. Artemisinins is one of the few drugs used to cure multidrug-resistant Plasmodium falciparum infections. Unfortunately, the scholars highlight, clinical trials from Southeast Asia show that artemisinin-based treatments are beginning to lose their effectiveness due to drug resistance, thus resulting in the dire need for genetic determinants for this resistance. As Winzeler and Manary note, a recurrent problem with chemotherapy is the emergence of the spread of multidrug-resistant P. falciparum parasites, making P. falciparum malaria complicated to cure. It is feared that this reduction in the efficacy of chemotherapy could result in malaria again becoming an incurable and fatal disease.\textsuperscript{78} With the developing to resistance to artemisinin the search for markers associated with resistance has become more urgent, and more feasible.\textsuperscript{79} Winzeler and Manary point out that study of artemisinin resistance is already influencing patient treatment, and interventions to eradicate malaria from regions where resistance has been observed. Nonetheless, the scholars add, it would be wise for the world health community to reduce reliance on this class of drugs.\textsuperscript{80}

Per Meltzer et al., influenza A virus is another example, which is responsible for the deaths of thousands of humans every year. Historically, influenza pandemics have occurred for
centuries, and have occurred three times (1918, 1957, and 1968) in the 20th century alone.\textsuperscript{81} April 2009 marked the first influenza pandemic of the 21\textsuperscript{st} century with the emergence of a new H1N1 influenza A virus strain (pH1N1) in North America that rapidly disseminated around the globe, responsible for more than 18,000 deaths worldwide. From the comprehensive phylogenetic analysis, Sant’Anna et al. noted that influenza A virus can change genetically rather fast, which enables them to evade recognition by the immune system and allow constant circulation among human populations - allowing for greater transmissibility and pathogenicity, and resulting in drug resistance. Sant’Anna et al. note that as of today, seven distinct pH1N1 influenza A virus lineages around the globe have been noted in the first months of the pandemic period.\textsuperscript{82} Sant’Anna et al. argue that genome sequencing allows for the monitoring of these evolutionary changes and provides fundamental information about the chronological and geographical distribution of the strains; and that data aids in vaccine development. However, studies concerning the molecular evolution of the strain of pH1N1 are reported to be scarce, resulting in the lack of data available concerning the evolution of the established pH1N1 viruses in the current post-pandemic period, which can compromise the local public-health vaccination policies.\textsuperscript{83} Sant’Anna et al. point out that it is important for public health agencies (globally) to monitor the circulating strains in order to ensure proper local prevention and control measures.\textsuperscript{84} The outbreak of pandemic (H1N1) in 2009 (swine-origin influenza A) infected >296,000 persons worldwide, which resulted in 3,486 deaths. Chen and Shi add that much important information that can help in promoting influenza diagnosis, drug-resistance monitoring, and vaccine development was brought out by sequencing many of the new strains of pandemic (H1N1) 2009 virus. However, Chen and Shi argue that researchers need to analyze the adaptive mutation of the
pandemic (H1N1) 2009 in order to evaluate the likelihood of viruses from other nonhuman species to adapt to humans.\textsuperscript{85}

According to Gire et al., the Ebola virus (EBOV; formerly Zaire ebolavirus) - one of five ebolaviruses - is a lethal human pathogen that causes Ebola virus disease (EVD) with a 78\% case fatality rate. Previously EVD outbreaks were confined to remote regions of central Africa - the largest had 318 cases and occurred in 1976. As the scholars highlight, the current outbreak in 2014 started in February 2014 in Guinea, West Africa – spread rapidly into Liberia in March, Sierra Leone in May, and Nigeria in late July – and was the largest known EVD, that expanded exponentially with a doubling period of 34.8 days. The scholars noted that 2240 cases and 1229 deaths had been documented in August 2014, resulting in a major (ongoing) public health crisis - therefore, there is a need for accurate and timely information in order to better target such outbreaks.\textsuperscript{86} Gire et al. also pointed out that epidemiological and genomic surveillance must be a continuous process. It is anticipated that new genomic technologies will be vital in the multidisciplinary international efforts to understand and contain such expanding epidemics and others.\textsuperscript{87} The next section looks at some of the applications of genomics in pandemics.

\textbf{4.3.2 Applications of Genomics in Pandemics}

One of the major potential uses of genomics tools is in the rapid identification of newly emerging viruses, as pointed out by Lei and Shi.\textsuperscript{88} There are many new genomic tools, such as high-throughput sequencing, viral and host mRNA and microRNA expression profiling, and microarray-based analysis of pathogen and host single nucleotide polymorphisms (to name a few). Lei and Shi point out that these tools have the potential to help identify the leads for therapeutic intervention, predict the new emergence of novel genotype/pathotypes with altered virulence, and also aid in the development of effective vaccines.\textsuperscript{89} Tim Downing adds that high-
throughput sequencing can decode measurable evolution of cell populations within patients associated with system-wide changes in gene expression during treatments. Downing also points that a multi-faceted approach can enhance assessment of antimicrobial resistance by assessing the transference dynamics between hosts to draw up a scheme of deterring resistance before it emerges by optimizing antimicrobial treatment protocols. As of today, scholars have noted that influenza is still considered a major public health concern in the U.S., despite the significant advancement in vaccine and virus research – responsible for over 200,000 hospitalizations and 30,000–50,000 deaths during seasonal epidemics. As such, rapid and accurate identification of an influenza outbreak is essential for patient care and treatment. Vemula et al. suggest that NGS-based “unbiased sequencing” can be effectively applied to investigate molecular characteristics of nosocomial influenza outbreak by using clinical specimens (such as nasopharyngeal swabs), and NGS-based sequencing moreover, offers added benefits through sequencing speed and throughput, and reduced costs. As pointed by Dziejman et al., the panic caused by the rapid spread of the pandemic H1N1 2009 influenza/swine flu around the Globe triggered the (urgent) curiosity of all - including governments, and the public - about the nature of this flu, and also its containment. Dziejman et al. argue that genomics is already playing a critical role in the surveillance and control of emerging infectious control, including resistant pathogens. They add that substantial data generated from genome sequences of individual isolates and strains of pathogens opens up doors to the identification of molecular changes, which enable the tracking of their spread and evolution through time, and also in the generation of vaccines, and drugs necessary to combat these diseases. Historically, cholera, a severe diarrheal disease caused by a bacterium called Vibrio cholera, was a public health nuisance and had caused several pandemics (about six
between 1817 and 1923). Dziejman et al. add that by 1900, cholera was no longer an epidemic and endemic disease; only to appear in 1961 as the “7th pandemic of cholera” that rapidly spread throughout the Asian mainland and in Africa, replacing classical strains as the cause of endemic cholera. The scholars highlight that although a significant amount of studies have focused on *V. cholerae* pathogenicity and its pandemic potential, the genomic sequence of this bacterium was only recently reported. Dziejman et al. argue that with the use of another powerful new tool, microarray technology, the genetic similarity among strains of *V. cholerae* isolated from diverse geographical locales and over decades of time was investigated. Therefore, they add that genomics can identify genes that lead to bacterial adaptation and fitness in human hosts leading to prolonged infections of human hosts. The scholars are optimistic that it will be possible to delete these genes systematically or develop better vaccines that can combat these pathogens soon.

According to scholars like Haagmans et al. (2009), “high-throughput sequencing genomics tools are providing unprecedented ways to analyze the diversity of the genomes of emerging pathogens as well as the molecular basis of the host response to them.” They add that such technologies allow us to identify emerging pathogens, and “analyze the diversity of their genomes as well as the host responses.” Haagmans et al. point out that since “zoonotic pathogens typically may cause variable clinical outcomes in human hosts that differ in age, nutritional status, genetic background, and immunological condition” - deciphering the complex interactions between evolving pathogens and their hosts is a great challenge. They add that a better understanding of the “relationship between the genetic variation and antigenic properties” can help predict the emergence of influenza virus (for example), and develop vaccines that are effective.
Per Robinson et al., outbreaks of infection can range from a few individuals to epidemics across countries or continents, and can have devastating effects on people and their societies. The scholars emphasize the need to investigate outbreaks, in order to terminate the cluster of diseases and to prevent similar occurrences. They also add that the identification and characterization of an outbreak strain can be useful in learning the mode of transmission, its source, and how to control and prevent it. Robinson et al. add that in the past, traditional laboratory and epidemiology was used to track and manage outbreaks. Thus, the laboratory could provide evidence to confirm or dismiss a common microbial cause. Additionally, an increase in laboratory reports of given pathogen could provide the first evidence that an outbreak is underway. However, sequence-based approaches are becoming portable and therefore are used more widely so that results can be easily compared between different labs around the world. The scholars also add that sequence-based approaches make archiving of information in national or international datasets easier, allowing isolates and outbreaks to be placed in the wider pathogen population context. Despite these advantages, Robinson et al. point out that there remain drawbacks in sequence-based typing - such as a lack of standardization, and lack of real-time data exchange between laboratories, due to costs and complex workflows.

Scholars like Esther R. Robinson et al. also argue that WGS has the potential to make an impact in the bacterial infection outbreaks in hospitals and community settings. G.Vernet adds that hospitals and communities with the improved understanding of genomics and virulence and resistance can better serve populations in the containment of epidemics, by limiting the spread of infectious agents and improving surveillance approaches. For WGS to be routinely used in clinical practices, Vernet adds that several challenges must be addressed - such as the need for improved speed, ease of use, accuracy and longer read lengths. Moreover, G.Vernet argues that
pharmaceutical companies can also use genomics in developing better vaccines, tailored drugs. Moreover, Vernet argues that reverse vaccinology is used in pharmaceutical companies in order to verify the sterility of injectable drugs and vaccines. Vernet adds that genomics has now found its place in all domains of activities in the field of infectious diseases, from basic to translational research, through disease diagnosis and surveillance, molecular epidemiology for outbreak investigation, and emerging infections monitoring. Nonetheless, Vernet adds that improvements in the storing, translation and sharing of WGS data need to occur before sequencing results can be trusted enough to guide decision-making. They add that the current trend to instrument size reduction, portability, and cost and turnaround time reduction will change the landscape in the coming years by allowing smaller and decentralized laboratories to access NGS technology. Given the improvements in accuracy and cost of these sequencing technologies, it will likely be able to overcome the financial and technical challenges soon; however, anticipated ethical and social challenges need to be addressed. The next section looks at the ethical and social challenges.

4.4. Ethical and Social Challenges

According to scholars like Sintchenko et al. and Geller et al., previous studies have demonstrated that genomics in infectious, non-communicable diseases and pandemics can be cost-effective, especially through highly integrated, comprehensive disease-control programs, which include routine microbial genotyping. Yet, incorporating multiple data sources, and integrating genomics in healthcare, and public health policies remain challenging due to ethical, legal and social implications (ELSIs). Genomics will play a huge role in the future in everything that is associated with health, and it is critical to anticipate and address the possible
challenges in the future. The next sections look at the challenges associated with the possible ELSIs.

4.4.1. Identifying Challenges

Geller et al. highlight that out of the 57 million deaths that occurred globally in 2008, 63% were attributed to NCDs – which pose a public health challenge - comprising mainly of CVDs (~48% of non-communicable diseases), cancers (~21%), and diabetes (~3.5%). They add that infectious diseases are also responsible for a large proportion of morbidity and mortality worldwide, which account for a significant component of disease burden. Infectious diseases vary by mode of transmission, and by the type of pathogen, and virulence. PGx studies have been identified in earlier sections as potential tools in the identification, prevention, and management of NCDs, as well as infectious diseases if implemented properly into clinical practice. However, Geller et al. point out that the procedures for control of infectious diseases in clinical settings and public health vary, “depending on the severity and chronicity, infectivity and virulence, modes and ease of transmission, and on the availability of treatments, vaccines, or other means of prevention.” According to the scholars these are important determinants of the ELSIs with genomic applications.

Geller et al. point out that, studies on genomics and disease control and ELSIs show that the ability to distinguish a human source of infection or a ‘super-spreader’ is a serious issue, where the identified people are at a higher genetic-risk for contracting or spreading a disease. They add that this ability creates potential questions of blame or legal liability, stigmatization, and risks to privacy. Given our lack of understanding of the predictive value of genotypic information, a major ethical challenge that may result from the variability, is how such information can be used to inform risk management policy. According to Geller et al., unique
ethical challenges may stem from the intersection of genomics and infectious disease control – ethical challenges that stem from the benefits of personalized medicine (which is to benefit particular individuals), versus those of public health (to benefit and protect entire populations). Scholars like Branković et al. argue that biobanks are invaluable resources in genomic research. However, much of the legal and ethical controversies are surrounding biobanks today due to the dual role it plays in containing samples, as well as data. The scholars note that confidentiality and privacy have been cited as an obstacle in the translation of biobank data into the clinical setting. This obstacle arises from a necessary pairing of biobank information with “personal and unrelated types” of health information. They add that issues mainly arise regarding the protection of data obtained from samples of patients who are afflicted with serious infections – which gives rise to fears of possible discrimination. Branković et al. state that discrimination can result from current interpretations of data, from future research, and upcoming innovations in genomic technologies. Addressing issues of data protection is equally important, especially in the handling of samples taken from individuals who are afflicted with serious infections. Genomic discoveries concerning such infections potentially create various forms of discrimination in the context of future discovery. Branković et al. highlight that the risks of stigmatization and discrimination arising from genome-based information (the disclosure of a patient's illness or infection status is a potential infringement of patient rights) cannot be underestimated, and needs to be addressed.

Scholars like Geller et al. have noted that in the context of infectious disease management, there is a conflict with public health priorities and individual rights and liberties - such as “autonomous decision-making; freedom of choice and action; privacy; and the right to know or not to know information about oneself.” When it comes to infectious disease
management, public health programs may already target people or subgroups with particular risk factors. However, the scholars also highlight that any possibility of ascertaining or reporting of any unobservable genetic-related risk factors raises issues of protection of personal information, privacy, and autonomy.\textsuperscript{112} Fragoulakis et al. observed that genomics is also feared to exacerbate challenges related to allocation of scarce resources, especially in developing countries where the resources are limited; and must be spent wisely to address social justice and the right for equal access in healthcare services by all the citizens in economically viable terms.\textsuperscript{113} Folarin et al. add that “sequencing data from infectious pathogens represent a unique opportunity for the identification of new drug and vaccine targets, which potentially have value for disease management and control.” However, the scholars add that these data are also responsible for creating genomics knowledge gap between developing countries and the developed countries.\textsuperscript{114}

It is known that public health priorities conflicts with individual rights and liberties, however, Geller et al. add that when the benefits to individuals are weighed against the potential harms to population, incorporating biomedical advances into clinical practice and public health can be justified. In infectious diseases, genomic discoveries have the potential to benefit at-risk and affected individuals and minimize harm to them by identifying more effective and preventive interventions. Any intervention with the likelihood of an effective immune response significantly outweighs the risk, and severity of ADRs would be ethically justified. Additionally, Geller et al. add, cost-benefit analyses and overall predicted impact on morbidity and mortality might also be a good indicator for the ethical justifiability of such preventive interventions. They further add that immunization programs may be willing to screen for the genetic risk factors following an immunization/vaccination event, if the genetic predisposition for ADRS can be identified.\textsuperscript{115}
Geller et al. states there can be a conflict between the public health framework and the legal and policy paradigm of genomics. Genomics places importance on privacy, which can result in individual rights getting less priority over public health's priority over the benefit of others. In the U.S. all the states have enacted genetic privacy legislation; however, the scholars are conscious that the scope of protection varies from state to state, and may also conflict with state public health laws, and remain unclear. Geller et al. also noted that there is, however, the Model State Emergency Health Powers Act that: “enumerates the powers that will be granted to state and local officials to protect public safety in the event of a public health emergency, and includes provisions related to mandatory vaccination and quarantine.” They highlight that many states have adopted some of the provisions of the model legislation. Geller et al. have also noted that the U.S. federal Genetic Information Nondiscrimination Act of 2008 (GINA) forbids discrimination from genetic information in any aspect of employment, including job placement. However, Geller et al. observed that host genomic factors might have additional legal and policy implications - such as increased liability faced by providers for vaccine-related injury in patients with genetic predisposition to ADRs to vaccines. Alternatively, people with genetic predispositions to ADRs may be exempt from mandatory vaccine laws affecting the herd immunity. The next sections look at addressing the challenges identified so far throughout the chapter.

4.4.2. Addressing Challenges

Olsen et al. argue that WGS has become the preferred method “to study bacterial virulence, investigate outbreaks, and characterize new organisms.” They add that species assignments of isolates that cannot be otherwise identified, and real-time molecular epidemiology of nosocomial infections, are also opportunities to affect patient care. Furthermore,
well-curated databases containing bacterial strain genotype–patient disease phenotype information are being developed for clinical decision support. As more strains are sequenced, and discoveries are made, Olsen et al. point that those relationships will need to be continuously reevaluated. However they add, data analysis bottleneck exists and must be overcome before bacterial genome sequencing can be fully embraced in a clinical laboratory setting, which requires new regulatory guidelines and reimbursement models to be developed to support better data harmonization and analysis, which will be needed in order for all the different data collected to translate meaningfully.  

Geller et al. point out ELSIs that arise due to the genomic sequencing information still lingers. They add that the proper use of genomic data about individuals in the context of public health or policy decisions is still unclear, thereby, making it difficult to initiate the utility of genomic information in the public health context. However, it is certain that individual genotyping and the information derived from it will affect personal liberties, and therefore, there need to be better discussions as to how the information can be safely utilized to protect, as well as benefit the people. Geller et al. add that it is evident that genomic data about individuals (their genomic ‘fingerprint’) might be necessary when decisions about prevention and treatment are considered, such as, the type of vaccine that will be appropriate for the person, and the effective dosage. They note that genomic data about individuals and groups might be beneficial in planning, assessing and developing public health policies.  

Scholars like Nii-Trebi highlight the importance of addressing emerging and neglected infectious disease outbreaks, which pose a serious public health threat - having social, political, and economic effects. Previous outbreak events have shed much light on the importance of emerging infectious diseases, and far-reaching advances have been made. However, pandemic
preparedness even as of today remains a major global challenge. Nii-Trebi adds that infectious disease-causing pathogens continue to demonstrate their capacity to emerge and spread rapidly by any possible means across borders, exhibiting high pathogenic potential, being able to evolve or mutate to resist drug attacks. The scholar emphasizes the need for greater international cooperation, involving local, regional and global network for surveillance of outbreaks. Nii-Trebi points out that much research collaboration has also been emphasized to enable sharing of data between different entities to strengthen the capacity for identification of microbial agents, to enhance vaccine developments, and other effective prevention strategies for infectious epidemics and pandemics. As Okeke and Wain point out, knowledge and genomic information combined can equate to be a global public good. However, several indicators as pointed by the scholars show that scientists from developing countries are not using genomic information or the tools that are available to analyze genomic information.

Scholars like Eisen and MacCallum point out that there is no evidence that genomic research will be used to alleviate the burdens of infectious diseases in developing countries, even though high-burden pathogens are targeted to be sequenced. They highlight that although there are existing problems of emerging infectious diseases in developing countries, it is evident that the researchers in developing countries have not been able to participate fully in genomics research, due to the technological isolation and limited resources. They emphasize the need for an international partnership that will benefit all. To this, Bartholomew et al. also add that much collaboration between local governments, and international agencies, scientists and educational institutions will be needed to help build scientific capabilities in developing regions. They add that educating the next generation of young investigators within the regions will also be necessary to move the genomic effort in infectious diseases forward, which in turn will
promote health security in developing countries. They argue that building the scientific capacity in developing countries will also add considerably to building trust and to the intellectual reserve needed to address the critical outbreaks of infectious diseases that act as a barrier to their overall development process.¹²³

It is clear that WGS is already transforming the practice of outbreak investigation. Sintchenko et al., argues that “molecular typing facilitates the detection of chains and patterns of infection transmission, and also the construction of epidemic trees.”¹²⁴ This capacity of pathogen profiling is especially important as changes in contact patterns often underlie the re-emergence of disease.¹²⁵ Bartholomew et al. note that, even though strong emphasis has been put on the successful translation and integration of laboratory diagnostics in the improvement of public health and clinical outcomes in medicine, there is a lack of a wide range of computational tools necessary to analyze these sequences in sufficient detail. Even though new, powerful, faster and cheaper sequencing tools are available in the developed world, and a deeper understanding of outbreaks can lead to better understanding of emerging infections, the scholars highlight that is not the case for developing countries where most emerging infections arise. Thus, the scholars recommend for effective, collaborative biosurveillance programs between regional and global entities.¹²⁶

As Eisen and MacCallum note that even though not all information about all infectious diseases is helpful, it is essential to have open, real-time access to information about other diseases, and other organisms that might impact spread or evolution. They add that opponents worry about possible risks and drawbacks to open access. An example they cite is of governments that avoid release of data (flu in Mexico) due to fear of discrimination, and fear of misinformation being spread. However, they also add that proponents argue that open source of
genomic resources can be extremely beneficial in addressing outbreaks, pandemics and biosecurity issues.\textsuperscript{127}

**Conclusion**

According to *PR Newswire US* (January 09, 2018), various advancements in genome sequencing tools: “have paved the way for the development of several precision medicine solutions.” Which they see as: “the most modernized trends in the healthcare industry that has projected tremendous level of progress in the last few years” – with the aim of making PM “more adaptable and focused towards genetic diseases” related to NCDs and infectious diseases among others.\textsuperscript{128} Leif et al. argue in favor of PM, that although certain NCDs such as T2D which are lifelong, incapacitating and affecting multiple organs cannot be prevented or cured and accounts for a substantial amount in direct healthcare costs – can however, be aided with genetic analysis (>95% of patients are diagnosed with T2D), and offered better-personalized treatment.\textsuperscript{129} Karczewski et al. also argue that PGx has the potential to eliminate the the flawed “one size fits all” paradigm for drug delivery, and deliver on the promise as an essential element of physician decision support.\textsuperscript{130} Chaudhry et al. asserts that PGx can impact the development of drugs, as early as the drug discovery process itself. They note that only 25–60% of patients respond positively to drug therapies due to variability in phenotypic and environmental factors, and up to 95% of these variations may be determined by genetic factors alone.\textsuperscript{131} Klaus Lindpainter also agrees that PGx is anticipated to revolutionize the face of medicine, “realistically,” by providing better ways to diagnose and treat illnesses - but it will be a gradual development process, building on the refined understanding of the disease mechanism, and the administration of preventative tactics.\textsuperscript{132} However, it has been highlighted by scholars like Ripudaman K. Bains, that there is a need for a coordinated international response to tackle
outbreaks in the future; and for economically developing regions to proactively take the lead to collaborate research projects to help address regional as well as global problems.133
Chapter 5: Relevance of PM in Public Health Genomics and Global Health Genomics

5.1. Introduction

Given the potential of PM in the development of more effective, personalized approaches to the prevention and treatment of infectious and noncommunicable diseases (NCDs), PM will have a significant impact not only on individual health, but public health, as well as global health.\(^1\) According to Rabah et al., it is an understatement to just say that genomics is “a powerful tool to understand the totality of the factors that contribute to health and disease” – it is a powerful tool that has the capacity to stratify the underlying causes of health and disease; the metabolism and absorption of drugs; the identification of those who will benefit from a drug and who will not; thereby, improving the effects of treatment, disease management as well as disease prevention of certain diseases.\(^2\) However, as Kenneth P. Tercyak et al. point out, this potential for tailored interventions for particular individuals, populations or subpopulations, raises ethical, legal and social implications (ELSIs) for public health and clinical practice.\(^3\) Muin J. Khoury also point out that public health plays a major role in ensuring the success of genomic medicine; because of its focus on the population that has the most vulnerable segment.\(^4\) Khoury adds that public health will have the priority to act as the controller and impartial mediator in informing policymakers, and other stakeholders about the types of technologies that will be beneficial for the positive health of the population.\(^5\) Moreover, Khoury adds that related public health responsibilities will be involving: directing patients to the appropriate providers, implementing specific programs (such as newborn screening), and creating general public awareness about genomics by implementing education and policy interventions.\(^6\) Many ethical and social concerns are also related to PM and global health - such as the social and economic disparities (10/90 gap) between developed and developing countries, is feared to increase in the era of PM.
The scope of this Chapter is to look at the relevance of PM in public health genomics, and global health genomics; look at the ethical and social issues that are anticipated to arise with PM, and also recommend some approaches to address the concerns.

5.1.1. Role of Public Health in Genomic Medicine: Infectious and Chronic Diseases

Public health played a major role in increasing the life expectancy, through improved sanitation and living conditions, and reductions in infectious diseases in the twentieth century. Today, genomics (through PM) promises similar potential for improving the health of individuals and populations. Public health genomics aims to integrate genome-based knowledge responsibly and effectively into population health. According to Gostin and Memorial, genomics offers an unprecedented promise of providing new tools for improving health and reducing the burden of diseases – chronic as well as infectious. They add that physicians and researchers have heralded genetic information in PM as the best way to maximize health care, and treatment benefits in the future – genomic knowledge will be used to classify disease, select a medication, provide a therapy, or initiate a preventive measure that is particularly suited to a given patient. As Hernandez, Lyla M. ed., notes that this would change the meaning of the Institute of Medicine's definition of public health, giving a deeper understanding to issues in health care that most people do not benefit from due to genetic variants (effects of vaccines) - making public health initiatives more efficient, as well as cost effective.

Family history and genetic testing, and other genomic approaches such as Pharmacogenomics (PGx), will play an important role in the personalization of prevention and treatment of common, chronic diseases. Scholars like Geller et al. are optimistic about the role that genomics will play in the management in high priority global public health concerns – such as in the prevention and treatment of infectious diseases, and prevention and containment of
acute and chronic epidemics (influenza, tuberculosis, and HIV). The scholars note that the genetic variants play a role on the severity of the illnesses, and with the genetic knowledge about immune response to these illnesses, they are confident that vaccines can be developed to better treat and prevent these (and other) illnesses. They point out, that research on genomics has already provided much information about the safety and efficacy of many of the vaccines.

Chronic diseases - such as diabetes, stroke, and cancer - all inflict the affected with many inconveniences, as noted by Minkyo Song et al., causing a great loss at a national level as well as at a personal level - directly translating into the longer duration of care needed, which equates to higher medical costs, and poorer function of the individual. According to the scholars, this means rising medical costs and health inequalities, with needs for improvements in medicine and related fields – both nationally and globally. Thus, the rational solution would move from ‘treating the ill’ to ‘aiding the healthy to maintain their good health’- a goal of PM in public health genomics – with the increased benefits in the burden of public health perspectives as preventive measures are applied to a larger population.

Elizabeth K. Bancroft adds that knowledge of genetic basis of diseases is expected to be beneficial for delivering healthcare and public health in several ways. First, the identification of individuals at higher risk of certain diseases will enable screening based on needs – leading to both personal and economic benefits, as screening enables earlier detection of disease such as various cancers; thus Bancroft notes, decreasing morbidity and mortality. Second, Bancroft adds, the data allows the stratification of people into different risk groups enabling better preventive strategies that can reduce the risk of disease development in individuals within a population. Third, genetic knowledge informs potential therapeutic targets and drug dosages in the treatment of disease. Bancroft further adds that previous research has documented that different people react differently to drugs, and this
presents serious clinical conditions - sometimes the drugs prescribed have no clinical benefit for the person. Genetics, through PGx, has been noted by the scholar to have huge potential in predicting the response to drug treatments, increasing efficacy and avoiding ADRs in public health.\textsuperscript{20}

Lindsey Mette et al. note that population-based analysis and implementation of PGx has the potential to maximize therapeutic benefit and avoid ADRs; and can guide pharmaceutical companies in developing more safe and effective drugs. Thereby Mette et al. adds, population-based PGx can help governments (in resource poor settings, without multiple drug choices, or with high burden of infectious diseases) efficiently use their funds, making healthcare more cost-effective and safe.\textsuperscript{21} Scholars like Lindsey Mette et al., assert that integrating PGx into national healthcare plans can be the mechanism to save lives through better medicine development and better provision.\textsuperscript{22} As Stefania Boccia adds that genomic medicine has been hailed as the future of healthcare, and public health genomics (PHG) is looked as more of a gatekeeper, making sure that the genomic knowledge and technology is responsibly implemented into public policy and health services for the benefit of population health. However, Boccia notes that the implementation of genomic medicine in public health practice has been extremely slow. They also emphasize the benefits of genome testing and screening, such as early detection of carriers of diseases such as rare diseases (RD) and cancer, which they argue can lead to benefits such as mortality reductions; and can be applied in public health as preventative interventions.\textsuperscript{23} Geller et al. agrees that PHG can also offer better understanding in the human and pathogen genomic factors to contribute to individual differences in immunological responses to vaccines, infections, and drug therapies. Thereby contributing to future policies and procedures for infectious disease management; and guiding of future vaccine development and treatment strategies, while taking
into consideration the various ethical, legal and social implications (ELSIs) for public health and clinical practice. The next section takes a closer look at the potential benefits and harms to individuals and populations because of genomics.

**5.1.2. Benefits and Harms to Individuals and Populations**

Multiple possibilities have been presented for improving public health by incorporating PGx into medicine – one of them being alleviating ADRs, and allowing for better drug development – leading to reduced social and economic implications of ADRs. As Mette et al. point out, incorporating PGx technologies in pharmaceutical development will have the potential to identify patient responder groups; thereby, preventing ADRS, and improving health which ultimately translates into cost-effective means of healthcare provision, and allowing increased access to medicine. Mette et al. also points out that PGx has great potential to target the three most frequently addressed infectious diseases that pose the largest burden globally - *malaria, tuberculosis, and HIV/AIDS*. Mette et al. note that the existing treatments are often insufficient, expensive, and difficult due to disease susceptibility, and drug metabolism in tuberculosis and malaria in the infected population groups. However, the scholars note the success of PGx in treating HIV globally.

Scholars like Heidi L. Rehm highlight that genomics is also being used across the lifespan of individual communities – from *conception to elderly care*, to provide personalized and informed precise approaches for optimizing health and combating diseases, such as *screening for carrier status for Tay–Sachs disease within the Ashkenazi Jewish population*. Other disorders such as *cystic fibrosis*, shared across all communities, are leading to broad recommendations for genetic screening. As such, Rehm adds that these tests are increasingly being included during preconception counseling to determine the risk for future pregnancy in the
United States. Rehm further comments, prenatal testing has been offered for more than 60 years on the basis of “heightened risk of a chromosomal abnormality,” suggested by ultrasound findings or advanced maternal age, and in rarer cases – “for a known familial pathogenic variant for a disorder previously identified in the family.” Moreover, the scholar highlights statistics from CDC that indicated a 6% reduction in infant mortality rate from congenital malformations between 2005 and 2011 due to preconceptual and prenatal genetic testing.

Opponents, however, are still unsure about the benefits of PM in public health. As Hernandez, Lyla M. ed., note, even though genomic discoveries have been anticipated to improve our understanding of infectious disease and inform new management strategies, opponents fear there may be potential harms without adequate countermeasures. It is evident from studies that ELSIs of PHG must be taken into consideration; especially before implementing PHG into policies. Hernandez ed., add that a serious inquiry about social justice should be made to ensure that the benefits and burdens of population-based genomics will be distributed fairly throughout society. The incorporation of PM into clinical practice and public health can only be ethically justified as long as the benefits to individuals and/or populations outweigh the potential harms – and as long as there is equity in the distribution of benefits.

Among the important challenges that have been identified by Geller et al. that relate to balancing benefits and harms between individuals and the population were: “minimizing threats to individual liberties; promoting justice in the distribution of scarce resources; and treatment of marginalized subgroups.” Stefania Boccia highlight that because there is a lack of clarity in the translation and utilization of genomics data in the improvement and better provision of health, it is crucial that public health practitioners take a more active role and embrace the...
changes by welcoming the innovation, and the personalization of healthcare to ensure that it works for the benefit of population health.\textsuperscript{32}

Song et al. emphasizes that genomic medicine is anticipated to cause many \textit{psychological effects} on individuals, such as \textit{fear of serious suffering in the future, and discrimination, and stigmatization}. Many scholars have also emphasized fear of genetic discrimination by employers and health insurance companies. Although \textit{GINA} was established in 2008 in the U.S. to offer protection to individuals, scholars have highlighted that it does not provide \textit{comprehensive genetic privacy protections}. Song et al. add that appropriate genetic counseling that requires accurate and clinically useful information derived from well-designed, high-quality research is also necessary since counseling helps weigh the benefits and harms.\textsuperscript{33} Discrimination and stigmatization is often feared due to the ability for genomics to predict the risk of susceptibility to, or transmission of certain infectious diseases, such as HIV. Geller et al. highlights that the \textit{knowledge of genetic-predisposition to sexually transmitted disease} may lead to \textit{stereotyping and marginalization} of the carrier; and can even result in the \textit{discrimination against entire subgroups} if, for example, there were correlations to any of the genetic variants.\textsuperscript{34}

As stated by scholars like Christine Aicardi et al., genomics information is different from other data since it discloses information not only about the individual but also about others, such as family members.\textsuperscript{35} They express that the notion pertaining to rights to privacy, confidentiality and self-determination entitle an individual to exercise control over the use and disclosure of information concerning \textit{his self} at every instance, but should be challenged from a broader understanding of the nature of the data.\textsuperscript{36} Anya E.R. Prince notes that there should be a balance between the harms as well as benefits in relationship to the rights and duties. Another area of concern highlighted in studies is whether to report/disclose incidental findings (IF), given the
widespread effects of genomic data. Even though there is a consensus that the researchers must return clinically useful results to individual participants; Prince note that the boundaries of this duty are not well defined. Some proponents support the idea of automatically disclosing the information in the patients’ clinical records. However, there are negative sides to this. As pointed by Prince, automatically disclosing findings will deny the participants to process the information first, and may put them at risk to discrimination by employers and life insurance companies by making this information readily accessible. Moreover, the scholar also emphasizes that the information remains in the patient’s medical record permanently.37

Geller et al. point out that genomics and Public Health can result in conflicts due to the prioritization of privacy in genomics on individuals, which are overridden in public health for the benefits of the population. They add that an individual's genomic factors may have additional legal and policy implications – such as screenings could influence decisions about access to therapy in settings with limited resources, or restrict children - screened as being super-spreaders - from going to school, placing a higher value on the harm that may be placed on others.38

Disparities in access to critical resources are another area of concern, which can be due to many barriers such as socioeconomic, cultural, or environmental barriers. Public health agencies act as the gatekeeper, making sure barriers are identified and addressed and whether the genetic tests are reliable enough for the population in the clinical setting. As E. W. Clayton noted, public health agencies has the role of developing strategies to educate both healthcare providers and patients about genomic medicine - such as "the Secretary's Advisory Committee on Genetic Testing and its successor, the Secretary's Advisory Committee on Genetics, Health, and Society."39
Although, as Geller et al., point out that it is highly unlikely that all the potential ethical and social issues will be identified at once, anticipating and discussing about such considerations will be helpful in guiding research questions and decisions about public funding, and contributing to the ongoing effort in the development of policy recommendations for genomic medicine, and its applications in public health and clinical practice in infectious disease, both nationally and globally. The next section looks at personal and societal concerns about genetics in public health, with a focus on the race controversy and race-based medicine.

5.2. Concerns about Genetics in Public Health - Race Related

As scholars like Rick Kittles note that genetic risk prediction is continued to be integrated into medicine to provide new directions to build PM plans through improved diagnostics, and the development of new drugs through PGx. Genomic research is largely population-specific, and classification of data by racial and ethnic groups raises unique ethical challenges. Kittles, moreover, noted that researchers and clinicians increasingly combine genetic information with a variety of non-genetic information in clinical management of common conditions, which can be problematic. Jaja et al. emphasizes in their study that random ascriptions (without much thought) of racial categories in genomic research in the context of health disparities, could become problematic and may have undesired and unintended effects, which may undermine the successful clinical translation of genomic research. The next two sections look at the concerns that are anticipated due to race-based medicine and genomic research.

5.2.1. The Race Controversy in Genomic Research

Opponents fear that genetic tests may increase health disparities, instead of improving health outcomes, if participation across all communities is not ensured. As Kittles note, currently, most diagnostic tests and information on risk assessment are specific to genetic
information based on European ancestry. There is little information about risk assessment in populations that have historically been underserved, or of color, in medicine.\textsuperscript{44} Therefore, Kittles emphasizes that it is important that we continue to study diet, lifestyle, socioeconomic status and other environmental exposures such as stress, discrimination, medical literacy, and so on, \textit{independently of race} to understand the gene-environment interaction that plays a role in diseases. Kittles points out that geographic distribution of populations of the same race may also vary, and this is an important area of much-needed focus.\textsuperscript{45} Although, increased knowledge of race and ethnicity is expected to aid in the prediction of disease etiology and treatment response; it is also feared to increase stereotyping and bias, preventing effective treatment for racial and ethnic minority patients.\textsuperscript{46}

According to studies by Kaphingst et al., significant differences by race/ethnicity in responses to genomic information were observed. They reported that race/ethnicity of an individual may be predictive to genomic risk, more than the genomic data; and noted that race/ethnicity was associated with “interest in receiving a genomic assessment, discussing genomic information with family members and with a doctor, and intentions to change health habits in response to the genomic data.”\textsuperscript{47} Nonetheless, Kaphingst et al. also noted that there is not enough data that show how race/ethnicity might affect responses from underserved populations regarding genomic information; since they observed that racial and ethnic minority groups have been underrepresented in genetic research. Despite the limited data on racial and ethnic minorities, Kaphingst et al. noted that Black women perceived fewer health benefits to genetic testing than White women. Healthcare-related distrust has been shown to be higher among Blacks than Whites. They also noted fewer positive and more negative attitudes were attributed toward genetic testing amongst Blacks and Hispanics than Whites, indicating less use
of genetic testing amongst individuals from racial and ethnic minority groups. They observed lower awareness and lack of knowledge between minority racial and ethnic groups and Whites. The scholars emphasize on further research to investigate the knowledge and interpretation of genomic information amongst the underserved populations. 48

Much debate surrounds the conceptualization of race, and genetics - emphasizing “the need for addressing ethical issues surrounding genetic technologies, genetic information, race, and health inequities” - all of which are essential to improve the public's health as pointed by Bonham and Knerr.49 They add that “race and ethnicity” are used extensively in identifying genetic susceptibility to various illnesses, and cancer screening is a good example that may benefit from this - leading to “early diagnosis.” In the fields of cancer research, treatment, and prevention, many complexities have been faced in the use of racial and ethnic categories to predict health-related outcomes, and medical decisions. While some clinicians agree that race and ethnicity are beneficial, and useful predictors, Bonham and Knerr are concerned that this will lead to the inappropriate utilization of race and ethnicity merely as a proxy, and will lead to inaccurate decisions.50 They voice other concerns such as the influence of unconscious physician stereotyping of patients, which can impact patient satisfaction and behaviors in clinical encounters. Bonham and Knerr strongly urge that there is a need to understand the causes behind racial and ethnic health disparities, and implementing interventions to address them is critical, and will include unraveling the effects of “implicit and explicit bias.” They further point out that this race related complexity has been illustrated in documentation of disparities in both risk communication and treatment in the fields of cancer.51

Disparities in the management of cancer-related pain between racial and ethnic groups, as well as in the utilization of surgery and radiation, have also been observed by scholars.
Utilization of genomic technologies and information also has the potential to exacerbate health disparities. Bonham and Knerr emphasizes that ethnicity and race not be used as *phenotypes*, but rather as social categories and groupings that can correlate with genetic variation in the human population, stating that, “viewing race as a phenotype can lead to barriers to effective patient care.” Genomic research currently highlights human variations and utilizes stratification of population to stipulate susceptibility to diseases, drug response, and other health outcomes. However, E.W. Clayton noted that certain racial groups were disproportionately affected by this stratification of risk factors and diseases, and this concern is further aggravated by the fact that health information is not private. Foster et al. adds that the development of a “broad cross-cultural consensus,” on the “social relevance of purported associations between genetic and other biomedical information and social identities,” can greatly reduce the risks of group stigmatization and discrimination. Furthermore, Foster et al., suggests that bioethicists can help researchers frame research findings that will draw attention to health disparities that exist between groups, and help design protocols that will prevent others from defining groups from “perceived biological differences.” The next section looks more intently at race-based medicine, and the issues anticipated with it.

5.2.2. Race-based Medicine, and Issues

From the very beginning of federal documentation of health disparities, racial and ethnic disparities in health status have been observed. Williams et al. pointed out that national policies have been implemented in phases to reduce and eliminate health disparities, and attain the highest level of health equity among all population groups. Specific chronic conditions remain prevalent across disadvantaged populations even though such policies are in place. Williams et al. also identified a need to eliminate disparate care among multiple population groups, and
increase the overall health equity through new knowledge of genomics. However, Gerard et al. voiced their concerns that such advances in knowledge will only exacerbate the disparities that exist today - especially if the information “is abused, misused or even incorrectly used” - and that is a concern in PHG. The genomic advances face many challenges specifically in the translation, interpretation and actual application of this new tool – finding optimal ways to integrate the information into disease prevention and health promotion will be critical.

According to Dorothy E. Roberts, the success of race-based medicine and its utilization depends on the approach to achieving racial equality and should be a medical, as well as, political concern. Roberts also noted that there is still no consensus among African Americans about the importance of race-based medicine; although there are opponents, as well as proponents regarding this new technology. Roberts add that some African American scholars have criticized race-based medicine as a scientifically flawed and commercially corrupted misuse of biomedical research on health inequities. They argue that this will create dangerous biological misunderstandings of race. While, Roberts add, proponents showed support by arguing that racial therapeutics will be successful in redressing past discrimination, and fulfilling longstanding demands for addressing the health needs of African Americans – such as the Association of Black Cardiologists who co-sponsored the trial to test the efficacy of BiDil, approved by the FDA in treating heart failure in African Americans. The National Medical Association and some members of the Black Congressional Caucus also joined in support of BiDil.

Proponents of PHG argue that the application of race-based medicine will be effective in the disease management strategies that consider that early identifiable risks will help tailor health promotion, and disease prevention messages for segments of the population in ways never seen
before. However, Gerard et al. points out that concerns arise due to the history of misuse of public health services in the past - such as the unethical research study of Tuskegee syphilis study. Therefore, Gerard et al. argues that past history of misuse issues a caution for public health to proceed cautiously, with clearly articulated goals, and methods with public involvement and accountability.  

Nils-Eric Sahlin and Göran Hermerén argues that genetics dictating which patients would be less likely to benefit from personalized medicine would result in a lack of fairness. Sahlin and Hermerén provide two interconnected principles defining distributive justice in medicine that have been identified as relevant in addressing this issue: (a) health care resources should be distributed according to need, and (b) no patient needs a treatment which does not affect him or her. Public health ethics has always emphasized issues of justice, with a concern that health benefits and burdens be distributed fairly across the population. According to Jaja et al., the FDA’s approval of BiDil has heightened the need to address the relevance, societal justifications, and implications of racial stratification in terms of existing health disparities in genomic research. BiDil is hailed as the first ethnic drug, designed and marketed for the treatment of heart failure in African American patients only. However, a critical concern raised by scholars like Jaja et al., is whether differential responses to drug treatment between racial groups are attributable primarily to genetic differences? Advocates for race-based medicine, such as BiDil, argue that racial disparities exist in illnesses and responses to treatment, and that race matters biologically, and therefore, doctors and researchers cannot be colorblind. Jaja et al., however, argues that from history it has been noted that colorblindness is acceptable, even preferable, with regard to social policies.

Roberts also voices the fear that race-based medicine can affect the direction of State efforts that are there to address health disparities and inequality, by diverting blame from
inequitable social structural causes and access to healthcare, to genetic explanations. Rather than addressing diseases, race-based medicine might play the devil’s advocate in shifting government’s responsibility for addressing the causes to blaming genetic variations. Moreover, much of the funding for developing racial pharmacogenomics is feared to cut into resources available for social strategies as Roberts adds - characterizing a disease as a “genetic disorder,” and placing the responsibility for ending health disparities on individual health decisions, ultimately relieving the sense of societal obligation to fix systemic inequities. Marketing for race-based medicine is also feared to promote the view that inequities resulting from neoliberal policies are caused by natural differences between blacks and whites – ultimately placing the burden on individuals for curing their unequal status, as pointed out by Roberts. Opponents of race-based medicine argue that the genetic explanation of racial disparities provides a ready logic for the staggering disenfranchisement of black citizens, as well as the perfect complement to colorblind policies, giving the reason that racism can no longer be blamed for the cause of their disempowered status. Furthermore, Jaja et al. states that given the United States’ history of racial discrimination, diverse stakeholders are afraid that drugs like BiDil will oversimplify the public understanding of genomic contributions to human health by reinforcing false notions of racial profiles - ultimately weakening the scope for equity in healthcare.

Genetic factors are advancing genomic research and reducing health disparities in many common conditions. However, studies suggest that the specific genetic variability pertaining to the specific clinical difference within the racial group is still not clear, and would require extensive scientific research. Such knowledge would be useful in eliciting how race specific variables can be beneficial in the context of genomics and health disparities. Alarmingly, studies note that many people self-identify incorrectly. Therefore, racial self-identification cannot
adequately substitute for genetic classification. Williams et al. point out that in order for PM to be successful, medical guidelines and policies have to ensure the inclusion of all racial and ethnic groups from diverse communities; otherwise, gaps in care between different groups may be exacerbated, as in the case today. There are fears of discrimination, based on those who have, and those who do not. Uncertainty about the costs of research and medical care could present challenges as well, especially to those of lower socioeconomic status (SES). According to Williams et al., it has been estimated that genomic sequencing can range from $1,000-$100,000,000 depending on the desired information. Differences across racial or ethnic groups in understanding the risks and benefits of genomic medicine could result in disparities of care related to use of, rather than access to, genomic medicine and personalized care. Federal agencies recommend the collection of racial or ethnic background information to address racial or ethnic disparities. Williams et al. emphasizes that it will be critical to understand the barriers and address the disparities that exist due to racial differences, and it will be necessary to allow analysis of patient, provider and system-level factors that play a role in creating the disparities.

5.3. Future of Precision Medicine in Public Health

Even though PM has significantly influenced clinical practice over the last two decades, and is now in a position to lead a change in public health practice, public health has yet to change significantly in its response to the use of PM. R.L. Zimmern noted that PHG was established in 1977, and placed genome-based science at its core with its official definition set by experts in the meeting in Bellagio in 2005 to be: “the responsible and effective translation of genome-based knowledge and technologies for the benefit of population health.” So far the public health approach has been to apply interventions to the population, framing the relationship between intervention and outcome concerning the population as a whole – paying little attention to the
individual’s genetic variation. Scholars like Zimmern argues that the concept of population in public health should be moved implicitly from being an entity in itself to a set of individuals, citing natural selection as working through individuals and not through populations – where they argue that population is the “derived abstraction,” while the “fundamental biological unit through which interventions work must be the individual.” 69

5.3.1. Current Priorities for Public Health and Economic Implications of Genomics

Current priorities in public health include early diagnosis of cancers and PGx that addresses therapeutic interventions. Angela Brand et al., argues that genomics, through PGx is essential in developing targeted drugs for different cancers, that can significantly improve response to therapies. For example, Brand et al. states that Herceptin only works for 15 percent of patients with breast cancer, “who overexpress a specific chemical receptor;” and Iressa, only works for 10 percent of patients with lung cancer, “with a mutation in a particular part of a different receptor.” It is evident from studies that only patients with these specific molecular features will respond to these drugs, others will not. This makes manufacturing of such drugs less attractive to drug manufacturers versus manufacturing drugs that work on most patients. However, Brand et al. argue that drugs that are effective for specific genetic characteristics targeting lung cancer, may also work against other types of cancers with that characteristic. Therefore, the scholars are optimistic that the genomic era can lead to personalized healthcare and pharmacogenetics-enhanced drug development to prevent, or better manage diseases. 70

Preterm birth (PTB), a major cause of death in children up to 5 years of age in the developed world, is also a major healthcare challenge, in the developing countries. Early birth in low-resource countries is the second greatest cause of death in young children - pneumonia being first. According to Newnham et al., the potential impacts on individuals, families, and society of
PTB are considerable – children born too early will suffer from many life-long disabilities, such as neurodevelopmental delay, hearing, and visual loss, cerebral palsy, and learning and behavioral problems. Dedicated neonatal intensive care units are vital to minimize any potential for life-long harm to such preterm infants, but costs considerably; however, the potential cost to society throughout the lifespan of the individual is significantly more. Newham et al. is optimistic that precision public health (PPH) is anticipated to offer opportunities previously unavailable.\textsuperscript{71} Although PPH has arisen from the emerging field of PM, there is far more potential to the concept of PM than just “drugs, genes, and disease,” argues Newnham et al. PM approaches can identify population groups rather than just individuals, yielding greater benefits.\textsuperscript{72} Therefore, PPH has the potential to benefit the right population at the right time.\textsuperscript{73} According to Newnham et al., a variety of population-based PTB prevention programs have already been implemented in different communities, that target the needs specific to their communities, aiming to overcome deficiencies that may be contributing to high rates of early birth. In the U.S., several programs have been launched aiming to overcome health inequalities – much of which has been resulted from the awareness of the very different rates of PTB among the various racial groups. Newnham et al. provide data from 2014 that shows that the rates ranged from 13.2\% in non-Hispanic Black women to 9.4\% in Hispanics, and 8.9\% in non-Hispanic Whites. Poor socioeconomic conditions and educational standards may be factors playing a role in the high rates of PTB. The scholars argue that applying the principles of PPH may enable progress that previously seemed unreachable.\textsuperscript{74}

According to Burke et al., genetics can help to identify groups susceptible to developing a particular health problem at the population level, such as the GWAS of the treatment response to \textit{Carbamazepine}, a medication which is used in the “management of epilepsy, trigeminal
neuralgia, and bipolar disorder.” Background genetic risk information can inform investigations of other risk factors, or of prevention approaches, and can improve the quality of health care.\textsuperscript{75} Belsky et al. states that PHG can serve as an institutional umbrella for these processes – that are necessary to adopt the ‘product’ innovations in genomics “by quantifying not only the impact of gene variations on the risk of the condition but also the effect of modifiable factors that interact with gene variations.”\textsuperscript{76} Genomic technologies can be beneficial in public health epidemiology to inform the policy and priority setting by monitoring the health statuses of at-risk and disadvantaged populations, as pointed out by Baynam et al. The scholars further add that this can be critical in attaining health improvements for those living with rare diseases in underserved populations - which are caused by destructive, but previously difficult to identify protein-coding gene mutations - through early diagnosis and best care.\textsuperscript{77}

Jaja et al. brings to our attention that PM is anticipated to be integrated into the healthcare system soon, and public health research will need to take part in the controversial discourse as to how to incorporate genomics into policies and practices that will benefit populations.\textsuperscript{78} Belsky et al. states that genomics provides a bridge between medicine and community-based public health, most importantly in the setting of clinical genetics. They point out that both genomics and public health focus on populations, with the intention to understand the mystery behind the genetic variations and the roles this variation play in dispositions to diseases, reactions to the environment, and most importantly in healthcare – “responsiveness to medications.” Additionally, Belsky et al. add that both genomics and public health recognize the importance of cultural, societal, and ethnic contexts in healthcare as a part of population health.\textsuperscript{79}
5.3.2. The Place and Priority of Genetics in Primary Care

According to E. W. Ebomoyi & Josephine I. Ebomoyi, population screening for rare diseases that can be prevented or mitigated with timely prevention would likely be an immediate application of genomics in public health.\textsuperscript{80} New genetic discoveries could also identify sensitive or critical periods in pathogenesis when intervention could be most effective, and also inform the selection of intervention targets.\textsuperscript{81} Ridgely Fisk Green et al. states that pathogen genomics played an important role in public health for decades and had been integrated into CDC’s activities through the \textit{Advanced Molecular Detection Initiative}, with the purpose of addressing applications of pathogen genomics technologies. Green et al. adds that genomics is already an important topic for \textit{Healthy People 2020} in their goals of providing “genetic services for individuals at risk for \textit{Hereditary Breast and Ovarian Cancer} (HBOC), and \textit{Lynch syndrome} (or familial colorectal cancer syndromes).” BRCA genetic counseling is a preventive service already implemented in healthcare and covered by most insurers. Green et al. argue that the \textit{Office of Public Health Genomics (OPHG)} at the CDC was created in 1997 with the goal of working with state health departments, and other partners to identify opportunities for genomics in the improvement of population health, and provide support for genomics-related public health activities.\textsuperscript{82}

PPH has the potential to protect many people from various types of cancers, CVDs, and diabetes. In 2008, the NIH indicated how cancer disease burden cost the USA nearly $210 billion; which included $74 billion in direct medical costs, $17.5 billion for lost productivity from illness, and loss of productivity due to unnecessary and premature death equating to $118.4 billion.\textsuperscript{83} According to CDC, despite the decrease in cancer deaths, the U.S. is expected to see an increase to nearly 2 million a year by 2020 due to newer cancer cases. As of today, cancer is a
public health problem in the USA, with more than 1.5 million people being diagnosed, and more than 500,000 dying from the disease. From research, it was noted that more than half of the cancer deaths could be prevented through healthy choices, screening, and vaccinations. Although, early screening tests can act as preventive measures for colon, cervical and breast cancers, by identifying the disease when treatment works best; CDC states: “screening rates for these cancers remain below national targets set by Healthy People 2020, the nation's agenda for improving the health of all Americans.” Moreover, CDC states that vaccines can also lower cancer risk - such as the human papillomavirus (HPV) vaccines (cervical cancer), and the hepatitis B vaccine (liver cancer).  

Although data from 2006 showed that CVDs accounted for over 40% mortality in the USA, killing about 95,000 yearly; researchers at the American Heart Association found that: “Between 2000 and 2011, researchers found the national heart-related mortality rate declined at an average of 3.7 percent per year, while stroke mortality declined at 4.5 percent per year.” They credited this decline to advances in biomedical research and technologies. Even then they cited stroke and heart failure to be the most expensive chronic conditions in the Medicare fee-for-service program in 2014. Projections by the American Heart Association show that nearly half of the U.S. population will have some form of CVD by 2035. Tikki Pang asserts that genomic medicine and screening technologies are anticipated to be vital in the reduction of strokes and other chronic diseases. Amongst the many benefits that genomic medicine can offer, he adds that the most important benefit is the early disease detection ability - when it is treatable and less expensive; stratify patients into groups that enable the selections of optimal therapy; reduce adverse drug reactions; improve the selection of new biochemical targets for drug discovery;
reduce the time, cost, and failure rate of clinical trials for new therapies; shift the emphasis in medicine from reaction to prevention and from disease to wellness.  

According to Leif et al., genomic medicine is also anticipated to play a crucial role in reducing the prevalence of diabetes mellitus (commonly known as diabetes) - a lifelong, incapacitating disease affecting multiple organs. They highlight that T2D presently cannot be cured, neither can it be prevented, and is associated with devastating chronic complications that impose an immense burden on the quality of life of patients. Data indicates the increasing prevalence rates of T2D in the adult U.S. population (estimated 6.3 with either diagnosed or undiagnosed diabetes). Based on an individual's family history it is evident that genetics plays a role in the risks of developing diabetes. It was interesting to see Murff et al. note the heritability of T2D diabetes: “approximately one in six patients who identified a relative as having diabetes were almost three times as likely to have a plasma glucose determination when compared with individuals without a family history.” Treatment for T2D includes diet and exercise, and drug treatment to control their glycemia. Unfortunately, scholars note that treatment of T2D has not been very successful, many resulting in ADRs. Zhou et al. argues that the advance of genomics has greatly increased our genetic understanding of the etiology of diabetes, especially pharmacogenomics (PGx). They highlight that PGx seeks genetic explanations as to why individuals differ in the reactions to drugs, concerning therapeutics as well as adverse drug reactions (ADRs). Zhou et al. also points out the role that PGx plays in the investigation of antidiabetic drug response. 

Baynem et al. reports on rare diseases, and the need for a national public health policy framework. Findings from their studies suggest that sharing of knowledge and experiences across different countries' rare disease networks and partnerships can help inform the
development of a Strategic Framework for Rare Diseases (RD) like it did in Australia (Western Australian Rare Diseases 2015–2018, RD Framework). The RD Framework has been able to provide health briefings to the Australian government on the need for a National plan and has guided in the precision diagnostic pathways and care into the Western Australian health system. Findings from Baynam et al. suggest that the RD Framework can be used as a precision public health framework for improving outcomes in rare disease populations, by informing public health with the population needs, early and accurate diagnosis that can provide the appropriate care. According to Baynam et al., there is an estimated 5000–8000 rare diseases; combined these affect up to 6–8% of the population. Additionally, they report that these amounts to “over 400 million people living with a rare disease,” making rare diseases a major global public health issue - and “80% of these are genetic.” Although, RD first manifests in childhood and continue across the lifespan and cannot be prevented or cured (yet), early diagnosis can result in early intervention and can aim to improve management and ultimately reduce the associated human, community and system cost.

Scholars like Brand et al., and E. William Ebomoyi & Josephine I. Ebomoyi define the role of public health in enhancing population health as: public health’s role being in managing the distribution and utilization of genomic applications with the intention of benefiting population health; and implementing the necessary evidence-based genomic applications to improve and prevent diseases, excluding or limiting premature utilization or misuse/overuse; and by serving as an unbiased convener of stakeholders. E. W. Ebomoyi & Josephine I. Ebomoyi also add that the Evaluation of Genomic Applications for Practice and Prevention (EGAPP) launched by CDC in 2005, systematically reviews and updates the validity of genomic applications, and makes recommendations for appropriate use, where prioritization is based on
“the level of evidence, the burden of morbidity and mortality that can be prevented in the population, and cost-effectiveness of interventions.” Moreover, E.W. Ebomoyi & Josephine I. Ebomoyi add that public health plays a role in evaluating the health impact of public health interventions using genomics tools, regardless of their current use of genomics. The National Health and Nutrition Examination Survey (NHANES) is used as an example by E. W. Ebomoyi & Josephine I. Ebomoyi, used at a national level to evaluate the health impact of interventions on different segments of the population. Stratification of population based on genetic risk prevention (high, low, moderate), can aid in the effective and efficient application of standard public health interventions. Genomics also has the potential to benefit the global population as well - the next section looks at the potential for global health genomics, specifically for developing countries.

5.4. Potential for Genomics for the Health of the Developing Countries

According to the WHO, fundamental social and economic disparities continue to exist between developed and developing countries with communicable diseases constituting the greatest component of the total disease burden across much of the developing countries. However, it has been noted in a Report by the Global Forum for Health Research that the disease patterns have shifted towards multifactorial "lifestyle" diseases, such as cancer, heart disease, and diabetes which were more prominent in developed countries before. According to a report by the World Health Organization, genomics research will play a major part “in the prevention, diagnosis, and management of many diseases,” which have been difficult or impossible to control. Since genomics research is a new technology, it requires high capital investment. There is a fear that this could lead to wider disparity in global spending ("10/90 gap") on health research between developed and developing countries. Burket et al., emphasizes
the need to address this disparity by stating that we can only move closer to realizing the goal of precision medicine to improve the health of individuals by anticipating and addressing the potential for inequitable access to health care occurring from using genetic information.\textsuperscript{104} The next two sections look at the potential applications of genomics in global health.

5.4.1. Noncommunicable and Communicable Diseases

The WHO reported in 2008 that an estimated 36 million, or 63%, of the 57 million deaths that occurred globally were due to NCDs, also known as chronic diseases – mainly CVDs (48%), cancers (21%), and diabetes (3.5%) – 80% (29 million) of which occurred in low and middle-income countries (LMIC), and a higher proportion (48%) of the deaths in the LMICs were premature (under the age of 70) compared to high-income countries (26%). As per the WHO's report, these were treatable (rheumatic heart diseases and type 1 diabetes) through health promotion, disease prevention, and comprehensive care. The WHO projected an increase in the total annual number of deaths from NCDs to 55 million by 2030 if appropriate action is not taken.\textsuperscript{105,106} As of date, the number of deaths has been staggering - 41 million people die each year globally from NCDs, which is equivalent to 71% of all deaths globally (WHO, 2018).\textsuperscript{107} As reported by the WHO, communicable diseases (also known as infectious diseases) place a significant burden on all countries and regions, especially on those living in poverty and those who are socially excluded or marginalized, and has been responsible for over four million deaths worldwide each year. The WHO recommends implementing (already available) interventions for prevention and control to greatly reduce this burden.\textsuperscript{108} Nishi et al. states that advances in genomics research have influenced epidemiology greatly – it can encompass all data on health and diseases around the world, gaining new insights on causal associations; and has also aided in the integration of molecular pathology and epidemiology, leading to the formation and
development of molecular pathological epidemiology (MPE). Nishi et al. further promotes MPE and social epidemiology by adding that these developments have been greatly beneficial to global populations since it allows scientists to learn more about different molecular pathology and pathogenesis of different disease areas, not just neoplastic diseases such as cancer. It is not far when MPE increasingly be used in the diagnosis and classification of virtually all diseases. Nishi et al. anticipated that MPE will enable the deciphering of the different etiologies of diseases and address health disparities in a global scale, and will have the potential to change the way in which global disease control can be addressed. The advancements in molecular medicine, including diagnostics, imaging, and targeted therapeutics can have immense benefits on individuals in global populations employing the interdisciplinary approach of integrative MPE and social health science. Babatunde O. Adedokun et al. advocates for genomics research, stating that genomics research can particularly be attractive for Sub-Saharan African (SSA) countries, where new technologies and products from genomics research can help alleviate the heavy burden of infectious and chronic non-communicable diseases (NCDs) – by bringing about significant improvements in diagnosis, prevention, and treatment of several disease conditions. Sarah Gibbon notes that efforts to align genomics with epidemiology and infectious diseases in global population health are in progress. According to the WHO, growing evidence suggests that better knowledge of the pathogen genomics will provide insights to the spread of infectious diseases within populations, and anticipate the emergence of epidemics and “new” or virulent forms of known infections, such as Creutzfeldt-Jakob disease, new strains of Influenza virus, Hantaviruses, and Human Sleeping Sickness. Novel vector control approaches are also being considered for the prevention of communicable disease such as malaria. Genomics is being applied to better understand variability in host
response to infectious diseases depending on gene families, with considerable progress being made in identifying a variety of gene families which are involved in modifying susceptibility to malaria and other infections. Moreover, Singer et al. notes that genomic technologies are anticipated to have the potential for the prevention, diagnosis, and treatment of HIV, malaria, and tuberculosis; and can also be applied to understand the genetics of bacteria, plants, and animals. Moreover, Singer et al. adds that genomics is expected to have direct economic effects on the pharmaceutical market – with growth projection from US $2.2 billion in 1999 to US $8.2 billion in 2004. Acharya et al. also argues in favor of genomic-related technologies, stating that they are changing global perceptions by becoming simpler and cheaper, to the point where older technologies in poorer nations can be easily replaced with newer ones. They add that genomic-technologies has made it possible to develop simple and easy-to-use tests for tuberculosis, hepatitis C, HIV, malaria, and other diseases. The polymerase chain reaction (PCR) is a fast and accurate technology for making millions of copies of a specific sequence of DNA. Besides being extremely sensitive, Singer et al. adds that PCR tests can provide results in hours versus days, and can detect difficult or impossible to grow (in cultures) infectious organisms, such as tuberculosis; or like HIV/AIDS which are dangerous to handle. Previously, PCR tests were only available in the industrial world; however, Singer et al., notes that the recent advances are beginning to bring this powerful tool within reach of the developing world.

Singer et al. further emphasizes that molecular diagnostics present a robust “set of methods” to address the health-related Millennium Development Goals: “Combat HIV/AIDS, malaria and other diseases; Reduce child mortality and Improve maternal health.” They also noted that “infectious and parasitic diseases” are responsible for 17 million of all deaths every year. With HIV/AIDS, malaria and tuberculosis being the three major killers, Singer et al. adds,
together claiming “at least 5 million lives a year.” They further add that “11 million children” have been estimated to still die before reaching the age of five. Singer et al. states that: in order to achieve this goal, improving public health for disease prevention will be important, but it will also be important to make sure there are effective methods for diagnosis and treatment for these diseases. They further add that developments of “rapid and accurate diagnosis, will not only increase the chances of survival, but also avoid waste of resources on inappropriate treatments, and help contain diseases.” 121 They also add that the antibody-based application is highly suited to the developing world since: “Antibodies are molecules produced by the immune system in response to infection,” which “can recognize and attack the proteins produced by the pathogens.” Singer et al. notes “that antibodies are specific, that is they recognize and bind to specific types of antigen,” making them “an excellent tool for the diagnosis of infectious disease.” They add that recently: “simple and rapid antibody coated dipstick tests have been developed that have increased the relevance of this technology for the developing world. Dipsticks can be used anywhere, without the need for laboratory facilities, running water or electricity” which can be scarce in developing countries.122

Singer et al. goes on to add that recombinant vaccines, another development of the genomic research, can attain many of the Millennium Development Goals: “Reduce child mortality; Improve maternal health, and Combat HIV/AIDS malaria and other diseases.” They add that the hepatitis B vaccine is an example: “which saves the lives of millions of people, including children, every year, and many HIV vaccine candidates currently under investigation are treated with recombinant vaccines.” Singer et al. adds to their argument that recombinant vaccines are promising “to be safer, cheaper, and possibly easier to store and transport than traditional vaccines.” The scholars add: “vaccines stimulate the body to produce a protective
immune response, and thereby, reduce the likelihood of serious infections.” Singer et al. moreover highlight that: “Advances in vaccine research are likely to have an impact not only on communicable diseases but also on non-communicable ones such as cancer.” Singer et al point out that pathogen genome sequencing can also contribute to the identification of: “the genes that play a role in helping organisms develop drug resistance and point researchers in the direction of treatments that can overcome the action of these genes.” Singer et al. add: “A serious health concern worldwide is the emergence of pathogen resistance to previously effective drugs.” The next section looks at the importance of pharmacogenomics and gene therapy.

5.4.2 Pharmacogenomics and Gene Therapy

According to Katherine Chadwell, the Agency for Healthcare Research and Quality reported that 770,000 injuries or deaths are related to adverse drug events each year in the USA alone - which costs between $1.56 and $5.6 billion annually. Although drug therapy can be impacted by many variables, such as age, organ function, or drug-drug interactions, Chadwell adds that it is estimated that pharmacogenomics dynamics could reduce this cost, since variations in the molecular analysis has already shown that there is considerable individual variation in response to drugs used to treat some of the more common diseases. Research suggests that the burden of ADRs on patient care has been found to be high globally as well. According to Ushma C Mehta, studies conducted in various regions of the world involving 419,000 patients, approximately 6.7% of all hospitalizations were due to ADRs - where Mehta notes that more than half of the ADRs were “preventable with improved prescribing, administration, monitoring and adherence.” Mehta also observed that “patients with HIV/AIDS were found to have an increased risk of ADRs” in developing countries. Mehta states: “Patients with HIV/AIDS were found to have an increased risk of ADRs. This is probably due to the effect of the disease on the
immune system (which is responsible for many idiosyncratic drug reactions) as well as the safety profile of the complex drug regimens that patients with HIV/AIDS are often receiving.” The WHO recognizes that genetic screenings are worthwhile in populations where there is a high frequency of side-effects due to genetic susceptibility to drugs used to treat common diseases. Although the burden of poverty-related conditions and infections remain substantial in the developing world, Burke et al. points out that the combination of increased affluence, urbanization, and life expectancy has led to global growth in the incidence of complex diseases. There is mounting evidence of diverging health outcomes within and between economically developed countries and low and middle-income countries (LMICs).

As noted in the Report of the Advisory Committee on Health Research, genomics always looked promising in the cancer prevention and treatment, and as such will no doubt be integrated into public health practice in the early identification of cancer. Although, age is a common factor for most of the oncogene mutations, studies from the WHO demonstrate that a much rarer group is associated with a strong family history of cancer, resulting from mutations of a family of genes called “tumor suppressor genes” which, evidence suggests, are inherited. Tremblay & Hamet argues that PGx and individualized drug therapy are "the building blocks of personalized medicine." Additionally, they state that pharmacogenetics testing will help to identify the differential responders, providing a basis for personalized drug treatment of a large number of patients. Per Donna Dickenson, sometimes overtreatment, or aggressive treatment such as chemo that is part of the "one-size-fits-all" cause side effects leading to deaths. She advocates for tailored medicine, stating that under such conditions, tailored medicine would not only be more humane but also more effective. She further adds that it would be possible to identify patients who are genetically programmed to respond more quickly to chemotherapy and
to give them lighter dosage than to “kill or cure.” Another important application would be genomic testing for individual variations in drug metabolism, as pointed out by Andrew Blix, “PM represents a major change in the way” health care will be delivered, and because cancer is fundamentally a genetic disease, advances in genetics and genomics have profound implications for oncology. Blix argues that PM offers the promise of treating diseases or predispositions identified in the individual genome with specific, targeted pharmacogenomics medicines dosed for the individual's unique metabolism; it can also be effective in determining fewer side effects for patients.

Genomics is also anticipated to play a role in disease identification and prevention of chronic ill-health – known to contribute to death, increased disability, and health care costs, which represents a substantial public health concern according to the WHO. Katherine Chadwell makes an important observation where she states that although PM cannot reverse health problems, it can offer the most effective treatment for a person's current chronic issues. She adds that the key component for healthcare will be focusing on prevention and earlier intervention with appropriate treatment, by addressing potential causes identified in a person's genetic and genomic makeup. Genomics is already applied in diagnosing monogenic diseases – the commonest being those involving human hemoglobin, the thalassemia and sickle cell disease and its variants, conditions which have a particularly high frequency in developing countries. As countries undergo the demographic transition, there is increasing evidence for the transition in the pattern of diseases from malnutrition to other chronic illnesses, such as cardiovascular disease, diabetes, and cancer, posing an increasingly severe health burden. Data presented in the Report of the Advisory Committee on Health Research, demonstrate that NCDs are accounted for the deaths of twice as many people in the developing countries than in the
developed countries. T2D is an example, according to the WHO T2D is also a crucial risk factor for CVDs, and appears to be reaching frequencies between 20% and 70%, doubling the global number of 150 million affected people to 300 million by 2025.137

Gene therapy is primarily used as medicine to correct defective genes responsible for genetic disorders, and as argued by Singh et al., gene therapy has the “potential to eliminate and prevent hereditary diseases.”138 Reports from the WHO also highlight the clinical impact gene therapy will have on cancer therapy, especially in the targeting of abnormal functionalities of oncogenes and drugs targeted to treat cancer and other common diseases.139 Scholars like Verma and Somia also argue in favor of gene therapy, stating that gene therapy can be instrumental in the eliminating and preventing diseases such as cystic fibrosis, which are hereditary diseases; and is a possibility to cure heart disease, AIDS and cancer. However, they also point out that amongst the disadvantages, gene therapies may not be effective due to immune responses which are short-lived.140

A significant challenge in demonstrating the relevance of public health genomics in LMICs, according to Burke et al. is to generate an evidence base that can confirm that a genomics approach is at least as safe, effective, and cost-effective in these settings, as other more traditional approaches, such as modifying environmental or social determinants.141 To add to this, Sarah Davies points out that the majority of new drugs coming out today have been tested on populations that cannot afford them, and the pharmaceutical industry is still able to maintain support for its argument that patents are justified in such conditions. She highlights the imbalance in the meetings that take place regarding pricing of medicines; where pharmaceutical companies exert more influence collectively than developing countries. For instance, at the joint WTO-WHO meeting and the WTO Doha meeting, more pharmaceutical representatives were
present than representatives from developing countries.  

Aresha Manamperi adds to the list of concerns by pointing out that despite the excitement about the potential promises of genomics on the population health of developing countries, it is still not 100 percent clear how these advances will affect the health of people living in the developing countries. She adds that although the genomic revolution is anticipated to offer new opportunities for the prevention of chronic disease from a public health perception; it is important to understand all the other factors involving biological markers associated with people and their predisposition to these diseases and the social and ethical implications in order to formulate public policies for genomic-based health care.

5.5. Challenges and Barriers to the Integration of Genetics into Routine Clinical Practice

Christopher Murray notes that the Institute for Health Metrics and Evaluation (IHME) predicts that there will be a widening of health spending between the world's poorest and wealthiest countries – with a projected 9% of GDP globally allocated to health spending by 2040, however, substantial variations will exist in the levels of health investment between the low- and lower-middle-income countries, and high-income countries. According to Murray while citing IHME, it is projected that: “High-income countries are expected to spend $9,019 per person on health in 2040, compared to the projected $1,935 for upper-middle income countries, $507 in lower-middle income countries, and $164 in low-income countries.” Murray notes that the IHME also states, a high number (about 35) of “low- and lower-middle-income country governments will likely not meet the international benchmark established by the Chatham House of spending $86 per person to provide primary healthcare. Many countries in sub-Saharan Africa are predicted to be the lowest spenders on health.”

130
According to Murray, the IHME report also found gaps between donor funding and disease burden in most regions, particularly concerning non-communicable diseases (NCDs). Although NCDs are a mounting portion of disease burden in developing countries, and given the expansion of funding related to NCDs from 2010 to 2011, Christopher Murray add that NCDs were not even a focus of health development assistance for the developing countries. In order to address this, there have been efforts put in place to help focus research efforts on diseases representing the most onerous burden on the world’s health, that seek to improve the allocation of research funds and facilitate collaboration between partners in both the public and private sectors. It is imperative that developing countries pick up in the race of genomics and work towards forming genomics research with a wider, integrated strategy to address the specific determinants of ill health for their countries. Although PM is anticipated to inform medical decision making through the use of genomics, there are fears that such use will not be equitable.

5.5.1. Justice and Resource Allocation

Scholars evaluated the effect of geographic ancestry on the interpretation of genomic data and found that the extent bias toward European populations had an adverse effect on identifying candidate variants in other populations. African populations have a disproportionate burden of disease; as a result, the high genetic diversity provides a greater rationale for using genomics to improve our understanding of the genetic basis for diseases - both communicable and non-communicable - and to use the data to guide personalized medicine. Mulder et al. look at the recent large-scale initiatives, such as the Human Heredity and Health in Africa (H3Africa) initiative that has taken on the initiative to address some of the implementation of PM in Africa. As Mulder et al. highlight, the H3Africa initiative is designed to make way for innovative genetic and environmental research for diseases affecting the African people. This initiative is
funded by the NIH and the Welcome Trust. Along with boosting research capacity at individual institutions and three biorepositories for storing project biospecimens as a shared resource, Mulder et al. add, the H3Africa hopes to focus on a diverse group of communicable and noncommunicable diseases and the genetic and environmental factors associated with those. Mulder et al. also note that the rise of premature death from non-communicable diseases is a public health issue in Africa that has prompted six H3Africa research teams to join forces to establish a combined African resource to enhance research in cardiovascular, as well as other complex traits and diseases.148

Communicable diseases, such as trypanosomiasis, HIV, and surveillance of microbial threats are also a focus of some of the H3Africa projects, among others. The surveillance project led from Nigeria helped to develop skills and infrastructure for pathogen research in this region and was instrumental in responding to the recent Ebola 2013–2016 outbreak which claimed 11,323 lives to date. The ill preparedness of the global community did exacerbate the situation. However, the event also produced significant contribution from the African scientists within the epidemic hit regions, and brought out the importance of strong international collaboration. Mulder et al. advocates for the partnership between West African research expertise and international partners, stating that such partnership has resulted in the formation of two key organization: “the Viral Hemorrhagic Fever Consortium (vhfc.org) and the African Centre of Excellence for Genomics of Infectious Disease (acegid.org),” which were, according to the scholars: “These organizations were instrumental in quelling the outbreak by utilizing polymerase chain reaction-based diagnostic tests to identify the first cases of Ebola in Sierra Leone in May 2014 and Nigeria in July 2014.” Mulder et al. also advocates for investment in infrastructure to support endemic public health challenges like Lassa virus, which they argue
have demonstrated the potential of well-established collaboration between domestic and international networks to respond to regional outbreaks that could not have been achieved in isolation.\textsuperscript{149} Mulder et al. state that research in areas of: “Microbiomes also play an important role in diseases” and have been focused within the H3Africa consortium, with the focus of microbiome-specific diseases, such as pneumonia in children, and cervical cancer in women. Mulder et al. add that the African Collaborative Center for Microbiome and Genomics Research (ACCME), based in Nigeria, “is a multicenter study of host germ line, somatic, and human papillomavirus (HPV) genomics and epigenomics….and the vaginal microenvironment and their association with cervical cancer.”\textsuperscript{150}

Pang Tikki and David Weatherall bring up an important point about the benefits of improving global health and reality. Although there are apparent benefits of genomics to global health, the reality is that the developed world made most of the advances in genomics, geared towards their priorities, which raises many concerns that need to be addressed for implementation of genomics into developing countries. Pang Tikki and David Weatherall point out that the “issues of confidentiality, stigmatization, and misuse of genetic information are high on the list of concerns.” They also voice the concern that there is a fear that genomics will create a “genetic underclass” that may be denied health insurance. Moreover Pang and Weatherall voice their concerns related to the health equity between the developed and developing nations due to genomics.\textsuperscript{151} They highlight the findings from the WHO: 80% of investments in DNA patents in genomics from 1980-93 were held in the United States. Only 13 (out of 1233) of the new drugs marketed between 1975 and 1999 were explicitly approved for tropical diseases relevant to developing countries. They strongly recommend that the quality and education in genetics and genomics be increased at all levels of society, both nationally and globally. Otherwise, it will not
It may not be possible to have the informed debates about the issues at hand, and those who will be in charge may be at risk for overselling the services a new, still ambiguous and rapidly expanding research field. However, they do agree that there has been a globalization of diseases, and with that in mind, medical schools, research funding bodies, industries, and governments of developed countries, as well as developing countries must form a mutually beneficial and equitable research partnership for the purposes of fighting global health inequity.152

Like other global public goods, global health and global health research suffer from insufficient investment as underlined by the 10/90 gap, and as previously mentioned. The problem is that, in allocating resources, decision makers take mostly national and local considerations into account, and not a worldview of needs for health and health research. As a result, opportunities to provide essential benefits for all are lost. Although the leading UN agencies for health take a global view on health and health research, they cannot alone sufficiently influence decisions at the national level to ensure the integration of a global perspective. Scholars from the WHO argue that there needs to be a multitude of actors involved in “world health research governance,” to study the problem and ensure that externalities are gradually integrated into the decision-making process.153

5.5.2. Reclaiming Genomics for Common Good - Need for Justice Approach

As noted by a Report from the Global Forum for Health Research, 2000, the “10/90 gap” is feared to be widened further since the current global research agenda is determined by developed countries, and are focused on the needs of the developed countries. This will undoubtedly result in products that are developed for the needs of the developed countries, and will have a negative effect of the needs and health of the developing countries.154 There are fears, as emphasized by scholars like Minkyo Song et al. that this gap will be exacerbated further by
The WHO states that the paradigm of health is shifting from simply “living a longer life” to “living a healthier and longer life.” However, people today suffer from chronic diseases which create many inconveniences in everyday lives, some of which require medical attention; and chronic diseases also cause a significant loss at a national level, as well as at a personal level. This directly translates into the longer duration of care needed, meaning higher medical costs and poorer function of the individual. Nationally, this means rising medical costs and health inequalities, which is further pronounced with improvements in medicine and related fields. Thus, the rational solution is to unravel the problem beforehand, at its causal origin, by preventing diseases before the occurrence, which is one of the goals of genomics.

Scholars like Kelly A. McClellan et al. highlight the anticipated benefits of genetics and genomics in the health and medicine of developing countries, and the UNDP Human Development Report (2001), advocates for building technological capacity for developing countries. McClellan et al. further, advocates for PM’s tailoring abilities to genetic variations of individuals, stating that it can give rise to many advantages such as optimizing patient care through guided medical decisions. They also note that tailoring medical treatment decisions using genomics also gives rise to many advantages for the society as well – such as integrating the use of personal genetic information into healthcare delivery is “hoped to result in significant cost savings by administering treatments only to those most likely to benefit,” resulting in cost-reduction and efficient healthcare delivery. The objective of healthcare is evolving from simply ‘treating the ill’ to ‘aiding the healthy in maintaining their good health.’ However, fears regarding the potential for misuse of genetic information are high, giving rise to the concept of ‘genetic discrimination,’ based on genetic variation from the perceived normal human genotype.
inform the medical decision, stating that: “policies or practices surrounding the use of genetic information in medical decision-making may have an unintended effect of denying individuals access to healthcare on non-medical grounds.” Some of the fears are justified by reflecting on past misuses of genetic science in the interest of advancing a national or international eugenic agenda. Other issues related to the equity in the provision of health services to disadvantaged groups in both economically developed and the developing countries also arise and require elaborate discussions not only about access to essential medicines but also about global justice and human rights.¹⁶⁰

The terrain of genomics research and genetic medicine has only been recently aligned with ‘Global health’ - even though the WHO has been consistently highlighting the relevance of genetics to addressing human health since the 1950s. According to Gibbons et al., genetic knowledge and technology is being used to address a wide range of healthcare challenges, encompassing not only ‘rare’ diseases, but also growing rates of non-communicable chronic diseases in low- and middle-income countries (LMICs), as well as infectious diseases. They state that genetics is also being utilized in large transnational epidemiological studies to address epidemics and pandemics such as “Malaria and Ebola virus.”¹⁶¹ Scholars like Gibbons et al. have highlighted the need to bridge the so-called ‘genomic health divide' through economic investment in research, and expanding the provision of genomic services and technologies to the ‘global south’ by including a greater diversity to encompass ‘minority populations’ from ‘other ethnic groups,’ and to ensure that “those most in need are not the last to receive the benefits of genetic research.” Despite the global expansion and ethical repositioning of genetic medicine and genomic technologies concerning social inclusion and justice, Gibbons et al. highlight that there is evidence of inequitability in stratified access and rights to health care resources.
Moreover, they point out that finding from research in the Sub-Saharan African countries demonstrated that research was only focused on infectious diseases (HIV, TB or malaria), while ignoring NCDs such as cancer and CVD, even though a steady rise in the incidence of NCDs was noticed, “with an even higher projected burden in the next 25 years.” It is evident that greater efforts need to be directed toward research into diagnostic and treatment technologies for conditions such as cancer and CVD in the developing nations as well.162

Even though genomics has significant characteristics as a global public “good,” these are not fully developed in developing countries.163 Gostin and Memorial write that, although knowledge is theoretically free to be disseminated, in practice, constraints, in the means of considerable investment, are often put on its use.164 According to Tikki Pang, some of the benefits of investing in genomics technologies are: strongly supported significant investment in infrastructure for translational research on the grounds will build capacity; shape the organization of health systems and services; result in more effective public health programs that is able to incorporate accurate measures of genetic, environmental, and social determinants of health and provide a powerful means of effectively evaluating new and existing public health interventions. A key question, according to Pang, will be about ensuring equitable access to genomic tests, vaccines, drugs and diagnostics procedures (that are needed for the diseases of the developing world) to those who need it. Pang recommends “a strong international leadership” scientific community, international organizations, governments, and industry is required through promotion of innovative partnerships and cooperation strategies,” in order to overcome existing barriers. Pang also recommends highlighting to the world leaders, about the potential of genomics to generate “economic and health benefits for developing countries,” to initiate a political motivation. Pang emphasizes that the application of the knowledge of genomics need to
be delivered to the “diseases of the poorest people as well, and that we all have a responsibility to help make these opportunities into realities.”

5.6. Recommendations: Delivering Genomics for Improving Health

As singer et al. best highlights, that most genomic technologies are developed for the applications of the developed countries, even though genomics has a potential to benefit both developed and developing countries – this creates a fear of the formation of a “genomics divide” between the two. They further add that if this inequity is left unchecked, this could lead to even greater disparities in health, between the developed and developing countries. Scholars like Baynam et al. have also pointed out that an effective mechanism for addressing these challenges can be through the development of policy frameworks by governments of both developed and developing countries, working in a joint partnership to alleviate the inequalities and address the challenges. Clearly defined policy frameworks, according to Baynam et al., can give directions to help ensure that health systems can translate and optimize the application of the new knowledge, and the rapidly advancing technologies, in a coordinated and strategic fashion- to improve the patient journey and outcomes for all people living with not just any disease, but also rare diseases. Sarah Davies is positive that soon genomics will be an integral part of the healthcare delivery system. Burke et al. also agrees that individuals will be more likely inclined to routinely have their full genome sequenced, shifting the burden of interpreting genomic data from research to the clinical setting. They highlight the need for addressing the many challenges that will need to be addressed by healthcare professionals and public health professionals in the era of PM. The next sections look at the areas of focus that will be needed and ways to prepare for future challenges.
5.6.1. Areas of Focus

Scholars like J Scott Roberts et al. briefly explains the various disciplines encompassed in public health genomics, stating that it is an extended interdisciplinary enterprise that includes many longstanding disciplines such as: “genetic epidemiology, biostatistics, health policy, and health education, as well as state-funded programs focused on surveillance and prevention of birth defects and heritable disorders.” Roberts et al. explains that amongst the many areas of focus is the mandatory population-based, Newborn Screening (NBS), provided by every state in the U.S. These tests are coordinated through each state's department of health, where a variety of disorder types are screened, such as: “inborn errors of metabolism, endocrine disorders, congenital heart disorders, cystic fibrosis and hearing loss” – disorders that Roberts et al. emphasizes as serious lifelong conditions without cure. The benefit is to detect these in newborns to prevent the progress of irreversible damages such as cognitive impairment or even death. Each year 12,000 children with rare inherited disorders are identified by NBS, who are then connected with life-saving interventions before irreversible health effects or death occurs.170

Gostin and Memorial talk about the next-generation sequencing (NGS) as being another emerging genomic technology with the potential to help improve the quality of screenings for current NBS conditions, by increasing the predictive values of NBS results. However, NGS raises many programmatic and ethical issues for NBS programs - NGS could potentially uncover additional, unanticipated information, such as incidental findings (IFs) associated with hereditary cancer syndromes for infants. Moreover, Gostin and Memorial are concerned that some of the information based on the results may not be immediately actionable for the child, and may harm the child and the families with unnecessary burdens of fear, and anxiety. Therefore, the potential harms on children and families should be examined before incorporating NGS into testing.
Additionally, both Gostin and Memorial and Roberts et al. add about the implications of lifelong metabolic conditions such as “PKU and galactosemia” which require special diets, and are expensive and sometimes lack coverage by third-party payers, leading to issues such as forgoing treatment because of inability to pay for treatment. Although, some states pay for the formulas and medical foods for such conditions; this service is increasingly becoming difficult for the state to provide due to cuts in state public health budgets. Recommendations have been made that these children receive appropriate and high-quality clinical care that maximizes health outcomes through long-term follow-up surveillance.¹⁷²,¹⁷³

Mulder et al. reiterate their concern about the equity of health in developing countries. Despite the growing incorporation of genomics into public health and clinical practice, they observed that for most of the people living with a rare disease globally, too much remains unchanged. More explicitly, there are still too many families for whom a diagnosis has yet to be provided so that they can access evidence-driven best care, “a core pillar” of our health systems. Due to a data deficiency, and consequently a knowledge gap, there is a “paucity of evidence,” and public health data on the impact of rare diseases on the health system, and the actual impact on the families living with the conditions and the wider community. For example, African data are poorly represented in public repositories. In order for PM to become a reality in Africa, more considerable reference, and control populations, and more appropriate data generation tools are needed according to Mulder at al.¹⁷⁴ Although many emerging technologies and approaches are providing opportunities to address some of the deficits, Baynam et al. reemphasize that there still remains a need for a shared global agenda, from governments and funding agencies, designed to maximize the impact and benefits that may be derived from the limited funds available for rare disease research.¹⁷⁵
The World Health Organization (WHO) is optimistic that genomics will play an important role in the control of infectious diseases in the developing countries. With the large datasets of drug resistance pathogens and regular surveillance capacity of genomics research, as highlighted in the Report of the Advisory Committee on Health Research, genomics has been expected to be an essential addition to public health measures in developing countries – especially in the control of emerging antibiotic resistant strains of pathogens. Studies from the WHO demonstrates that individual drug response has major implications in the control of infectious diseases, as such, the WHO, in its report, is optimistic that the clinical application of genomics will have positive effects in the health of the population globally. Moreover, the report also emphasizes the need for health ministries in developing countries to develop formal processes to test and evaluate potential genetic screening programs, to ensure the local needs and cost-effectiveness of the programs. It has been advised by the WHO to integrate genomics alongside other traditional and proven healthcare interventions in order to avoid any negative effects.

5.6.2. Legal and Policy Considerations, and Educating Professionals

Understanding the ethical, legal, and social issues in the translation of genomic information into practice is essential to provide patients, families, and communities with competent, safe, effective health care. Amidst the rapidly developing technology of genomics, it has already been identified by many research studies that there is a need for health provider education and competency. Healthcare professionals often look to professional codes of ethics specific to their practice when seeking ethical guidance. They need to recognize that their actions and those of others providing healthcare based on genomics are of significant concern, since a single act may simultaneously benefit one person while harming another. According to the
WHO: “ethically, legally, and socially responsible genomic research requires openness, not privacy, as its organizing principle.” To be responsible and effective, the WHO adds that large-scale genomic research should take place in the “view of the public and the law,” while adopting openness in risk disclosure and informed consent; with elaborate dialogue and data-sharing among researchers and participants; and thoughtful self-regulation.  

Although public health genomics has the potential to provide immense benefits to human health - the benefits must be delivered within the framework of the law, and in a manner that adheres to core ethical principles of human subject research. While GINA was established to protect individuals from discrimination, it is not comprehensive and fails to formally forbid the use of genetic information in “setting rates or determining coverage for life, disability, or long-term care insurance,” as noted by the WHO. Moreover, as the WHO notes that much of the regulation of genomic research falls on medical practice or direct-to-consumer genomic services. Additionally, individual states have their own approaches to regulate genomic services and research that adds to the issue. Appropriate regulation will be the key to technological advancement, as noted by Katherine Chadwell, who recommends the diligent and cooperative partnership between the genomics community to make sure that an emerging regulatory framework incorporates, “certain fundamental distinctions” where applicable.  

The WHO also emphasizes that education and competency are crucial to translating the benefits of genomics to the patient, and for guarding against potential harms not just nationally, but globally. The WHO adds that developing countries need to keep up with the education and training in genomics in order to apply PM and reduce the 10/90 gap. As highlighted in the report by the WHO, developing countries will need to forge international partnerships between academic researchers and local universities in order for potential genomic advancements to
evolve. Scholars like Ojha and Thertulien emphasize the need for education at a societal and healthcare professional level about genetic tests' scope, stating that “genetic and molecular assessments” will soon become a routine component in healthcare. They stress that continuous assessments of the screenings and disease identifications will be needed to ensure this technology is beneficial to all.

Challenges have been cited by Baynam et al. in the implementation of PM in the U.S. that includes limited evidence for clinical use and lack of data from diverse populations. Capturing structured “phenotype-disorder” knowledge was also highlighted as challenges that need to be addressed since they are critical for maximizing the understanding of RD. Moreover, Baynam et al. emphasize that “achieving this in the context of the real-time clinical data acquisition” is essential to enable clinical and research breakthroughs in disease identification. Furthermore, the scholars add that the incomplete linking of detailed phenotypic terms to genomic variants presents a limitation in providing clinical confidence around variant calls, therefore, in order to address these limitations there is a need to adopt “standardized phenotypic nomenclature, and disease classification terms and coding, to facilitate genotype-phenotype reference databases and privacy-preserving data sharing.”

In order to address issues of lack of diverse populations, there is a need for the development and implementation of guidelines to support decision making in clinical settings. Mulder et al. has noted that the infrastructure developed by the H3Africa consortium has contributed significantly to PM by providing the needed “phenotyped cohorts across different ethnic groups, background reference population genetic data, and the development of the skills and infrastructure to collect, store, harmonize, analyze, and interpret the data.” Mulder et al. adds that the he H3Africa consortium infrastructure has not only improved our understanding of
NCDs but has also prepared laboratories in Africa to fight against pathogen outbreaks. As noted by the scholars, the Ebola outbreak in 2014 prompted African scientists to prepare themselves with the equipment and the skills. However, implementation of PM in clinical settings in Africa faces ethical challenges that relate to questions about resource allocation and equity. Making sure that the introduction of PM is not taking away funding for other important healthcare programs that affect the larger population will be critical. One definite recommendation from the scholars, for research and care to contribute to reducing global health inequality effectively - is to make sure that interventions are improving the fate of the worst off. More evidence-based cost-benefit assessments to explore, whether and when the introduction of PM is desirable and ethical are needed.  

There is a need for global benefit sharing and development of novel technologies such as PM, as identified by the *International Bioethics Committee of UNESCO*, and this calls for international collaborations between developed and developing countries, that ensure that both are benefiting. As emphasized in the report by the WHO, the national governments of each of the countries will need to consider the issues that are related to the interests of their people. WHO has pointed out that most genomics and pharmaceutical companies have more expertise in negotiating, and therefore, it has been recommended by the WHO for the governments of the developing countries to acquire negotiating expertise. The WHO recommends that developed countries initiate medical education that is also focused on the needs of the people of developing countries. The WHO highlights the growing problem of the increasing commercial interests that are driving the research agenda in the developing countries, which will need to be addressed. According to the *Genomics and World Health: Report of the Advisory Committee on Health Research*, it has been recommended that the WHO takes the lead in increasing awareness of the
complex problems, and encourage the developed countries to take a more global view of medical education and research activities.  

**Conclusion**

Genetics and genomics integrated into mainstream healthcare will contribute to a significant change in practice, affecting the delivery of healthcare at all levels. As Conley et al. note, genetic and genomic information is being integrated into the management of nearly all common diseases. Scholars like Gilbert S. Omen argues that public health genomics will have the responsibility to ensure that the next generation of “human genomic research and commerce” are practiced responsibly, addressing the substantial new issues. Genomics has contributed greatly to the development of effective interventions that target the molecular basis of diseases, as reiterated by Clayton. Hall et al. also notes that the successful utilization of this new technology will depend not only upon the costs of genetic screening, and effectiveness on reducing the morbidity and mortality rates of the conditions, but also our ability to prevent misuse of the genomic information through effective public health policies. According to the main argument of the *Genomics and World Health Report* (2005), genomic technologies open up many possibilities for the benefits of health of developing countries, and this technology should not be considered as a luxury for a few, but should be considered a necessary tool for all. A crucial factor that sets up the vicious cycle of the 10/90 gap, as cited by D. Vidyasagar, is the “paucity of research” in the developing countries. Investigators are attempting to quantify this gap. In light of all these arguments, we can agree with the *Global Forum for Health Research’s Report* that the only way to correct the 10/90 imbalance is to create capacity development by establishing the core of trained people needed in developing countries to do
cutting-edge research and play their part in the global research agenda, thus contributing to the
correction of the 10/90 imbalance.\textsuperscript{203}
Chapter 6: Social and Ethical Implications of Integrating Precision Medicine into Healthcare

6.1. Introduction

Understanding the underlying concepts of human genetics and the interactive role of genes, behavior, and the environment will be crucial to the appropriate collecting, and applying of genetic information and technologies, in the improvement of disease diagnosis, and treatment in the era of PM. \(^1\)

Juengst et al. point out that the completion of the HGP opened up possibilities for PM as the “paradigm shift” in health care, leading to discussions of the pros and cons of this technology. There are many benefits of PM. However, advances in PM also gave rise to ethical and social implications that need to be addressed before PM's potential can be fully realized. Proponents argue that PM is more “personalized,” “predictive,” “preventive,” and “participatory” than the conventional medical routines. \(^2\)

Plenty of genetic tests are already available to help people make informed decisions about prevention and treatment of diseases. However, research indicates that the public knowledge and attitudes need to be taken into consideration if PM is to be utilized in clinical care. \(^3\)

PGx, an area in PM, has the potential to stratify either patients or diseases by using individual’s genetic variations to target prescribing medicine, and preventing ADRs; which as Demissew Berihun Haile et al. point out, ranks as the fourth and sixth leading causes of mortality in the US alone. \(^4\)

Despite the many challenges, PGx is believed to be an area of genomic medicine where PM could have an immediate impact soon. \(^5\)

Given PM’s potential, the implementation process has been slow so far due to many ethical and governance challenges. As Jusaku Minari et al. note, there are implications for the meaning of validity of consent, due to the blurred boundaries that exist between research and care in the
healthcare system, that also increases the potential for discrimination. These scholars also argue that the increased sharing of personal information, which is the basis for PM, raises concerns about privacy, commercialization, and public trust. This Chapter looks at the social and ethical implications of PM’s integration - taking into consideration the public knowledge and attitudes about PM, and the potential it has on the healthcare system; identify and address various challenges in the integration of PM into clinical practice, and also recommend some approaches to address the concerns.

6.1.1. Integration: Looking at Ethical and Social Concerns, Challenges and Needs

As scholars like Simone Vernez and Sandra Soo-Jin Lee point out, PM has been promised for decades to revolutionize the healthcare delivery system, by improving individual health through the utilization of personalized risk information, drug metabolism, and thereby predicting whether individuals are carriers for certain diseases and so on. They add that the very foundation of PM promises to reshape the personalized health profiles of individuals, through active public participation in order to achieve better health outcomes. Scholars like C.H. Song also asserts that the reduced cost and high accuracy of results of these tests have already created a pathway for sophisticated clinical testing and better identification of pathogenesis. However, Henderson et al. are concerned about the various debates around the ELSIs surrounding genomics and have impacted the implementation process of PM into the clinical settings. They add that the benefits of PM must be weighed against these challenges posed by the technological, financial, ethical and cultural limitations - and they are right about that. Among the most frequently raised concerns cited by the scholars include those related to privacy, data protection, insurance, genetic discrimination, and the management of unanticipated results whose clinical significance is uncertain. Moreover, Song highlights the critical issues related “to data integrity,
misuse of results and return of incidental findings, refusals of health insurance and job discrimination because of familial risk,” that have been repeatedly identified as causes for concern - for both practitioners and patients.¹⁰ Scholars like Rodolfo Valdez et al. have argued that better legislation should be in place to protect consumers against any future discrimination by insurance agencies and that critical ethical dilemmas and challenges associated with the integration of PM need to be addressed in order to speed up the proper delivery of PM.¹¹

According to the International Bioethics Committee (IBC), genomics raises issues regarding respect for autonomy. A person’s genetic data is ideally considered as personal data, and should be accessible only by the person the data belongs to. However, genetic data is different in that it relates to the person, as well as other family members, and even the community he/she belongs to – hence, respect for privacy becomes a concern in the era of PM. Although information from a person’s genetic makeup is supposed to be beneficial in the diagnosis and treatment of diseases, it can be harmful by causing uncertainty, and anxiety and moral burden. Genetic tests can present psychosocial risks of distress, anxiety, and confusion; as well as stigmatization and discrimination, particularly when only the risks can be identified, without providing adequate treatment or prevention – this may also have a detrimental effect on the quality of the decision-making process. People who share their genetic information may need counseling regarding the results, and the reliability of the results, and with interpreting the uncertainties and uncertainties.¹² Additionally, as Sonia M. Suter point out, the individual might also face discrimination in employment, insurance, and other venues. She adds that many fear that any information regarding personal genetic makeup, regardless of how beneficial they may be in identifying and predicting risks (even for some inherited cancers), may be viewed as potentially harmful given the possible psychosocial risks.¹³ Moreover, IBC adds that autonomy
in genetics is challenging because of the implications the genetic information holds for the person being tested, as well as their relatives, and their communities - due to the shared nature of the genetic information. This gives rise to issues of ‘right not to know’ and/or not to disclose information, especially when there are situations where family members have to be informed regarding preventable or treatable diseases. There still exists a lack of sufficient information about the genetic makeup which makes it challenging to understand its significance meaningfully. Opponents of PM also fear that good health may eventually be seen as a personal choice and a result of responsible behavior; and this might have implications for justice as well.\textsuperscript{14}

Juengst et al. talk about the virtues of PM, and they state that the most attractive virtue to all is PM's promise to shift the focus of healthcare from \textit{disease treatment} to \textit{disease prevention}. The prevention of diseases is meaningful to patient advocacy groups since this promise to spare families and communities the suffering. Juengst et al. also state that for clinicians, healthcare institutions and commercial service providers - prevention promises “better outcomes and the extension of services to asymptomatic at-risk patients who seek to manage their health better.” For health policy-makers and public health agencies, Juengst et al. add that prevention promises lower healthcare costs and better population health measures.\textsuperscript{15} Prevention of disease, according to Juengst et al., is a classic public health goal, one that measures “the reduction of morbidity and mortality caused by the target disease within the screened population over time.” However, many fear that the screening tests and interventions for prevention may initiate new ethical and social dilemmas, especially related to eugenics (newborn screening for genetic diseases is an example), even though such interventions are still in the realm of individual, rather than public health interventions, and cannot be viewed as eugenics. Given America’s history of eugenics, the scholars suggest that it would be wiser to be certain that PM has not failed to focus on issues of
eugenics (even if they are but shadows). Therefore, Juengst et al. emphasizes the importance of analyzing the logic and scope of prevention in PM.\textsuperscript{16}

Incidental Findings (IFs) and the return of results have become challenges for researchers in PM, as noted by Henderson et al. They state that it can be taxing to know exactly what information and how much of it to disclose to participants since the results are often of uncertain meaning or significance - and may lead to misunderstanding, confusion and even harm.\textsuperscript{17} Moreover, they add that the scope of biospecimens research has been credited for the challenges with IFs in clinical research. The generation of large amount of data that pertains to the identification of multiple mutations, potentially associated with complex disorders like cancers, lead to the identification of IFs. The scholars argue that there is a critical need for appropriate protocols for handling a high volume of IFs, and also being aware that research subjects may have the expectations that information of potential clinical significance can be found.\textsuperscript{18} IFs are challenging because they are difficult to interpret, and are becoming more significant due to the increasing use of high-throughput sequencing in medical practice. Effective disclosure and regulation policies for various clinical and research settings are important to not only respect autonomy, but also to avoid harm, and encourage the sharing of possible benefits. Since the science of genomics is still young for clinicians to understand the significance of much of the results, the findings do not offer much clinical utility, and this may pose issues of whether to disclose the findings. As a result, this also presents informed consent challenges, as well as negative psychosocial consequences.\textsuperscript{19}

Cost and affordability of PM is another ethical issue. Although, the cost of customized treatment is anticipated to decrease substantially, and proper use of treatment is anticipated to lead to considerable savings in healthcare due to fewer inappropriate or ineffective therapies.
However, as pointed by IBC, cost is still relatively high as of today, and given the variability in the levels of health insurance, it can be difficult to provide equitable healthcare even within a country. As pointed out by IBC, it would certainly be unethical if a person could be treated but could not afford the treatment. Given the lack of certainty of the information about gene mutations and variants, cost-benefit analyses are needed to assess the clinical utility and validity of the procedures as well are what diseases it pertains to. Moreover, IBC highlights that regardless of the promises of PM, we must not forget our priorities to the development of treatment of neglected diseases, such as rare diseases and tropical diseases that are faced by most of the populations around the world, especially in developing countries. IBC also adds that PM is also feared to create pathways to the ‘commercialization of medicine’ through the practice of Direct-to-Consumer (DTC) genetic tests, which is feared, will change the doctor-patient relationship, and also change the way healthcare is delivered. DTC holds the promise of promoting the consumerism of individual health and incentivizing economic growth. As IBC notes, DTC tests have acquired an economic value, under the guise of therapeutic research, whereby they can provide individuals with information about their genetic makeup and provide them information about their risks for certain illnesses. However, DTC is challenging because it provides easy access to commercial genetic tests without the need for medical professionals, unless individuals are uncertain about the results, and would wish to consult medical professionals. As highlighted by Sutter, DTC tests cover a wide range of genetic variants, associated with genetic illnesses. The issue related to DTC is the generation of more information in the clinical context, than what has been inquired, leading to the generation of IFs. Moreover, as highlighted by IBC, DTC tests represent a business sector that is not contained within borders.
and pose challenges that need to be approached at the international level. DTC is an example of the globalization of healthcare services that make national regulations imperative.\textsuperscript{23}

Data integrity has been identified as another significant challenge in PM – particularly issues related to standardization of data; sharing of data, and proper analysis; and translation of data. PM has prompted the development of new laboratory guidelines and standards around the world, resulting in the publication of numerous partially overlapping guidelines, as McGowan et al. notes, some extremely general, while others are focusing on specific diseases or specific steps in the process.\textsuperscript{24} The proper translation of genotyping is critical in the era of PM.\textsuperscript{25} Analytic failure of a single genotype may lead to a catastrophic result. Śliwczynski and Orlewska point out the need for greater efforts to protect consumers against potential harms of “premature translation of research findings.”\textsuperscript{26} The challenge for PM is to develop a network, which links different “layers” of information relevant to health and grounds it with individual patients who share their data, as noted by Kennet Offit.\textsuperscript{27} Although, it is evident that there are a lot of benefits of PGx testing, it has been observed that data integration, and effective communication of the different databases have still been an issue for the clinical implementation of PGx, resulting in the slow pace of clinical implementation of PGx testing as observed by Yuan et al. Barriers include the inadequacy of professional clinical guidelines for PGx genotyping, phenotyping, and reporting; and also the inability to transfer PGx testing results to the EMRs, which Yuan et al. suggests should be linked to CDS tools “to aid clinicians' understanding, interpreting, and utilizing PGx information.” Moreover, they note that there is a reluctance to use PGx testing amongst many healthcare providers due to a lack of training that has to do “with correct interpretation and reporting of PGx variants.”\textsuperscript{28}
Marc S. Williams observed the need for significant investments in the areas of: 1. 

*Infrastructures* - to produce, store, link, and share the data- which includes sequencing and secure high-throughput technologies, as well as reliable and standardized electronic health record systems. 2. *Education* – for the general public, clinicians and other stakeholders about PM to inform, and raise awareness about the applications of PM, that will lead to the increased level of participation in large-scale population sequencing, as well as disease-specific research, and ensuring that PM research efforts are translated to the daily patient care. With the issues of data integrity, comes the issues associated with EHRs, which are becoming a part of the routine care in the hospital and clinic settings. Williams states that effective use of EHRs has been shown to: “improve care outcomes, patient safety, and care coordination, with the potential for cost savings.” Moreover, Williams note that fully functional EHRs are capable of collecting, synthesizing, and translating data that represents knowledge important to the clinician in the form of point-of-care, “just in time” education, and CDS, which are of great importance in genomic medicine. Moreover, McGowan et al. adds that EHRs can help non-genetic healthcare providers to stay well informed about the genomic advances with the tools mentioned earlier, overcoming certain knowledge-based barriers.

Education of clinicians and public, as well as appropriate tools for data collection in the healthcare setting were also identified as barriers in the integration of PM in clinical settings. Sboner and Elemento note that privacy and HIPAA compliance are important in a precision medicine workflow, because genetic data are patient data, and can be linked to patient identity, even if temporarily anonymized. They also add that informatics plays an important role in nearly every aspect of a precision medicine program. However, Zhou et al. point out that multiple reasons like sensitive testing methods, lack of PGx knowledge and skills in clinicians,
all attribute to the limited application of PGx biomarkers in clinical practice. Caudle et al. point out that, “a lack of knowledge of how to translate genetic test result into clinical action based on currently available evidence,” was another reason why genetic data to guide medication use was not utilized. They highlight the need for new educational models in medicine, with a greater focus on information management, to provide healthcare providers with “the required diagnostics, informatics, and decision support tools.” Routine clinical care generates a significant amount of data from patients using family history (FH). Although self-reported FH may not be complete or accurate, it can still be useful in the risk assessment for patients with documented clinical validity and utility. Sboner and Elemento argue that reporting is a key step in a PM workflow; and also useful in the communication of results to patients and physicians. The scholars emphasize that inconsistent reporting must be avoided at all costs. There is a need for better FH tools and reporting. Family history has been identified by studies as a great diagnostic tool, which can help guide decisions about genetic testing for the patient and at-risk family members. Furthermore, it has been emphasized in studies that early identification of increased risk can allow for necessary steps to be taken to reduce risks. The next section looks at legal and equity issues that are anticipated in the era of PM.

6.1.2. Legal, Equity Issues

Genomic information can provide tailored screening and prevention strategies in healthcare if it is used with FH and other environmental factors. As Sweet et al. add implementation of PM requires diverse genomic data, to develop optimal methods for information delivery. Sweet et al. brings to our attention about the issues of limited knowledge/information with which participants consent to genetic tests. They argue that this raises unique issues related to participant expectations, such as “overestimation of developing a
disease, causing unnecessary worry, anxiety, risk, and expense.” 42 Fakruddin and Chowdhury highlights the various concerns raised by PGx, such as possible social and economic harms, such as discrimination, stigmatization, or marginalization of groups due to “being difficult or expensive to treat.” The scholars voice their concerns that this can lead to the controversial issues of equity and can make it difficult for the just distribution of therapies for all.43 As noted previously, genome sequencing may reveal information about the health of participants as well as their families, leading to issues of privacy and access to information.44 45 Manolio et al. argue that the early identification of “responders and nonresponders” to treatment could result in improved therapeutic effectiveness, and may result in avoidance of unnecessary exposure to harm, and side effects. Manolio et al. note that despite the successful tailored prescription of medications through PGx, there is a fear that exists about such drugs not being accessible, or will result in inequity and discrimination, and fear that the treatment flagged as unsafe maybe the only treatment option available, and therefore being denied by insurance companies. 46

Liu et al. emphasize that certain legal issues, such as knowledge of a person’s genetic makeup, and the implications it may have, need to be discussed before PM can be implemented. They further explain that knowledge of a person's genotypic information can be a serious concern because it opens up the genotypic information about the person, the family, and even the community of the person - resulting in the breach in privacy of the whole community, whose consent has not been taken. This can also lead to the creation of a group susceptible to a particular drug, having the possibility of having a particular disease in the future and so on. There are pros and cons to this. It can prompt over worrying and taking extra unnecessary steps, or it can lead to early lifestyle changes that will lead to prevention and treatment. However, the prediction of no treatment or cure can be psychologically harmful. PGx is also feared to have the
potential to the opening up of some constitutional issues like those of getting some special incentives or of minority status.  

PM is still in its infancy as far as evidence for benefits goes. Based on a workshop summary by Fakruddin and Chowdhury, an estimated 6% of eligible patients would benefit from a well-evidenced genomic test that identifies a treatable condition, and they credited this to the implementation of inconsistent clinical testing. Other ethical issues related to available evidence and the level of certainty to warrant clinical introduction were also highlighted by Korngiebel et al. Relevant factors such as the scope of estimated benefits, existing alternative treatments, potential harms and the overall quality of evidence were suggested to be taken into consideration with full consideration of the views and preferences of all stakeholders by Korngiebel et al. Furthermore, they added that implementing promising new tests in a timely fashion may be beneficial if they are tied to the collection of data that reduce uncertainties about tests outcomes over time. The potential to automatic updates to EMRs with patient clinical utility validated provides exciting possibilities for implementations of research advances. However, Korngiebel et al. were also concerned that such growing knowledge and understanding might lead to issues such as “reporting of incidental findings (IFs), and whether to contact patients” - leading to undue burden as well as “medico-legal risks.” Collins and Varmus noted that ensuring equal access to genomic technologies will also be important in reducing disparities in chronic disease outcomes. They argued that rigorous evaluation of delivery approaches that increase the likelihood that appropriate and affordable support services accompany genomic technologies to individuals and/or systems would be critical to success.

Colleen M. McBride questions the uniqueness of genomic information, stating that it is debatable whether genomic information warrants special protections beyond those in place for
standard medical information. He states that concerns and fears of genetic information vary by country. He provides examples of the fears that exist in the U.S. and the U.K. regarding genetic information, stating that in the United States of America, fear of discrimination by employers and health insurers is the main concern; whereas, the use of genetic information by life insurers is the major concern in the United Kingdom. McBride points out that in the U.S. many states have their own legislation that protects people from genetic discrimination by employers and health insurers. McBride further adds that in April 2008, the U.S. Congress passed the Genetic Information Non-discrimination Act (GINA), which affords national protection of genetic information, a step that will help lower the barriers between participation and clinical use of genomic applications. 

Juengst et al. highlight issues related to regulation that provoke ethical concerns. They emphasize that costs related to PM, if not attained, will limit the ambitious goals of tailored therapy and other forms of healthcare services, thereby limiting access and bringing social justice challenges to PM's priorities. They add limiting PM to patient-risk stratification based on ethnic, racial and socioeconomic conditions, will only add to the existing social issues. Andrew Smart et al. warn us that “pre-prescription genotyping” may lead to further stigmatization and social discrimination by labeling people as “good responders” or “nonresponders” or “difficult to treat.” Smart et al. emphasizes that this would further create insurance/coverage issues and also add to psychological consequences.

According to scholars like Smart et al., secondary information about diseases risk/prognosis by PGx can also have broader social implications associated with genetic testing. Although it has been argued that the ethical issues of PGx testing are distinct from those in disease testing – it is difficult to maintain this distinction – leading to important implications for the governance of PGx testing. Smart et al. note that resource allocation and priority setting
made by financially pressured healthcare providers already raise issues of justice in PGx, and based on this context - PGx has the potential to further widen inequality.\textsuperscript{56} As with all new innovation, PGx products are expected to be significantly more expensive than conventional products, which raise issues about the distribution of access to the better treatment they might offer. It is evident that people with private healthcare will have access. On a global scale, this means that healthcare systems in less affluent countries would not have access to PGx products.\textsuperscript{57}

Smart et al. point out that PGx intervention may need to address ethnic and racial inequalities in drug development due to financial obstacles, since PGx interventions would lead to the underrepresentation of some groups, resulting in the inhibition of discovery and development of PGx intervention of such groups. Moreover, Pharmaceutical companies might be financially less inclined to develop products for socially disadvantaged people, leading to the socially marginalized ethnic minority groups having the worst access to PGx products. Additionally, Smart et al. voice their concern of racism, and the practice of linking of PGx to ethnic and racial groups, even for the most honorable ends, they point out should be recognized to have associated social risks. The first of these risks, according to Smart et al. is “the danger of reinforcing discredited crude biological notions of race.” The second is “the potential for the whole population groups to suffer from stigmatization.” \textsuperscript{58} Lastly, they state that “experience has shown that research and clinical decisions based on ethnic or racial classification often lead to poor or ineffective care.” All of these combined, according to Smart et al., pose a serious social risk that may exacerbate the patterns of inequality already faced by some socially disadvantaged groups.\textsuperscript{59} Smart et al. further argue that PGx has the potential to create new risks in drug development through \textit{selection bias} that may create inequalities between \textit{genetic sub-groups} –
resulting in the unequal distribution of drug response profiles and ultimately adversely affecting the people of these groups in the event of inadvertent or inappropriate off-label prescribing.\textsuperscript{60} They add that the introduction of PGx may lead to treatment being inappropriately denied on the basis of probabilistic data, and there is danger that access to services may depend on geography, education or wealth, because the necessary service infrastructure may not be in place due to initial costs. To ensure equal access to PGx services, it will be important to ensure comprehensive and easily accessible PGx services in public healthcare systems.\textsuperscript{61}

Smart et al. also recommend that governance frameworks that accounts for the novel aspects of PGx should be established, with the aim to ensure control over the collection, storage and use of personal genetic information to protect privacy and confidentiality and prevent discrimination resulting from misuse of both primary and secondary information. They add that there should be guidelines for health professional services, as well as the possibility of legal sanctions where necessary. They add that it is critical to make sure measures are taken to ensure that ethnic and racial groups are included in the process of testing and developing new drugs; and that professional education and equality programs should be introduced to ensure that prescribing practice is based on evidence and not prejudice. They suggest that such a framework of policy recommendations involves new responsibilities for multiple stakeholders such as “industry, government, research funders, health services, clinicians and patients;” and adopting such a framework will help to ensure that the introduction of PGx is managed in a way that ensures equitable sharing of benefits, and \emph{just} clinical practice and research activities.\textsuperscript{62}

\textbf{6.2. Public Attitudes towards Genetic Tests}

Findings from research show that the public attitudes toward genetic testing depend on the positive or negative outcomes/benefits of the tests. However, it was also found that the level
of knowledge and awareness, and concerns or fears about the uncertainty of the application results and data access, also plays a role as to whether people would like to have genetic tests. According to Vermuelen et al., family history (FH) was identified as a good genomic tool that helped in the assessments of diseases. Although, participants in favor of using FH on themselves, were reluctant about the implementation of the data generated by FH in clinical settings. In order to implement PM into the clinical settings, there is a need to find out whether people will be willing to use the various tests available through PM. This section looks at the public attitudes towards genetic testing in the prevention and treatment of noncommunicable diseases, and how FH can be used as a tool for assessing risks and benefits.

6.2.1. Attitudes towards Genetic Tests

As Natarajan and O'Donnell note, despite the rapid evolution of genomics, patients and providers still have a “limited understanding” of human genetics. They highlight the need for accurate representations and education regarding incremental risk and modifiable risk from “genomic risk scores” for appropriate interpretation. Bailus Walker Jr., also notes that it is still not clear how the environmental history affects the genetic makeup in manipulating a person's health risk/disease susceptibility, and response to treatment. According to findings from Valdez et al., informed participants are more likely to choose genetic testing for the disease and adapt to lifestyle changes to prevent it. Miller et al. made the observations that most participants expected the genetic knowledge to be useful (and even considered the information as important health information for other family members) and permitted action (they approved relaying the relevant risk information to relatives as well) to avert harm. It will be important for legal and policymakers to look into population-based testing for genetic markers for inherited diseases, such as breast cancer while considering screening tests for all. Based on a survey by
Shaw and Bassi that looked at the randomly selected people's attitude about personal and societal issues of genetic testing and disease susceptibility; it was found that most respondents were optimistic about the benefits of the testing, and their attitudes were related to their interests in having control over the diseases (if it had a cure); and if the test was highly predictive. The survey also found that respondents were not willing to grant access to results to anyone other than doctors and family members, and were hesitant to allow the government, religious leaders, and the courts any form of involvement in regulating genetic testing. According to Shaw and Bassi, these findings have important implications for researchers struggling to find some solution to issues related to population-based genetic testing for inherited diseases.68

Shaw and Bassi also noted that while genetic testing for disease susceptibility is already offered to certain high-risk individuals (such as women with a family history of breast and ovarian cancer) - there is considerable debate about whether to offer genetic testing to all members of the public. They argue that there are tremendous benefits of population-based genetic screening. The identification of people genetically susceptible to certain diseases, allow for early detection, prevention, and early treatment programs targeted specifically for those individuals. Also, such screenings greatly reduce the disease-related anxiety for those people who do not have the genetic markers. However, Shaw and Bassi also point out that there are numerous societal and personal costs of population-based screening programs that will need to be taken into consideration, stating that wide-scale genetic testing will be very costly in financial terms. Moreover, they add, people with genetic markers will face considerable personal distress, and anxiety, and may face potential discrimination from insurance companies and employers. Considerable discourse needs to happen around the ethical and legal issues, which will help with the understanding of the public attitudes about these topics, especially lay opinions and attitudes
concerning the complex issues surrounding genetic testing. It is crucial that researchers in this area be knowledgeable about the cultural and social aspects which are likely to influence the attitudes of people to genetic testing.\textsuperscript{69}

Shaw and Bassi also suggest that people generally desire to have control over their environment, and it is likely that respondents would be more likely to want genetic testing when there is a chance that the information would give them some control over their future health.\textsuperscript{70} People wished to reduce uncertainty or ambiguity in their lives, and Shaw and Bassi noted that many women were motivated to engage in genetic tests for susceptibility to breast cancer to reduce uncertainty and to have control of the disease. From the same survey, they also observed that respondents were also concerned that the tests were not “conducted by the wrong people.” \textsuperscript{71} Shaw and Bassi note, these results support previous findings that lay attitudes about genetic testing were complex, and attitudes were related to personal interests about the tests - positive attitudes were associated to greater interest, while negative attitudes were associated with less interest – as was knowledge of genetics.\textsuperscript{72} Previous research by Tambor et al. suggests that demand for genetic testing for breast and ovarian cancer susceptibility were high, even among those at relatively low risk of carrying a mutation.\textsuperscript{73} Women without a FH of breast and ovarian cancer have also shown a high level of interest in testing.\textsuperscript{74} Tambor et al. also noted that attitudes toward mammography were important predictors of interest in testing. Data from focus groups conducted by Tambor et al. suggest that helping family members was a strong motivation for genetic testing. Women who reported that having regular mammograms gave them a feeling of control over their health were more likely to be interested in testing, than those who did not believe that mammograms gave them a feeling of control. Tambor et al. also noted that the possible knowledge acquired through genetic testing, and “the subsequent improvement in

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decision-making ability” might appeal to individuals who are motivated by a desire to maintain control over their health.\textsuperscript{75}

Furthermore, findings by Tambor et al. indicated that only 6% of the respondents reported that their mother was diagnosed with some form of breast cancer, and of these, only 14% had been diagnosed before age 50. Fifty-one percent of respondents reported that they were aware of the breast cancer gene. Sixty-nine percent said they were interested in being tested to find out if they had a breast cancer gene. Twenty percent said that they would not be interested in testing, and an additional 10% said they did not know. Data also found that women younger than 60 were three times more likely to be interested in the test; white women were over twice as likely to be interested as African American, and other women. Additionally, women who believed their family would benefit if they had a mammogram were twice as likely to be interested, and women who believed that regular mammograms gave them a feeling of control over their health, were almost three times as likely to be interested in genetic testing, as those who did not agree that mammograms gave them a feeling of control. However, the scholars emphasize the need for more research on the various psychosocial factors associated with the interest in genetic testing that will allow for legal and ethical scholars to have a better understanding in public sentiments, and better prepare them with the issues of privacy and regulation concerning population-based genetic testing programs.\textsuperscript{76}

Vassey et al. observed that hundreds of genetic loci associated with an increased risk of many complex conditions were uncovered due to advances in genetic technology.\textsuperscript{77} According to a survey conducted by Vassey et al., of the 521 young adults, two-thirds reported some interest in tests that could tell them about the risk for heart disease, T2D, and stroke. They also noted that individuals “with a first-degree FH of at least one of the three conditions were more likely to
report some interest than those without a family history.”

Vassey et al. also observed that participants with greater risk for future CVD, and T2D may be receptive to genetic susceptibility information to help motivate that change. Knowledge of genetic susceptibility may motivate young adults with higher personal risk for noncommunicable diseases, such as diabetes, to improve their diet and exercise. However, Vassey et al. are not convinced that genetic tests could motivate behavior changes, and suggested coupling a few other strategies with genetic tests.

Even though PGx testing is critical in PM in determining the right dosage, and the right selection of drugs, Susanne B. Haga estimated that only one-fourth of outpatients were taking medications with PGx information. Previous studies assessed that public attitude toward PGx testing was not the same as disease susceptibility genetic testing. Most people were suspicious of the safety and efficacy of race-based drugs, and preferred individualized genetic testing versus race-based medications, even though they were concerned about cost, privacy, and discrimination - as noted by Susanne B. Haga.

Haga also observed that PGx test implementation, like other genetic testing, will be influenced by patient attitudes and interests, and therefore, it is critical to ascertain the public's interest and perceived barriers to this application. Scholars like Natarajan and O'Donnell also noted that many consumers will forgo testing if a test's predictive value is low, or if there is not much to reduce risks. It is a well-recognized fact that individuals respond differently to drug therapy – some may benefit, while others may not. Variations within families and between individuals regarding the processing of probabilistic risk information, and ability to act on it, still exists. As Kenneth Offit highlights that there is a need to take psychosocial context seriously in the translation of genetic risk information. Kenneth Offit states that there is worry that even one
strong ADR resulting in harm to the individual can have profound psychological or even legal consequences in the era of PM.  

While looking at public opinion towards genetic testing, Henneman et al., presented results from surveys conducted from 2002-2010 that showed that public opinion towards genetic testing had been a changing process. However, the percentage of people having heard of genetic tests remained the same over the years, and cancer tests were reported as the common test and remained the same as well. Respondent's beliefs differed, and depended on the age and education as demonstrated by the results. Henneman et al. compared results between 2002 and 2010 and found more interest in knowledge about genetic makeup and disease susceptibility between respondents in 2010. They also found that 43% in 2002 vs. 64% in 2010 believed that the knowledge would help them live longer, and that genetic tests should be promoted, although there were still about 37% who believed otherwise. Additionally, a larger number of respondents in 2010 anticipated increased use of genetics in the next 10-15 years. Overall, findings demonstrate that people are aware of the genetics behind the common chronic disorders, such as diabetes; however, it has also shown that the public had limited knowledge on how genetic risk factors influenced the development of the disease. Braithwaite et al. found that higher education and income were associated with a stronger interest in having a genetic test. It was also noted that several psychosocial factors were linked to interest, especially increased the perception of personal risk, the anticipation of a positive impact of genetic testing, increased cancer-related worries, and high need for certainty. Braithwaite et al. also looked at the role of uncertainty in genetic counseling from a clinician's perspective and noted that there was little research done in this area. Braithwaite et al. pointed out that the attitude toward uncertainty was “hypothesized to be positively related to the intention” to have a genetic test, with people who
hold more positive attitudes toward certainty being more likely to intend to have the genetic test.  

Braithwaite et al. also studied the intention to undergo genetic testing for hereditary cancer and noted that 17% reported feeling unsure about having the test, with a further 11% not intending to obtain genetic testing. Braithwaite et al. attributed this change in attitude to healthcare systems, and other barriers such as, “financial barriers, transportation barriers, emotional and social barriers.” The authors also noted a lack of association between perceived risk and testing intentions in the respondents with a family history of colon/breast cancer. They noted that “the participants with more negative attitudes toward uncertainty” would be more likely to undergo the test while those seeking more certainty may be discouraged from having the test once told about residual risk. As Henneman et al. pointed out, most diagnostic tests are only available to those as identified as “having a priori high risk,” maybe due to positive FH. Henneman et al. also noted that advances in genetic testing actually increased public expectations about the application, and therefore, genetic testing will not meet much public opposition. They state that these are important implications for all stakeholders, including policymakers. However, they emphasize the need for responsible dialogue with the public regarding the possible social and ethical consequence, that has to do with inequity, and promoting policies that will address these issues.

According to the researchers at the Genomic Medicine Institute's Center for Personalized Genetic Healthcare at the Cleveland Clinic, FH can be a great tool that can help in predicting an individual's risk of developing certain diseases. Scholars like Alspach, and Yoon et al. advocate for FH as a tool stating that family medical history depicts everything about the patient, including the person, health issues, and familial influences such as genetics; and reflects essential
risk factor information about various disorders including coronary heart disease, diabetes and cancer - and reports risk factors with a high degree of accuracy. The information generated by FH can guide risk-specific recommendations, including referral to a specialist for evaluation and possible testing.\textsuperscript{94,95} Many of the Risks for NCDs such as certain types of cancer, heart diseases, and diabetes have both a familial and a lifestyle component. Besides, it was observed that completing a Family Health History (FHH) assessment promoted intended communication with family members about chronic disease risk. Familial risk is significant, with up to 52\% of colorectal cancer, 19\% of breast cancer, 72\% of coronary heart disease, and 30\% of diabetes diagnoses attributable to familial history.\textsuperscript{96} Educating people through the use of a FHH assessment tool may be one way to promote health and motivate people to act to prevent chronic disease.\textsuperscript{97} The next section looks more elaborately at FH as a tool, and people’s attitudes toward FH.

6.2.2. Attitudes toward Family History as a Tool

Valdez et al. argue in favor of FH stating that FH is “a simple, yet powerful clinical tool with multiple uses in the clinical setting.” They add that FH can be applicable in informing decisions about screening, and early treatment for chronic conditions that can help with patient education, and prevention of the conditions. Moreover, FH information can help clinicians build a relationship with the patient, and understand the other factors that play a role in the disease mechanism, such as behaviors and environment.\textsuperscript{98} Yoon et al. observed that Americans were not good at collecting or documenting their FH, although from a survey it was found that 96\% thought knowledge of FH was important for their health. They also noted that physicians did not fare better either in collecting FH from patients, and in interpreting, and using the information to recommend interventions. Yoon et al. attributed this lack of documentation by physicians to
attributes like lack of time, lack of compensation, and lack of training to collect and interpret the information. As Godman et al. noted, the variable predictive yield of GWAS have demonstrated the need for a thorough understanding of genetics related to diseases, and patient populations, and not just the expression patterns of the gene expressions. Moreover, Khoury and Mensah point the issues with healthcare providers, and eliciting FH in medical records - where they noted that FH is still not completely documented, and optimally used in the clinical practice. They emphasize the need for public and healthcare provider awareness regarding the importance of FH as a risk conveyer for health and disease prevention. Khoury and Mensah makes an important observation that FH can initiate the process of building a link between “the one-size-fits-all” approach to prevention, and the “one-person-at-a-time” approach to genetics.

Valdez et al. points out that FH can be a consistent and “independent risk factor” for many common chronic diseases in many ways, such as: the combined effect of shared genes and environment is captured in a single concept; it shows the change in data over lifetimes of people; it is also an inexpensive and easy-to-use approach to identify genetic risk compared to genetic testing. Another main objective of using FH for chronic diseases of “complex etiology”, as identified by Valdez et al., is to assess health risks using a few simple assumptions, such as “the number of the affected family members, their ages at diseases onset, and the presence of conditions known to be inherited among them” – all of these impact the level of familial risk. Although the scholars admit that combining these factors to determine risks can be challenging, FH is still considered “a consistent risk factor” for common NCDs such CVD, some cancers, and T2D, and the associations are typically reported as “odds ratios or relative risks.” Therefore, the scholars assert that FH can guide risk-specific recommendations for disease management and prevention.
Moreover, it has been highlighted that FH information could be used to motivate people at an increased risk to engage in healthier behaviors. As Valdez et al. point out that the main objective of the risk stratification is to identify individuals with a high risk for a condition, who may benefit from a referral to a specialist or testing. Scholars like Alspach also argues in favor of FH stating that the information can be useful for healthcare professionals in many ways. Alspach highlights the importance for FHH that it is needed for "establishing, updating, correcting, maintaining, accessing, and sharing this information among and between family members, as well as with various health care professionals." Although, privacy and confidentiality concerns overshadow the importance of familial risks in developing chronic diseases, and slow the implementation process into clinical settings, Alspach adds that it is important for healthcare professionals to keep in mind that the FH, as of today, is still the most reliable and valid tool available to make patient assessments, and provide guidance to patients safely.

Alspach furthermore, reiterates the importance of “creating, updating, and sharing a family health history” as being empowering to individuals, “by making them more proactive in their personal health and lifestyle surveillance, allowing them to make more timely and informed health-related decisions, improving their health outcomes, minimizing the development of serious complications, and offering them peace of mind in place of anxiety or fear of the unknown.” Screening tests can help people with an existing FH detect the disease earlier, when they are treatable, like cancer; and also can detect risk factors such as high cholesterol, and high blood pressure, which are treatable and can reduce the chances of getting other NCDs. According to CDC, tendencies towards acquiring such NCDs “can cluster in families,” and FH offers important information for identifying risk to diseases in a family, and “members of the
family can take steps to get tested for those disorders, and take steps to lower their chances of developing, and dying from those disorders.” 112 As scholars like Carroll et al. point out that a lot of work will be needed to facilitate the adoption of FH into primary care setting, its integration into the EMR with “automated clinical support algorithms.” Carrol et al. also highlight the need for more research on the value of FH risk communication “as a motivator for appropriate screening.” 113

Adequately documented FH is essential. Scholars like Alspach states that the current standard utilizes the documentation of 3 generation of relatives by birth: “You, Your children and your maternal and paternal aunts and uncles.” The information sought for inclusion primarily relates to major medical disorders, diseases, and/or conditions associated with a hereditary or familial component, and the person's age when the disorder was first diagnosed. Alspach makes a good observation that other environmental and lifestyle factors may also affect inherited risks, such as diet, addiction, even intermixing of different racial and ethnic backgrounds, and can be beneficial if documented. Also, Alspach adds, for every family member who is deceased, relevant data points that are important knowledge, “are age at the time of death, the cause(s) of death, and, when known, the person's age at the onset of that cause.” 114

Damman et al. observed that FH appeared to be prominent in participants’ risk perceptions and interpretations. They noted that actual examples in the family led to a clearer picture of the diseases, compared with people who had no examples in the family.115 Another observation that was made was participants liked the detailed query in FH, and participants talked a lot about FH in their answers to interview questions about their risk interpretations, which indicated that FH largely influenced their perceived susceptibility. They highlighted that a previous study also revealed that a detailed familial risk questionnaire contributed to users' risk
acceptance and motivation to adopt healthier lifestyles among people with a positive FH. They also observed that putting more emphasis on the FH of diseases in risk communication may have reverse effects for people without a FH of diseases, who do have other risk factors. Damman et al. also add that previous studies have demonstrated that the absence of diseases in the family can also lead to low perceptions of risk.\textsuperscript{116}

Kimberly M. Kelly et al. also asserts that FH is essential for assessing the risk of disease and diagnosing disease. They state that some individuals are at moderate to high risk of cancer compared with the general population because of FH. Familial forms of cancer are thought to account for approximately 10\%–20\% of all cancers; this does not include family members with no personal history of cancer, who may also be at risk for familial cancers. Thus Kelly et al., highlight that these high-risk cancers affect a large number of people in the population and require earlier initiation of screening, more frequent screening, and often, specific types of screening. They highlight that the challenge is to determine who is at general population risk and who is at moderate-high risk. Communication about FH information is critical to distinguishing those at higher risk concerning the number of family members and quality of diagnosis.\textsuperscript{117} In addition to cancer and other NCD diagnosis, Parrott et al. note that studies have found that FH played a positive role in diagnosing blood clots, which can be difficult to diagnose in women. Studies were done on 20 women who experienced a first venous blood clot between the ages of 18 and 50 years, identifying causal attributions the women made for thrombosis after the event. Results showed that women with awareness of FH of blood clots, had diagnosis sooner, thereby promoting survival and efficiencies in health care.\textsuperscript{118}

Parrot et al. bring to our attention that millions of individuals in the United States manage to live with venous thromboembolism (VTE) that has become an illness of uncertainty, affecting
health status, and personal and social relationships.\textsuperscript{119} As Parrot et al. note, despite the human toll in deaths and morbidity - the United States, United Kingdom, Canada, the Netherlands, and Australia, have restrictive policies constraining the use of costly tests to diagnose VTE. Other actions associated with diagnosing VTE include FH screening for genetic contributors, but these have not been part of the standard medical history collected by PCPs.\textsuperscript{120} Scholars like Parrot et al. emphasize the awareness of FH to conditions such as venous blood clotting risks. They highlight that FH information functions as a gatekeeper to diagnostic resources, which in turn relates to policies aligned with genetic testing.\textsuperscript{121} Parrot et al. point out that results that show that diagnosis of VTE is often a long and costly path through many systems of care warrants attention from a healthcare cost efficiencies perspective. Efforts to increase awareness regarding the role of FH and genetics in VTE may improve the survival rates linked to blood clotting events. However, Parrot et al. also points out the concern that overemphasis on the role of FH and genetics may lead to neglect of numerous environmental contributors, and events which may have negative consequences. They also noted that individuals often prefer to conceal rather than disclose personal or negative information about them. This tendency toward self-concealment appears to persist in the realm of symptoms linked to VTE. Parrot et al. suggests that a society that emphasizes self-reliance, together with the geographic distance between family members and the growing number of families without biological connections may all positively contribute. They highlight that these barriers to knowing FHH suggest that there will be situations in which only genetic testing can provide insights relating to inherited risk for thrombosis. As Parrot et al. state that this makes it more important to emphasize awareness in cases where it is possible.\textsuperscript{122}

Research by Kelly et al. has elucidated many shortcomings in the collection and use of FH information. To begin, Kelly at al. highlights a variety of factors which are associated with
poorer accuracy of FH information, such as “more distant family relation; less distinct type of cancer; unaffected status; lack of awareness of family history; inability to research family history; inability to distinguish between benign and malignant disease; and lower disease prevalence in the family, or fewer family members with the disease.” They point out that these are important for risk-communication, and may be because of lower family connection, weaker family bonding, or not understanding importance of accurate information when communicating about FH of conditions such as cancer. Kelly et al. also add that the method of collection of FH information may be problematic due to the physicians’ lack of training, and understanding the risk levels of patients, and inability to communicate the results to other healthcare professionals, “resulting in underestimates and overestimates of risk.” 123 The next section looks at potential approaches that can address the social and ethical issues that may arise in the integration of PM into healthcare such as regulatory standards, policy considerations, and tools; as well as the importance of collaboration and education.

6.3. Recommendations

Precision medicine's application requires the accumulation of massive amounts of health and biologic data. In 2015, President Obama launched the Precision Medicine Initiative (PMI), with the commitment of developing not only technologies, but also the infrastructure of harnessing and sharing data from a national cohort of one million volunteers. As Geoffrey S. Ginsburg points out, PMI's main two components include a near-term focus on cancers, and a long-term aim to generate knowledge applicable to the whole range of health and diseases.124 In order to integrate PM into routine healthcare, Sperber et al. suggest the need for strategies that facilitate the integration of genomic data within existing EHRs, and educate stakeholders about the value of genomic services.125 Many challenges have been brought up by previous studies.
However, three challenges seem to reiterate: 1. Increased priority of integrating genomics within the health system electronic health record (EHR). 2. Increasing knowledge and beliefs about genomic medicine within the clinicians. 3. Engaging patients in the projects.\textsuperscript{126} This section looks at approaches that can be helpful in integrating PM into the regular clinical routine.

\textbf{6.3.1. Regulatory Standards, Policy Considerations and Tools}

Advances in health information technology have enabled the facilitation of data collection, analysis, and sharing of information across institutions, scientific disciplines, and geographic boundaries. According to Diamond et al., this has great potential to transform healthcare in clinical settings, quality, and public safety. However, many issues observed in previous studies included incomplete data (no 100\% participation) and “dirty data” (incomplete, inconsistent, or wrong data).\textsuperscript{127} According to Manolio et al., this is a common challenge that all facilities face due to the poor collection of data from multiple sources, and analyzing of that data in a central location without efficient data cleaning mechanisms, which results in errors that are not fixable without the proper understanding of the source data.\textsuperscript{128} Unclear organizational policies, inconsistent modes for integrating genomic information into the electronic health record system, and concerns about the cost of testing for patients and institutions, are known barriers that have been reported in previous studies. Other factors related to poor uptake as noted by Manolio et al., include providers’ lack of understanding on how to interpret data, patients’ lack of understanding about how the tests work and the effects of the results, that all lead to decision makers to not consider genomics at all in healthcare delivery.\textsuperscript{129} Manolio et al. suggest that implementation of genomics in medicine would also benefit from establishing common infrastructure such as a catalog of various information, similar decision support tools, and collaborative projects to pool resources and identify best practices.\textsuperscript{130}
The time lag in the gathering and post-processing is another challenge that affects data integration - both gathering, and post-processing take time. Recommendations for addressing this challenge include using a networked technical architecture; and a federated governance model that will preserve the original data, and ensure data cleanliness, while protecting patient privacy. As highlighted by the scholars, clearly delineated information policies, and technical standards must be set “that will lay the foundation for an environment of trusted population health data sharing” of data - otherwise, the sources experience repositories of data as black holes, with data disappearing into the repository, never to return.\textsuperscript{131} Manolio et al. also states that challenges in implementing point-of-care tools need to be recognized, with considerations on the evidence needed for high priority healthcare targets with the best risk/benefit ratio and strongest evidence needed to determine which variants are actionable, the patient/group, and the clinical situation.\textsuperscript{132} They add that generating clear evidence of benefit for genomic interventions will remain challenging, and comprehensive strategies will need to be implemented to generate the necessary data to evaluate the impact of potentially important variants on clinical outcomes.\textsuperscript{133} Point-of-care tools have great potential to advance PM in clinical settings. In order to realize this potential, there needs to be collaboration between the technology division (such as Engineers) and healthcare professionals to work on solutions to ensure the PM goals are achieved without any compromises.\textsuperscript{134}

According to research by Makowsky (2017), the importance of addressing adverse drug events (ADE) was brought to attention, stating that ADEs account for a large proportion of preventable emergency room visits and hospitalizations. Having a FH tool where patients can also complete a validated screening for medication-related problems during primary care clinic visits can be helpful in prioritizing patients for pharmacist consultation in medical practices, even
though it may be challenging to implement into practice. Research by Walter et al. shows, there remains limited documentation of the impacts of the serious (Idiosyncratic) “ADRs on patients and the health system at a population level.” Walter et al. suggest that “the availability of jurisdiction-wide hospital admissions data, combined with International Classification of Diseases–10th revision (ICD10)-based approaches for identifying ADRs,” can increasingly be possible to evaluate rare ADRs. While there are limitations with ICD-based methods, Walter et al. point out that there is considerable scope for population-level data on ADRs to quantify their burden, and identify areas in need of closer investigation. Moreover, Walter et al. highlight that although the prevention of (Idiosyncratic) ADRs is demanding; ADRs can be reduced using a combination of approaches. They add, using enhanced monitoring of patients who have a history of ADR or who belong to a high-risk group, can help detect early signs that may lead to the prevention of serious ADRs in patients. Technologies, such as computerized decision support tools in monitoring both drug dosage and clinical warning signs can also play an important role. ICD based approaches can contribute to the timely population-level epidemiological evidence by providing the surveillance system for monitoring ADRs and associated drugs, thereby minimizing the possibility of dangerous drugs remaining on the market. Emerging machine learning methods can also help in the prediction of drugs’ potential to cause ADRs, by using information on a drug’s molecular structure and by helping to identify high-risk drugs before they reach the market.

Extensive genomic and phenotypic characterizations also raised challenges related to data sharing, informed consent, and the reporting of IFs with potential implications for clinical care. Previous research studies also noted that most physicians and other healthcare professionals were inadequately prepared for the genomic advances that might be relevant to their patients, and were
not adequately prepared to use genetic tests in their practices. Challenges associated with the potential misuses of genomic information that can cause unnecessary anxiety, discrimination, increased medical costs or diverted resources also need to be recognized and avoided. Sperber et al. highlight that clinicians need information about the genetic test, ideally in readily-accessible formats that clarify the strength of the evidence supporting its use, potential harms, and alternatives. They recommend that implementation strategies should also offer clinicians the guidance to ensure that patients are making informed decisions (in a shared-decision approach) based on the best evidence available, which includes recognition that the best evidence available may have significant gaps.

Due to the substantially reduced cost of sequencing of DNA, a wide variety of direct-to-consumer (DTC) genetic tests have been made available by commercial companies in the last decade, with the involvement of healthcare professionals. As discussed by Allyse et al., proponents argue that DTC provides genetic information to consumers, which enhances the autonomy of consumers, allowing them to be in charge of their healthcare management without the intermediary of doctors and hospital appointments, and it is information that consumers have a right to, and also protects their genetic data against insurers and employers. Opponents, however, argue that providing genetic tests in “the absence of medical supervision and genetic counseling,” raises concerns regarding potential misinterpretation of test results by consumers, which may lead to unnecessary distress and/or inappropriate healthcare decision-making.

Scholars have asserted that the information provided is often misleading or inadequate, reducing informed consent, and not sufficiently sensitive to the potential influences of ethnic and racial differences across human populations due to only relying on large data sets generated from studies of specific populations in making their estimates. Kalokairinou et al. point out that the
rapid advance of genotyping technologies, and their decreasing costs have made DTC tests increasingly available to consumers, thereby, outpacing the development of effective regulation of such commercial services. Hudson et al. voice the concern that the quality of DTC tests may be low due to the “fragmented regulatory environment for genetic testing in general.”

Hudson et al. cite recommendations made by the American Society of Human Genetics that can be effective:

1. DTC companies should promote transparency by providing relevant information about the offered tests in an easy to understand manner, to permit providers and consumers to make informed decisions. 2. Ensuring that providers are aware of the tests that DTC companies are providing, as Hudson et al. point out that “some of these tests may lack analytic or clinical validity.” 3. Ensuring the analytic and clinical validity of genetic tests offered by the DTC companies, and ensuring that the promises made are true and not deceptive, and the relevant agencies of the federal government should take appropriate and targeted regulatory action. In the future, DTC companies may be wise to usher in new collaborations between patients, consumers, medical providers, and regulators that maximize the benefits of genetic information through the empowerment of patients and providers. More research and discussions among different institutions that include legislative institutions to potentially identify different legislative tools that may be useful in helping guide DTC genetic testing companies to act responsibly.

Among the many ethical issues that have been identified, issues of inequity are a big concern. Gershon et al. point out that PM is likely to be expensive in the beginning, and “may negatively impact equity and access to drugs.” The objective will be developing drugs that target a specific population, on whom the drugs work best, and this targeting will need careful
implementation to avoid race/ethnic-based stigma. Genetic profiling for drug response based on an individual's race is problematic, since not all people from the same race will have the same variations.\textsuperscript{149} The ethical concerns raised by pharmacogenomics also extend beyond the individual and extends to family members, other relatives, and individual's ethnic group.\textsuperscript{150} Collins and Varmus bring out the issues of conflicts that may arise between families “over testing for high-risk genomic markers,” due to implications of test results for people who have not been tested, and because of stigma within families, and within society. Other concerns noted were the possibility of discrimination and stigmatization, the loss of privacy and confidentiality, and the appropriate boundaries for human intervention. Collins and Varmus states that GINA (2008), prohibits the discrimination against individuals based on genetic information related to health insurance and employment, and can serve as a legal precedent and template for penalties on the illegitimate use of an individual's genetic information.\textsuperscript{151} The next section looks at the importance of collaboration and education in PM.

\textbf{6.3.2 Collaboration and Education}

Collaboration between multiple actors is necessary in order to integrate PM in healthcare settings.\textsuperscript{152} The PMI promises the collection and sharing of a large amount of data from one million volunteers, which will allow improved access to data across multiple networks. Integrating genomic information into EHRs in clinical setting allows improved access to data across different networks.\textsuperscript{153} Manolio et al. are excited that PMI will allow for research advances to provide better assessment of disease mechanism, risk, and optimal therapy into many aspects of health and healthcare.\textsuperscript{154} Alcalde and Rothstein argue that PMI emphasizes engaged participation and open, responsible data sharing, will allow participants in accessing information about their health, as well as the research. They add that there will also be a need for advancing
the regulatory frameworks nationally, by implementing a strong collaboration between the researchers, government and other public and private entities.\textsuperscript{155} Sperber et al. state that educational campaigns to increase knowledge of genomic medicine among all will be most effective if linked to local observable efforts.\textsuperscript{156} PM can still be very individualized in public health, if public involvement is initiated in the early implementation process that takes into account the “social norms, culture, risk perception, and family factors among other personal information.” Sperber et al., also add that engaging patients to facilitate within family communication is also a very effective strategy; to not only obtain complete FH information, but also for pursuing cascade testing. They further add that good strategies will include knowledgeable providers, who are effective in interacting with their patients in two-way communication, to elicit the contextual factors for a comprehensive consideration of options for and impact of genomic approaches.\textsuperscript{157} Moreover, they add that policy implications can encompass support to speed up linking data across systems and broader-based education of physicians and the public, about the use of genomic information in personal health decision-making to make personal health decisions.\textsuperscript{158}

Knowledge of PM, and its applications and limitations by the individual, are essential for buy-in and utilization. Educating the public and healthcare providers is especially important in order to make PM a success. Per Y.W. Francis Lam, recommendations to improve clinician knowledge about the applications of PM include the availability of a variety of educational materials for clinicians to learn about interventions and how to utilize them in practice.\textsuperscript{159} As suggested by previous studies, new paradigms in medical education are required which will be essential in enabling students to understand, accept and apply an integrative approach to health care, in accordance with PM.\textsuperscript{160} Other suggestions by scholars like Korngiebel et al. to educate
the public, include the implementation and use of the innovation by using mass media, to communicate with large audiences - such as news articles on TV, the radio, and local newspapers. They add that email press releases forwarded by senior leaders within health systems and externally to the general public and local media and journals with a potential reader are another strategy that can be employed to create public awareness, and gain trust - thereby creating public participation. They further emphasize that community participatory approach, such as focus panels with patients to obtain input to develop patient educational materials, and PGx education tools and research study strategies will draw more participants. Given the broad scope of PM and the need for a large amount of diverse data, Sperber et al. point out that “it will be increasingly important for the European Medicines Agency and the FDA to collaborate on the development and establishment of harmonized guidelines for genotyping and biomarker testing, and their incorporation into future targeted treatments, to guide companies.” This could include standardizing trial data documentation. Ginsburg emphasizes the importance of education in the application of genomics and PGx of health professionals and the public to move the implementation of genetics into healthcare setting. As of today, there are no broad initiatives to disseminate genetics and genomics education among medical professionals, trainees, and the public at large. Also, education and proper skills will ensure that individuals and population groups are protected from psychosocial and financial harms. Ginsburg also adds that the continued leadership and collaboration among schools of public health, state health departments, and other public health partners will be instrumental in ensuring genomics is effectively utilized in the prevention of chronic conditions, and ultimately promoting health of the population.
Khoury and Mensah suggest that public-private collaborations will generate the resources and expertise needed for an evidence-based genomic medicine that will benefit both. They add that CDC and others are looking to develop a sustainable public-private collaboration to create the evidence-base needed for genomics and identify the gaps for further research initiatives. As Lam notes, predicting individual response to drug therapy has been a goal of PM in every therapeutic area. Advances in PGx have raised the public expectation that access to personalized drug therapy is around the corner. However, barriers and logistical challenges such as knowledge gaps in healthcare professionals, and lack of proper tools, have been cited by Lam as the reason why implementation of this technology is still far away. In order to overcome the spectrum of challenges and for PM to succeed, Lam adds that an expanded educational scope that includes all stakeholders within the PM innovation ecosystem will be instrumental, rather than merely focusing on simply educating current and future health practitioners. Lam highlights that PM can only be achieved with all stakeholders in the field, only with a broader vision of a “knowledge ecosystem,” working together and occasionally accepting a paradigm change in the current approaches to implementation.

As Henderson et al. state, the scientific complexity of genomic research and the high degree of public interest in PM has highlighted the need for increased scientific literacy through public education. Despite the highlight of this need, the scholars argue that the uncertainties and ambiguities existing within the genomic research, results as treatment distinction as perceived by potential research subjects, thereby presents challenge to efforts aimed at improving public understanding about genomic research. Many topics of concerns were highlighted by the ELSI Congress of 2011 which includes: informed consent, disclosure, data-sharing, special groups, privacy, and confidentiality. The topics that remained consistently reiterative as the major
focus of ELSI investigations related to PM, as highlighted by Callier et al., include topics such as consent, disclosure, data sharing, privacy, and confidentiality - for reasons already covered in previous sections of this chapter. The scholars have highlighted the critical need for exploring topics involving particular indigenous, ethnic, and racial groups. The need for more research that explored the topics of social justice, such as fairness and equity in research, about disclosure, group harm, use of race as a category in research, and genetic discrimination was also cited by Callier et al. It is well known, for instance, that genomic studies have historically focused only on research participants of European ancestry. Scholars like Callier et al. have noticed a sharp decline in publications on important, yet unresolved questions related to how investigators define race and ethnicity in precision genomic medicine (PGM) research - and few articles were observed that focused on recruiting minority populations to PGM research. Since PGM research seeks to understand the roles of diverse genetic variation and environment on health, the scholars emphasize the need for revisiting these issues. The scholars also raised concerns about the changing international context of PGM research – which remains underexplored in the ELSI literature - given the increasingly global nature of ELSI research.\(^\text{170}\)

Due to the level of global collaboration required to understand genomic research findings and benefits to diverse populations in the United States and elsewhere, multi-country ELSI research collaborations should be encouraged and may increase given initiatives like those funded by Human Heredity and Health in Africa (H3Africa), which funds African investigators conducting PGM research and ELSI studies. Another related concern observed was the number of low ELSI investigations that focused on justice, which is a key principle of foundational research ethics. As more communities from around the globe participate in PGM research, it will be essential to address these issues for the benefit of participants from international and native
groups – especially participants who are interested in finding results. Similarly, ELSI guidance specific to PGM research in cancer, heart disease, and other major public health priorities is needed since these could positively impact participants’ PGM research experiences. Timing and progression of the research process and the desire to translate research into clinical care can become an emerging ELSI issue, since private and public entities will need guidance on disclosure and marketing policies as partial details about genetic risks emerge. As medical interventions aim to become adaptable across the full spectrum of life (from birth to death) to a variety of diseases (common and rare), disease states, and populations, the research will also consider the effects of diverse variables – such as age, gender, and location – on health and health outcomes. Along the way, a correct balance of broad and population-specific ELSI guidelines will be essential in the future to further inform PGM studies.

Scholars like Y.W. Francis Lam argues that even though people are receptive to genetic tests and prescribing, there must be some educational efforts that will alleviate their concerns regarding privacy and confidentiality during the process of pharmacogenomics testing implementation. There should be ways to protect patients' privacy and promote the application in clinical practice. Besides, national protection of genetic information afforded by the 2008 congressional passing of GINA should be emphasized to minimize discrimination concern. Addressing these concerns could further facilitate the integration of genomic services to clinical practice, as well as encouraging informed patients to participate in necessary research to advance the approach.

IBC brings to our attention the enormous inequalities that exist in the distribution of wealth between the developed and developing countries, stating that these are acting as a barrier to the sharing of scientific advances and its applications, which are fundamental human rights.
Gaining scientific knowledge is a matter of justice, and is true for lower and middle income countries (LMIC) which can contribute significantly to the scientific progress through equitable participation in research. However, a lack of resources in LMICs is acting as barriers in the implementation of genomic applications. Genomic knowledge has been defined as “heritage of humanity” in the “Article 1 of the Universal Declaration on the Human Genome and Human Rights (UDHGHR),” thereby making it a common good, which should be allowed open access to. Although this leads to many issues of informed consent and confidentiality and data privacy due to data sharing; it also appeals to the international community to confront the issues of right to access to scientific knowledge, with the initiation of protection of intellectual property.  

Moreover IBC add that with the reach of genetic research extending beyond national borders, it is inevitable to address the ethical issues through international frameworks and standards for the direction of such research. Moreover, IBC also add that the establishment of universal norms will not be useful, given the differences in social and cultural sensitivities. It will however be beneficial for international organizations to develop ethical framework in the form of declarations, reports and guidelines. Such a framework will be especially important for countries without any national or institutional instruments in place for genetic research.  

It has been further stressed that sharing of benefits are established between countries - and developing countries should receive support to build the capacity to undertake genomic research capacities that will support research in health services. There is a need to foster scientific and cultural cooperation between industrialized and developing countries in order to help developing countries build the capacity to participate in generating and sharing scientific knowledge that is appropriate to the needs of the developing countries, thereby addressing global health issues.
IBC highlights that the United Nations can be instrumental in making fundamental normative
decisions regarding the safety and efficacies of the tools.¹⁷⁷

Due to the vast differences in health care systems, available resources, and diverse
population needs, there may be an increased need for genetic counselors who are specialists, and
genetic counselors who are generalists in parallel, in the era of PM. While genetic variation has a
role in common complex diseases, Wicklund et al. add, it “does not fully explain the etiology” of
the diseases. An individual's environment, as well as lifestyle, should be taken into consideration,
in order to be able to treat and prevent disease precisely.¹⁷⁸ Because of the difficult nature of the
results of genetic analysis, Wicklund et al. suggest special training in ethics for people
communicating the cases of diseases with multifactorial traits or new variants with unknown
impact on the individual. They also recommend that Doctors should be knowledgeable about
genetics in diagnosis, therapy, and prevention of diseases, as well as the ethical implications of
the results. According to Wicklund et al., the amount of information that can be obtained from
the current testing options has highlighted the importance of understanding the client’s
perspective, values, culture, and beliefs so that genetic counselors can determine the most
relevant and critical information for each client – but most importantly they need to be able to
address the psychosocial implications of the tests and results for the patient and their families.¹⁷⁹
Greater collaboration between physician and genetic counselors will also be needed, in addition
to the incorporation of education in ethics and genomics into the medical school curriculum.

With the advances of genomic technologies, calls were made to bridge the ‘genomic
health divide’ through economic investment in research, and expanding the provision of genomic
services and technologies to the ‘global south.’ Calls were also made to widen the scope of
genomics to include a greater diversity, which will encompass minority populations from other
ethnic groups, and ensure that those who are in most need of genomic research, are not the ones to receive it the last. Calls were made to make sure that those in the developing parts are given the ‘right’ to become participants in, and potential beneficiaries of genomic research. However, there are ethical issues that are becoming apparent owing to genomic research and technologies - issues in terms of social inclusion and justice, as well as inequitable stratified access, and lack of rights to health care resources are some of the anticipated issues that are most likely to arise due to the emerging technologies of genomics in the global scope. These issues demands for a critical and engaged attention. According to IBC, benefits to health protection and health care resulting from advancements in human genetics, should be a “fundamental right of every human being, to enjoy the highest attainable standard of health,” this should include access to healthcare and medicine. Moreover, scientific progress should alleviate - not deepen - inequalities within and among countries, and should not “be used for discriminating against individuals or groups.”

Due to the rapid implementation of biobanks that are raising issues of data protection, internationally implemented safeguards should be in place to protect participants, and foster trust in research activities. It is important to implement an international public registry of DNA mutations and variants. Given the costs of genomic infrastructures, it is unlikely that LMICs will have much access to large scale genetic technologies. However, it is recommended that LMIC governments begin developing genomic policies addressing the human and technical capacity within the context of their national economic and sociocultural uniqueness. Research is needed to identify the promising technologies and the barriers to their applications, in order to bring the benefits of genomics into the health of developing countries. Developing countries need to generate their expertise in addressing the scientific, ethical, legal, social, and policy aspects of genomics. Leadership development programs are needed to create a constituency on genomics.
policy in developing countries, which will strengthen the capacity to participate in international negotiations. Building scientific and policy capacity also involves forming productive and mutually enhancing partnerships with centers of excellence, wherever these may be; while existing centers should be identified and supported, and new centers should be established.¹⁸²

Deepening and updating of ethical reflections need to be reflected in the existing declarations, warranting revisions - this task can be performed by “UNESCO” with its well-established role as a global forum for global bioethics, and relying on the contribution of its institutional and expert bodies. The World Health Organization (WHO) can act as a mediator and neutral broker between states, which are responsible for respecting, protecting, and fulfilling the human right to health, and the pharmaceutical sector, which can contribute relevant products and services. However, the WHO’s role should not be primarily to incentivize the pharmaceutical sector directly but to facilitate and complement its activities to achieve alignment with global public health needs of the developing world. The WHO will provide a neutral platform and act as an independent broker and conveyor on important and controversial issues. The WHO can also function as a mediator when needs arise in developing countries. The WHO can also promote public-private partnerships, including product development partnerships, and convening working groups to provide expert advice to decision makers and resolve controversial issues through collaborative discourses.¹⁸³ So far, the World Health Organization’s main priority has been to improve equitable access to medicines for people and patients living in the developing world. In this regard, it has acted as a neutral broker to provide a platform for discussing important issues such as the need to link innovation with access, to delink R&D costs from the pricing of medicines, and to explore feasible and workable alternatives to the traditional IP regime as an incentive mechanism.¹⁸⁴ Because of the complex nature of genomics, the WHO needs to work
more closely in the future with other international organizations (e.g., World Intellectual Property Organization and World Trade Organization) and important stakeholders, including the pharmaceutical industry. These efforts need to be pursued in parallel with the building and strengthening of R&D capacity and self-sufficiency in the developing world. The WHO also provides technical advice through specific programs in the relevant areas. This in-kind support and the association with the WHO can give more visibility to such initiatives. According to IBC, human genome must not be interpreted only “as raw material,” but must be considered as “one of the premises of freedom” by all. It is crucial to acknowledge the opportunities that the scientific advancement of genomics is likely to offer, as unique tools against diseases, that these opportunities should not become the privilege of few. As the IBC emphasizes, human genomics should be viewed as the heritage of humanity and entails sharing both of responsibilities and benefits.

Conclusion

As Olvey and Bootman rightly states, that the sequencing of the human genome was one breakthrough in recent history that holds many potential benefits to modern medicine, in the name of Precision Medicine. In addition to providing economic value, PM aims to utilize the genomic knowledge for identifying of patients at risk for developing diseases, in order to prevent, early diagnose, and in the drug development of more targeted therapies - to personalize healthcare. PGx is also anticipated to play a critical role in addressing ADRs and toxicities. PM also promises improved care and prevention of chronic diseases in healthcare setting, both nationally and globally. From studies, it is evident that there is increasing appreciation and acceptance of PM within people, making it easier to implement PM. However, according to scholars there are challenges that need to be addressed otherwise the data generated will be
useless, raising ethical and social issues that need to be addressed. Personalized genomic medicine (PGM), with its goals, is promoted as the ‘new paradigm of healthcare.’ The interpretation and ranking of promises differently, which include individualized diagnosis and risk prediction, more effective prevention and health promotion, and patient empowerment - carries ethical and social implications for the realization of PGM as an approach to healthcare. Substantial work highlights the challenges that frame the external social barriers, but very little information is present that depicts what PM might look like in practice, which creates much confusion and unease. We should be mindful of the goals of PM as promised to the people, because different interpretations of its goals can take genomic research and healthcare in different directions, some of which we are fearful of, such as eugenics and exacerbation of inequities and lack of justice. The fruits of this technology should be a common good, and with that in mind, PGM should be considered as a social practice. Therefore, developing a responsible transition plan for PGM will require careful empirical mapping and analysis of all the issues anticipated.
7.1. Introduction

Integrating personal genetic information into healthcare delivery is hoped to tailor medical treatment decisions to optimize patient care; and thereby resulting in significant cost savings by administering treatments only to those most likely to benefit. All of these expectations also raise questions about the upcoming changes in healthcare organizations (HCOs), costs, and ethical obligations of HCOs. As scholars like Moeckel Pritchard et al. point out, overcoming challenges in these areas will likely require strategies to be implemented that are straightforward, provide clear solutions, and can drive systemic and cultural changes.¹ Moreover, Fillerman, Gary L., eds., add that a roadmap to advance PM in healthcare systems can be built with a clear understanding of the set of challenges, and the best strategies for overcoming those challenges.² The purpose of this Chapter is to look at the organizational ethical issues that may arise in the era of precision medicine, and how HCOs in the United States can prepare themselves in order to be ready to address these challenges, while delivering healthcare services that meet the organization’s mission, equipped with the tools needed.

7.1.1. Looking at Healthcare Organizations – Healthcare as Services

According to Fillerman, Gary L., eds., HCOs are expected to provide healthcare to the sick and vulnerable individuals, and this represents a profoundly moral practice. Healthcare professionals are inherently considered as effective moral agents, rather than (only as) skilled professionals mainly because of their professional code of ethics and their values – providing treatment and care to all.³ Communities place a high degree of trust in their hospitals, because they are a community asset, and they have a responsibility to be trustworthy, and accountable to those they serve.⁴ The study of ethics assists administrators, clinicians, researchers, and
policymakers address ethical questions and challenges. Over time, hospitals have been widely established to address healthcare needs in particular communities. Healthcare boards have important ethical responsibilities and duties. In order to look at the ethical duties and roles of healthcare leadership, it is important to understand the nature and purpose of healthcare.

Healthcare is a necessary human service, not optional - people need healthcare services to maintain health, fight disease, and live satisfying, productive, and happy human lives. As scholars like G. Magill and P. Lawrence point out that healthcare is a special type of business, where its ethical foundation is rooted in the commitment to provide care, and ethical practice is evaluated by how well its actions align with that core commitment. However, most hospitals were built to address the health needs of specific communities, not just individuals, to advance community health and welfare. Therefore, Magill and Lawrence argue that the ethical commitment of HCOs clearly extends to communities in which they are a part, may as well extend beyond the local community served, due to today’s interconnectedness. Martien Pijnenburg adds that HCOs, as institutes are also structured by the society, and have a moral responsibility at the level between individuals and the state, and HCOs institutionalize this responsibility through the practices of solidarity with individuals in need for healthcare. Pijnenburg also adds that solidarity in HCOs is expressed through their caring activities – within the context of HCOs, this caring is a joint practice, where institutional care is an organized, multidisciplinary, and structured activity, and solidarity is inherent to this joint practice of care.

While explaining the roles of HCOs, Pijnenburg adds that HCOs have different roles – caregiver, organizer of care, and a public agent. He further elaborates the primary existence for HCOs as a caregiver is to give care – good care that requires competence in the technical and moral sense of the word, as well as a sound balance between personal, professional, and
organizational values. Pijnenburg further adds that meeting these requirements ensures that the HCOs are ethically practicing solidarity and providing the gateway to sources of solidarity.\textsuperscript{10} HCOs also preserve solidarity by the way they organize their caring activities, notes Pijnenburg - creating the proper conditions for responding to the needs and wishes of different stakeholders, where organizations make use of a mix of different moral understandings – focused on rules and scientific validation, as well as on efficacy and efficiency, and on human resources management. The scholar further adds that balancing between these mixes of different moral understandings can also lead to many problems, since every singular understanding tends to become most important.\textsuperscript{11} Pijnenburg explains that HCOs are also called public agents since they operate on behalf of and in favor of a community that wants to take responsibility for its ill members – where HCOs bear the moral duty to act as the “corporate citizens.” In this role, he states that HCOs take responsibility for those who are unable to access healthcare and advocacy on issues that are in the interest of the public's health. The Catholic Health Association (CHA, 2008) of the United States advocates for “a just and compassionate healthcare system.” According to CHA, this is not labeled as solidarity; however, the combined efforts of the members to improve the situation of vulnerable citizens, is how solidarity should be understood as. Through the public advocacy of solidarity, HCOs can contribute to its preservation of solidarity.\textsuperscript{12}

Robert T. Hall states that non-profit HCOs, in the United States, are offered tax exemption because of their social obligation to provide “community benefits.”\textsuperscript{13} According to the WHO, the primary rationale for the not-for-profit organizations is both economic and social.\textsuperscript{14} Fillerman, Gary L., eds., argues that the community benefit is an essential dimension of the healthcare services; so is playing a part in the local and national advocacy for an equitable, accessible, and effective healthcare system - which contributes to the good of the community.
They add that HCOs are also communities of practice - bringing together physicians, nurses, administrators and a variety of business professionals - providing services through a complex community of care. Moreover, Fillerman, Gary L., eds., highlights that HCOs are organized health systems, intended to benefit the population at large. Hospitals may be different in sizes, but they are similar in purpose – provide some healthcare to those in need using specialized staff and equipment – and this similarity is also why they have similar stakeholders. Per Fillerman, Gary L., eds., a Stakeholder is any individual/or group who can affect or can be affected by the organization's achievement of the organization's objectives, and includes – “patients, families, healthcare financing organizations, buyers, community organizations, professional and non-professional staffs, and professional associations and unions that represent them, regulatory organizations, accrediting organizations, trustees or the governing board, other administrators, suppliers, other hospitals and clinics, and the community in which the hospital resides.” Fillerman, Gary L., eds. add that each of these individuals or groups can affect or be affected (or vice versa) by the achievement, of the hospital's objective, and by the decisions made on their behalf. They add that hospitals are unique in their visions and prioritize different commitments. Understanding a specific hospital or healthcare organization requires understanding its specific purpose - and how it achieves that purpose.

With the advances in medicine and informatics technologies, hospital care remains the single largest category of health spending as of today. Fillerman, Gary L., eds. elaborates that data from 1960 to 2000 demonstrate that half of the improvement in survival among heart attack patients was attributable to technological advances. The scholars points out, although these advances yielded many benefits, they also added to the demand for medical services and costs of providing care. In 2014, approximately 50% of the rise in healthcare expenses over the past
several decades had been attributed to advances in technology. However, Vogenberg and Santilli emphasize that technologic innovations in PM will have to keep up with the changes, and successful innovations will require providing a meaningful return on clinical or economic investments, or both – requiring new metrics to determine such value calculations. Pijnenburg notes that it is evident that an HCO needs enough financial margins in order to fulfill its mission to care. But he points out that although these are products created by markets such as medicines and technology, the fear is that market principles like competition and maximizing profits can become dominant and lead to the suppression of care according to medical needs and to equal access. Pijnenburg highlights the tensions that exist between market and care, since they cannot be considered as mutually exclusive. Additionally, Pijnenburg points out that efficient use of means and time, evidence-based care, and the prudent management of human resources present many constraints on the goods to be pursued by any HCO – although they are not equally important and must be weighed. However, the most important consideration for any HCO is caring for people.

The American society considers the provision of healthcare to all as a moral obligation, and it expects healthcare to be safe, effective, patient-centered, timely, efficient and equitable. The demand for healthcare is being raised because of advances in medicine, such as genomics and PM, the rising implications of chronic conditions and a population that is aging – and with the increased demand comes rising expenditures that healthcare organizations have to manage with tight budgets without compromising its quality. Fillerman, Gary L., eds. add that HCO leaders have the ethical responsibilities to recognize and understand moral complexities, and consequences to the decisions they make; and they have the responsibility to nurture and maintain organizational culture. They add that HCO leaders must ensure that the system they
oversee function productively, that they change alignment with their purposes and goals, and that they have a framework in place that can identify, and address ethical or moral issues effectively. Moreover, HCO as a community of care and employer has an ethical responsibility to cultivate a work environment where patient-centered quality care is delivered; in which community members are both stakeholders and beneficiaries; and where work is just, respectful, and mission-driven. As observed by V.T. Grigorean et al., HCOs should have Organizational Ethics (OE) – which refers to a set of principles, codes and beliefs and values - to guide and regulate their actions. Grigorean et al. state, OE is in itself an aspect of the organizational culture – that consists of moral life, the rules and standards to guide employee relationship according to the needs of all those involved. They add that the ethics is a means to calibrate moral issues in certain contexts and can be implemented and managed through ethical committees, codes of ethics, specific policies and procedures, ethical audits, training programs in ethics and so on. Grigorean et al. further argue that the ethics is rooted in the assumptions that healthcare is a necessary human service and a social good; and healthcare organization leaders and boards must understand and act in accordance with their special responsibilities as caregivers, community members, and employers. As demonstrated by various studies, ethical codes can be implemented at various stages, and can include codes for the whole institution, and also for the various departments and clinics; for human resources and legal departments, as well as for the employees; making clear the values important for the organization, which becomes the priority for the organization as a whole. As studies have reflected, it is insufficient to develop ethical codes which only ensure the ethical and legal practices formally. Most companies state that those ethical codes are useful but not sufficient. It is important that leadership support and sanctions for unethical behavior – otherwise the efficiency of such codes will be limited.
Scholars like Aditya Simha and John B. Cullen point out that an organizational work climate is also essential to look at and implement in HCOs – they define it as the shared perceptions of procedures, policies, and practices, (both formal and informal) of the organization. Simha and Cullen, moreover, add that there are many climates: ethical, innovation, creativity, communication, diversity, justice and safety climates and so on. All these climates are known to influence behaviors of organizational actors – an ethical work climate constitutes to the perceptions of what constitutes as right behavior, and becomes a psychological mechanism through which ethical issues are managed. HCOs should be mindful of the various scandals that have taken place in the history of once-respected organizations such as AIG, Countrywide Financial, Lehman Brothers, and Siemens AG, to name a few – where insider trading, embezzlement, corporate fraud, and workplace bullying were all traced back to the influence of ethical work climates, which were at the center of their ethical scandals – raising public fear and mistrust for organizations. Simha and Cullen argue that an ethical climate influenced HCO would be influenced by ethics in both decision making and behavioral responses to ethical dilemmas, which would be reflected in various work outcomes. Given the many organizational scandals mentioned earlier, the World Health Organization (WHO) states that it is important that the HCOs be able to hold on to the community and public trust; and therefore are built on ethics and leadership which abides by the ethics of the organization to uphold the moral foundations. It is important that the role of leadership is clearly defined, and the role is both a practical good and ethical priority. The next section looks at the ethical and legal duties of the leadership in HCOs.
7.1.2. Ethical and Legal Duties of Leadership

According to the WHO, a good health system contributes to good health and ensures inequality does not exist or does not worsen - to all population that it serves. Filerman, Gary L., eds. writes in "Managerial Ethics in Healthcare: A New Perspective," that the health system has the responsibility to try to reduce inequalities, preferentially by improving the health of the worse-off, through interventions where possible. The objective of good health according to Filerman, Gary L., eds. is “twofold: the best attainable average level – goodness – and the smallest feasible differences among individuals and groups – fairness.” According to the authors, “goodness” indicates that the system serves the people as expected, and “fairness,” indicates that the system serves the people equally, without discrimination.29

As articulated by IOM, HCOs are expected to have these essential values of care:

1. Safe – avoiding injuries to patients from the care that is intended to help them.
2. Effective – Per Fillerman, Gary L., eds., this is providing evidence-based services to those who will benefit, and not to those who will not benefit (overdose, or overuse).
3. Patient-centered – Care that respectful and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions.
4. Timely – reducing waits, sometimes-harmful delays for both those who receive and those who give care.
5. Efficient – avoiding waste, including waste of equipment, supplies, ideas, and energy.
6. Equitable – Care that is of the same quality, provided to all regardless of personal characters.30

As Fillerman, Gary L., eds. write, healthcare is perceived to have a moral core by most Americans. The responsibility for framing this moral core and seeing that it is implemented in the day-to-day business of any HCO is the responsibility of all hospital stakeholders, specifically
those in the leadership positions. The governing board establishes the mission, values, and vision of hospitals. According to Fillerman, Gary L., eds., the board also selects the Chief Executive Officer (CEO), who selects the leadership team. Responsibilities of the board include helping the CEO implement the mission, values, and vision developed by the governing board.

All board members have ethical obligations to exercise their responsibilities in a way that advances the mission of the organization, understand that they are not representatives of any constituent groups, and that they are required to have good personal judgment in order to make an independent judgment for the good of the organization's mission.

Organizational leaders commit to contributing to the moral climate of the organization - to the mission and their purpose. There is a requirement for greater attention to alternative forms of care delivery and partnership, relationship with neighboring HCOs, variations in healthcare financing, emerging community needs that must be taken into consideration as part of the leadership responsibilities. Fillerman, Gary L., eds. insist that members must assist management in responding to the new world healthcare delivery and financing. Healthcare boards are entrusted with ensuring the delivery of high-quality patient care, as they note. Directors have a vast and essential responsibility to oversee every dimension of care delivery, including protection of patient's rights, promoting a culture of safety, monitoring key quality measures, ensuring sound structures for clinical research, and approving all forms of physician relationships. The quality committee of the board reviews quality measures and safety, and patient safety data. The committee also works with management to advance the adoption of best practices, and systems of control and continuous improvement. Other responsibilities, as noted by Fillerman, Gary L., eds., include ensuring that services are provided in a way that reflects patient wishes, and choices in a manner that genuinely improves health, and reduces the risk of
adverse outcomes.\textsuperscript{36} According to the authors, the board also has a fiduciary responsibility to guide and oversee all dimensions of workplace justice and human resources. It requires a review of policies and performance concerning employee relations and satisfaction labor relations, compensation and benefits, training and development, and evaluation methods.\textsuperscript{37} They have an obligation not merely to conserve past and present promises, but to guide the organization toward the future while maintaining a commitment to mission and core values. Organizational integrity is animated by the past but always reaching toward the future.\textsuperscript{38}

According to Treviño et al., OE can guide HCOs with a broad range of organizational phenomena - from individuals' attitudes toward ethics initiatives, to the organization's approaches to dealing with ethical concerns. They note that senior management perceptions play a significant role in several key aspects, such as the perceived goals of efforts to foster ethics and legal compliance in the organization; perceptions of the overall ethical environment within the organization; and perceptions of employees' willingness to seek ethical advice within and to report ethical problems to management.\textsuperscript{39} Moreover, Treviño et al. point out that the ethical climate of the organization influences behaviors and attitudes of the employees – which consists of employees' perceptions of the organization's support for ethical behavior via the reward system, consistency between formal ethics policies and everyday practices and decision making, and senior executives' concern for and support of ethical conduct. They highlight that perceptions of the reward system's support for ethics are particularly important; especially the belief that ethical employees are the ones who get ahead and that unethical conduct is disciplined. Treviño et al. note that recent changes in the \textit{Federal Sentencing Guidelines for Organizations} give renewed attention to the importance of organizational ethics and ethics culture, and senior leadership - especially senior managers, are perceived to play an important
role. It has therefore become important to understand senior managers' perceptions of organizational ethics and how those perceptions compare with those of lower level employees, in order to implement better organizational ethics climate.\textsuperscript{40}

Scholars like Treviño et al. have further noted that the intensity of contact that individuals have with an organization increases their tendency to define their own identity regarding their relationship to the organization. Senior managers have been noted by the scholars to typically experience a unique degree of intense involvement with their organizations, and play a key role in building the organization's reputation, serving as agents representing the interests of multiple organizational constituents - as opposed to lower level employees, who according to the scholars are less likely to identify with the organization and are more likely to identify with their workgroup, department, or unit. It was also noted by Treviño et al. that these different identities with different roles, led to differences between how senior managers and lower level employees perceived issues.\textsuperscript{41} Gary R. Weaver emphasize that managers must pay attention to moral identity and moral agency – and avoid even the smallest of amoral behavior since it can create a vicious cycle, leading to the normalization of amoral behavior in organizations. Weaver also highlight that the provisions of opportunities for virtuous action in organizations are equally important, providing the resources necessary for moral agency. He adds that organization-level initiatives are not isolated from institutional phenomena. Therefore, weaver emphasizes that policymakers need to pay attention to how larger, macro-cultural forces advance or inhibit the development of moral identity in organizations. As moral agents, managers are responsible for choosing and changing the organizational situations in which moral identity either thrives or dies.\textsuperscript{42}
According to studies by Treviño et al., recent changes to the *Federal Sentencing Guidelines for Organizations* mandate that organizations “promote an organizational culture that encourages ethical conduct and a commitment to compliance with the law.” However, Treviño et al. also note that some issues can result from senior managers believing that the ethical environment is already quite positive, since this may result in them not doing as much as they are supposed to do in order to uphold executive ethical leadership. Observers have noted in studies that, as is, most executives already devote little of their resources to organizational ethics. As pointed out by Treviño et al., such neglect of ethics can lead to additional problems, such as worker cynicism, or reduced willingness to report ethical problems, particularly if lower-level employees perceive that ethical problems do exist, while senior managers do not. Treviño et al. state that more effort is needed by senior managers to find ways to seek out the perceptions of lower level employees (in the hierarchy) in order to better understand issues. The scholars also suggest that the efforts undertaken by organizations (surveys, as an example) may not be sufficient, and need to create better opportunities for lower level employees to interact directly and regularly with senior managers about ethics issues so that executives can gather high-quality information, perceptions can become more aligned and executives can communicate their commitment to ethics on a regular basis.\(^{43}\) They further suggest that initiatives can include more interactive ethics training at different hierarchical levels, better communication across organizational boundaries, and more research to investigate tactics to align senior manager and lower level employees’ perceptions of ethics.\(^{44}\)

As Sidney Dekker point out, the charitable and public interest activities of a not-for-profit healthcare organization constitute a substantial part of the organization’s corporate social responsibility, and because of their tax exemption status, the *Internal Revenue Services* (IRS)
and state tax agencies hold them responsible for maintaining a level of public interest activities high enough to justify their tax relief. It is therefore important for such organizations to maintain its public trust and character by abiding by its mission and social responsibilities. Dekker states that healthcare is laced with complexities due to the continuing developments in the organization and delivery of care. However, Dekker argues that new technology and new drugs, as well as new procedures and new management, all allow practitioners to be more successful at what they do; but he also adds that these same things can also create “new pressure points, new gaps, and new failure modes.” One example of such new technology that is anticipated to have the potential to improve healthcare outcomes profoundly is precision medicine (PM). However, Aronson and Rehm note that the results of the advances will require time to implement even though “genetics is already being used to direct clinical decision-making, and its contribution is likely to increase.” They add that fundamental changes will be needed in the infrastructure and mechanism by which data is collected, stored and shared in healthcare settings to speed up the advances. This will create a continuously learning healthcare system with seamless cycling between clinical care and research. There are also ethical and social implications that need to be taken into consideration in order to prevent future issues and move the transition of the implementation process smoothly. Moreover, Aronson and Rehm add that patients must be educated about the benefits and risks of sharing their information. The next section looks at PM - the economics, and the impact it will have on healthcare systems.

7.2. Precision Medicine in Healthcare

As Kathryn A. Phillips et al. point out, the term “personalized medicine” has had many name changes: from being known as “stratified medicine,” “pharmacogenomics,” to the recently termed “precision medicine.” Regardless of the different terms, it is clear that Personalized
Medicine/Precision Medicine is anticipated to result in higher quality, lower-cost healthcare because of its targeted therapies to patients, which are more effective and safe.\textsuperscript{47} Muir Gray et al. adds that clinicians now have access to an increasing array of tests with a better understanding of the patient's genetic makeup, that allows them to determine which genetic variant exist in their patients. Gray notes that despite the many benefits of PM, opponents fear about the ethical implications anticipated with PM, especially how it will relate to equity, and roles of healthcare payers, clinicians, and patients in the optimization of the potential of PM without reducing equity.\textsuperscript{48} This section looks at the economics, and the anticipated impact PM will have on healthcare systems.

7.2.1. The Economics of PM

Today, technology in healthcare has progressed into a learning healthcare system, in which data from prior clinical experience provides an ever-expanding resource to guide continuous improvements in health care.\textsuperscript{49} As such, PM through genomics has great potential to bend the cost curve - genetic testing is anticipated to be cost-effective and even cost-saving, although it has been noted in many studies that its ability to do so will depend on many factors - the cost-saving promises have yet to be realized.\textsuperscript{50} Phillips et al. state that decisions about how to assess the value of these technologies, which technologies will be adopted, and who will pay for them will have to be made soon - in all the areas that economics can address. PM is also of interest because of the increased emphasis on patient-centered care that takes into account patient variability, including genetic differences.\textsuperscript{51} So far, a lot of promises have been made for PM’s sake, but this Chapter will look at the hypes, as well as the myths.

Aspinall and Hamermesh state that PM is anticipated to dramatically lower the overall cost of healthcare, mostly by providing early identification and initiation of treatments which are
supposed to be optimal for the patient. Today, healthcare faces a big problem of giving drugs to patients that do not benefit from them. According to the scholars, it has been demonstrated from studies that most drugs prescribed are effective in fewer than 60% of the treated, costing the healthcare system billions of unnecessary dollars. They use the example of Herceptin test to detect for overabundance of HER2 protein in breast cancer patients, and costs about $400. Aspinall and Hamermesh assert that identifying which patients should, and which patients should not be treated with Herceptin - can save tens of thousands of dollars per person. They add that in the case of HER2-positive patients, it can prevent cancer from metastasizing; and in the case of HER2-negative patients, it saves money and resources by not prescribing a drug that will not help them. 52

According to Derrick S. Haslem et al., PM as a cost-saving approach has been debated for a long time. Although recent findings suggest that precision oncology represents an important translational medicine paradigm, associated clinical outcomes are still maturing. 53,54 They state that the advances in genomic technologies have made the genomic analyses of human malignancies technologically and financially feasible for use in the clinic. Moreover, Haslem et al. point that the clinical outcomes of information (such as, survival and cost-effectiveness) to guide targeted treatment in patients with cancer remain unreported and challenging. 55 Although it is anticipated that the targeted cancer therapies will ultimately result in improved clinical outcomes, the scholars note that there is still no information that demonstrates the impact of implementing sophisticated technologies such as NGS on the cost of cancer care, versus standard care. 56 They attribute this lack of information to the limited availability of data (clinical outcomes) and limitation on data sharing that are making such cost associated measures so difficult. 57 They emphasize that it will be critical to measure the cost associated with precision
cancer medicine for its sustainability, in an era of increasing healthcare cost and limited resources. 58

Molecular diagnostic (MDx) testing is an area in PM, as highlighted by scholars like Akhmetov and Bubnov, has become a cutting-edge technology of present-day clinical practice - widely used in numerous areas including oncology, cardiology and many other areas. They add that advances in diagnostic testing is changing the way healthcare will be delivered, expanding diagnostic testing into more portable, easy-to-use, cost-effective, and less time-consuming platforms. Akhmetov and Bubnov also point out that in a report by AEI Brooking Joint Center for Regulatory Studies, it was projected that testing for variants that guided “the initial dosing of warfarin could provide USD 1.1 billion in annual savings to the US healthcare system and could prevent 17,000 strokes with 85,000 bleeding events.” Moreover, MDx tests aiding in guiding physicians’ decisions on treatment, is leading to overall cost savings for healthcare centers. MDx is also noted by Akhmetov and Bubnov to “improve adherence, compliance, and willingness to undergo treatment or prevention through a better prognosis of disease occurrence and prediction of the response to treatment.” 59

Akhmetov and Bubnov also add that MDx testing is also being used in pharmaceutical companies, as it facilitates the discovery of biomarker-based therapies targeting the cause of diseases instead of symptoms. These biomarker-based diagnostics, as the scholars note, if used in clinical trials can boost the chances of regulatory approval, and enhance prescription. Akhmetov and Bubnov also states that MDx is said to be critical in determining individual risk for disease development, leading to the prescription of efficacious therapies. MDx is further thought to be critical in appraising the response to therapeutic interventions during the overall treatment, preparing viable disease management strategies, and so on. Akhmetov and Bubnov add that new
generation MDx can add “downstream value” by their evolving characteristics such as higher accuracy, higher throughput, shorter testing time, simplicity, portability, cost-effectiveness, and so on. However, Gronde et al. are critical about the rising global health care expenditures and drug prices. They state that people are doubtful that innovations will lower the drug prices. Even with the promises of PM and targeted drug therapies to curb costs, the scholars argue that it is expected that the drug pricing and funding crisis will deepen and reach a critical level for even the wealthiest countries.

Duffy and Crown criticizes the present “trial and error” or “one size fits all” approach to the cancer treatment, as inefficient and resulting adverse effects and toxicity. They argue that PM has the potential to increase efficacy and decrease toxicity. As Aspinall and Hamermesh state that advances in PM have enabled drug companies to develop tools that can distinguish the subtypes of what was once considered as “a single disease,” as well as chemical agents that target each of these subtypes. They also add that what used to be known as deadly cancers, are now managed as chronic conditions, by treating them early. Examples include leukemia and lymphoma, which were the only types of blood cancer that could be identified, today 38 types of leukemia and 51 types of lymphoma are known to us. Proponents of PM argue that personalized approaches will increase the probability of positive response, being given only to those who will benefit and reducing toxicity and side effects on others, will also ultimately lead to overall cost savings.

Aspinall and Hamermesh state that many tests are available today to spot many of the genetic differences, allowing drug dosages to be customized. For some cancers, diagnostic tests can help doctors assess the aggressiveness of the tumor and, determine on the type of treatment, such as surgery or less invasive treatment. Drug therapy based on individuals' genetic makeups
is also suggested to result in a clinically significant reduction in adverse outcomes, saving billions of dollars in avoidable costs.\textsuperscript{66} Although there are assumptions that Lynch syndrome and gene expression profiling for breast cancer can be cost-effective - these assumptions are not enough - and are not helping speed up the implementation of PM into the health systems. Scholars like Rebecca S. Eisenberg observe that new technologies like PM may cause much uncertainty about how best to use them and whether they should be modified, even after they enter clinical practice.\textsuperscript{67} G.S. Zaric notes that although PM has promised a reduction in cost, there is still a need for more formal analysis of the cost implications of companion diagnostics. According to findings, the United Healthcare reportedly spent $US500 million on genetic tests in 2010. However, Zaric notes that payers remain skeptical that the costs of diagnostic tests will be offset by more selective use and fewer side effects, and sarcasm still looms about whether increasing the use of PM will reduce costs. Zaric emphasizes the need for the evaluation of cost impact of companion diagnostic test implementations.\textsuperscript{68}

Oncology remains the largest segment for FDA-defined marketed \textit{theranostic} drugs (integrating diagnostic testing to determine the presence of a molecular target for which a specific drug is intended) that are on the market and has not been known to have lowered cost of drugs by stratification.\textsuperscript{69} Greater than 40\% of all marketed products are Oncology drugs – such as Herceptin\textsuperscript{®} and Gleevec\textsuperscript{®}, labeled as “niche busters” - drugs targeted to smaller patient populations but commanding premium prices, allowing them to achieve annual sales >$1 billion.\textsuperscript{70} As noted by scholars like Amit Agarwal et al., the major driver of growth for companion diagnostic deals is the potential economic benefits for drug developers early in drug development, to select patients for clinical trials, and reducing costs and shorten the time to approval for drug developers.\textsuperscript{71} Ultimately, the scholars argue that this only shows that PM will
lead to a more restricted market that drives prices of drugs up, and not down, by population stratification.\textsuperscript{72}

Jane Null Kogan states that “although spending on genetic tests currently accounts for only 10\% of health insurers’ total laboratory costs,” it is expected that the increased utilization will drive these costs upward at an annual rate of 15\% to 20\% - with a projected cost for genetic testing “to reach $15 to $25 billion by 2021,” an increase from $5 billion in 2010. Jane Null Kogan also adds that genetically targeted therapies pose an even greater cost risk for payers, since targeted therapies are classified as specialty medications with the promise of benefits not available from conventional drugs, with no substitutes - they are considerably higher priced.\textsuperscript{73} Jane Null Kogan adds that spending on specialty medications is growing each year and is expected to account for 235 billion, which is half of the total annual pharmacy spending by 2018.\textsuperscript{74} Despite the slow adoption of PM into healthcare, Thomas Reinke notes that many health systems are implementing PM. Reinke notes that Geisinger Health System and Kaiser Permanente are two examples of integrated health systems that are building comprehensive, costly genomics programs, with the goals to develop innovations in care, expand population health initiatives and respond to health reforms that emphasize value-driven accountable care.\textsuperscript{75}

According to Clay Christiansen, PM will be disruptive in its ability to drive down health care costs without compromising quality or outcomes, and while PM is held at high esteem for revolutionizing healthcare delivery, significant challenges stand in the way of its wholly disruptive potential.\textsuperscript{76} Despite the conceptual potential of PM, scholars argue that PM may increase costs without increasing benefits.\textsuperscript{77} Akhmetov and Bubnov note that more evidence is required to prove the value of PM. However, they add that PM focuses on accuracy and feasibility, and cannot be considered as solid evidence.\textsuperscript{78} There are currently no concrete, unified
databases of economic evaluations of PM, making it difficult to assess the value of PM across studies and interventions. The next section looks at the impact PM is anticipated to have on healthcare systems if implemented.

### 7.2.2. Impact on the Healthcare System

Brothers and Rothstein states that advance in technology have caused PM to expand in scope as well as complexity, and they anticipate the trend to continue in the years to come. With all the expansions of scope and complexity in PM, the scholars emphasize that it will be necessary to consider broader issues, such as the implications of the significantly increased amount of health information associated with PM (privacy, discrimination, physician-patient relationships and liability); and concerns about the potential of PM to aggravate disparities in healthcare (the input-output problem, cost, and access to healthcare and access to information technologies). According to Phillip Fasano, data shows that about 1.5 million preventable drug errors occur in the United States each year killing 100,000, and doctors can reduce this by 55 percent by adopting EHRs and electronic prescription. Fasano adds that integration of such technologies into health systems can result in a more affordable healthcare by all. Fasano highlights that cost savings for PM can be hard to calculate, since prevention and preventive care cannot be patented like blockbuster drugs or design for high-tech MRI machine. Although the US and other countries are investing in multibillion-dollar projects to implement effective EHRs, according to Mirnezami et al., it is unclear how effective this system will be in terms of performing genetic tests, since EHRs have been reported by physicians in a survey, as poor system for online test ordering, and not optimal CDS tool. Additionally, EHRs raises increased privacy risk since EHRs are typically comprehensive, and contain records over an extended period, with the ability to instantaneously distribute the information to multiple parties.
As highlighted by Brothers and Rothstein, protection of informational health privacy is of utmost importance; inappropriate disclosure of sensitive information may cause individuals to suffer from embarrassment, stigma, discrimination and other harms to their dignity. They also add that improper disclosure of sensitive information may result in receiving poor quality of healthcare because of stigmatization or discrimination by providers (such as withholding specific information). Moreover, the scholars add that public health harms are feared due to loss of privacy, thereby resulting in individuals to decline treatment for infectious diseases, mental illnesses, substance abuse or other sensitive conditions. Kimberly Shoenbill et al. point that ethical issue surrounding genetic data adds to the risks. Potential benefits are outweighed by data that are not clinically and analytically valid; and inaccurate data will have negative consequences in guiding care, and will likely be harmful. Shoenbill et al. highlight that health information technology (HIT) professionals will have more responsibility in ensuring data protection; by making sure that effective data security and governance are put in place.

Fasano states that “big data” – large databases and care registries – are the big thing that people are talking about today – that allow for the amass and analyzing of massive amounts of data searching for breakthroughs in the treatment, prevention or prediction of illness. He adds that advances in technology have provided many benefits, such as benefits after disasters - the aftermath of Hurricane Katrina led to the panicking of medical staff over effects of the hurricane on access of patient records. According to estimates from economists of RAND Corporation, the potential for health benefits for using technology in healthcare for the entire nation was staggering. They estimated a 2.2 fewer million drug errors, preventable medical errors slashed significantly, saving lives and money by 4.5 billion to be precise. Fasano adds that the computerized monitoring system could find millions of people 65 and up who did not receive
important vaccinations such as influenza and pneumonia saving 20-38000 lives, and also alerting those who have not received screening for colon and breast cancer, can help by detecting cancer earlier so that it can be in treatable stages. However, big data can only be successful if it can ensure security and privacy of personal data. Per Abouelmehdi et al., big data analytics “carries many benefits, promises and presents great potential for transforming healthcare, yet it raises manifold barriers and challenges.” They point out that new information systems and approaches are needed to prevent breaches of sensitive information and other types of security incidents to make effective use of the big healthcare data.

Mirnezami et al. note that the physician-patient relationship will also be affected by PM - especially on time-pressured clinical encounters, and on eliciting FH. The scholars point out that there may be possibilities that PCPs will make trade-offs, such as spending less time on some patient complaints, in order to spend more time on others. They add that this might lead to an unsatisfactory physician-patient relationship, as well as the possibility that certain signs of conditions may be overlooked until they become more serious. They add that healthcare professionals will also need better training in order to be prepared for PM. International-Level attention would probably be beneficial both nationally, as well as globally. Lack of counseling services, as well as patients having to assume larger roles in their own health management may be another issue faced by patients. The development of PM will almost certainly increase personal injury litigation in the United States. It is feared that greater complexity of systems/technologies will lead to increased risks for errors by providers, and this will cause more harm to the patient and create the potential for liabilities for the providers. It has been well documented that many physicians lack formal training and experience in the fast-moving field of
precision medicine, thereby, raising concerns regarding their ability to meet a changing and more demanding standard of care.\textsuperscript{93}

Scholars voice their concerns regarding the advances in technologies which have led to the commercialization and easy access to tools, such as Direct-to-Customer (DTC) genetic tests, that can exploit people's lack of awareness. Patients' will need to adapt to key changes that include monitoring and managing their own health in the era of PM. Mirnezami et al. voice their concern that such detailed, open-access molecular information raises critical ethical questions regarding data handling and privacy, and therefore, strict regulation will be needed in providing the security. They argue that unless implementation processes to safeguard against the marketing and distribution of bogus products are put in place, PM and other scientific approaches will have no clinical effectiveness, and will create mistrust, and also affect the patient-doctor relationship. Therefore, PM will warrant for unprecedented collaboration among all healthcare stakeholders.\textsuperscript{94}

Stratification of patients in PM raises critical ethical issues. According to Jason N. Batten, dividing patients into smaller subgroups for targeted interventions allows scientists, to differentiate between the genetic variations responsible for the disease, and allow them to develop treatments that are effective for those particular groups of patients.\textsuperscript{95} However, this also causes concerns for stigmatization, discrimination, as well as labeling of people in a socially undesirable category or as “untreatable” – which becomes sensitive information. Batten adds that clinicians also face ethical challenges in deciding whether to generate and disclose certain prognostic estimates.\textsuperscript{96} Per Jason N. Batten, obtaining the data in PM is also ethically challenging, since at times the data is collected at great cost- even harm - to patients, raising questions about benefits versus harms in the implementation of a stratified approach to patient care. Notions of informed consent also poses challenges in PM, since there are many
unanticipated uses of the data collected that gives rise to unanticipated results. The possibility of losing the person amidst the data is also a critical issue.

As of today, PM has not been able to deliver on its promises of providing better-targeted treatment with lower costs. Neither has it been able to provide the targeted treatments to causes of illness that are hard to treat – such as rare diseases. Tabor and Goldenberg write that more than 25 million Americans suffer from over 7,000 rare conditions, with an incidence of 1 in 200,000 or less. However, PM has only focused on approaches to studying more common complex conditions such as heart disease, diabetes, and high blood pressure. Unless PM starts addressing these conditions, PM will fall short of the promise it made to targeted treatment to rare diseases, and will lose public trust.

Tabor and Goldenberg have noted that access to therapeutic innovations, still remain inaccessible, and raises ethical issues. They cite the example of Nusinersen for the treatment of spinal muscular atrophy (SMA) - a rare recessive neuromuscular condition cited as the most common cause of death in infants in the United States. They state that the cost of Nusinersen ($370,000 per year for life, after $750,000 in the first year), and the way it is administered (intrathecally), raises issues of how beneficial this “miracle drug” is, when patients cannot afford it even though it is lifesaving. Tabor and Goldenberg state that Nusinersen for SMA is just one of the recent examples of innovative targeted and precise therapies based on a genetic diagnosis that have had implications for patients beyond effectiveness. However, this demonstrates how high-cost and high-risk interventions are only available to those with power, money, and access, and will likely exacerbate existing health disparities and potentially exacerbate the burdens of specific diseases or disease risks.

Given the history of minority groups’ experience in unequal and unethical treatment in research in the US, there exists a certain degree of mistrust of the medical and scientific
community, which resulted in a low enrollment rate of African Americans and other minority groups in many research studies. Furthermore, concerns of minority groups in the US include unjust distribution of new resources, and the potential for genetic enhancements are anticipated actually to exacerbate these disparities. Hildebrandt and Marron state that with the advances of precision medicine technologies such as CRISPR/Cas9, such concerns must be taken care of during the enrollment phase of new trials of CRISPR/Cas9 to warrant the adequate representation of minority patients; and ensure that these historically mistreated groups are provided with the adequate protection as well.\textsuperscript{101} Hildebrandt and Marron note that minorities have been underrepresented in research; and if there is not adequate range of clinical variants it will not be feasible to tailor therapies that are specific for the minority population; and consequently, underrepresented minorities will miss out on potential gene therapy benefits.\textsuperscript{102} It is also feared that gene therapies, once commercially available will exacerbate the gap between the wealthy and the poor. Per Hildebrandt and Marron, some of this inequity in access is hypothesized to be a result of conscious or subconscious racism and differential treatment in medicine as well.\textsuperscript{103}

It has been hoped that PM will contribute to the elimination of health disparities. Unfortunately, many critics have argued that PM can exacerbate health disparities instead of alleviating disparities. Brothers and Rothstein observe that the collection of medical data and access to health services, and information technologies in healthcare will likely escalate the disparities that already exist. They argue that much work that focuses on disparities within communities, as well as fair access to healthcare globally will be needed.\textsuperscript{104} Opponents of PM argue that work to explain race-based health disparities have inadvertently bolstered the mistaken belief that racial groupings can simply be used to generalize the biological realities. They argue
that highlighting genetics as an important route to addressing health disparities may only obscure the importance of social, cultural and economic factors in perpetuating disparities. The next section will look at the controversial issues that are anticipated to arise in healthcare, the implications of transformation and the institutional solutions that can address the issues.

7.3. Controversial Issues and Healthcare

The advancement of medical progress raises issues of costs and inequities due to technological innovations. Advancement in research in PM leads to the creation of extensive new knowledge, and more future knowledge - making enhanced health a moral obligation. Craig E. Johnson states that “healthcare organizations must be led and managed with integrity and consistent adherence to organizational values, and professional, and ethical standards” - in order to identify and address ethical challenges that can stem from various areas, and affect multiple stakeholders. According to Craig E. Johnson, organizations run into trouble when they fail to identify, and communicate their core values, or fail to live up to them. There needs to be an organizational culture in place that not only provides high quality, value-driven healthcare but also promotes the ethical behavior and practices of individuals throughout the organization, allowing the organization to act as a moral agent. This section looks at the implications of the transformation of HCOs - in the form of issues, as HCOs prepares to integrate precision medicine - and the possible institutional solutions.

7.3.1. Implications of Transformation – Moral Expectations

Scholars like Gallagher and Goodstein observe, the changing structure of healthcare delivery from community institutions to modern technological corporations that offer the residents of a community a collection of diagnostic and therapeutic interventions, has led to the emergence of organizational ethics issues. They further note, in order to sustain this transition
while maintaining the quality of services, and keeping up with the costs, HCOs are struggling to assess and manage their duties to an ever-expanding array of stakeholders which include health care professionals, subscribers, and the community. With the recent advances in genomic sequencing and PM, Hazin et al. point out that there needs to be a lot of technological innovations incorporated – such as the EHR system. The EHR is anticipated to be critical in optimally using genomic information for the diagnosis, treatment, and prevention of disease that will allow the potential of genomic medicine to improve patient care outcomes, and lower healthcare costs. However, they also note that existing EHR systems are yet to be ready and will need remodeling to include genomic clinical decision support tools, to provide point-of-care tools to physicians to practice genomic medicine. By ensuring health interventions are tailored to individual's genetic makeup, the scholars are optimistic that PM will be able to reduce health disparities in the U.S.

According to Hazin et al. EHR integrated with decision support tools will be critical to enable PCPs to use genomic medicine at the point-of-care. However, they also note that integrating EHR geared towards PM also has ethical implications – on patient autonomy, confidentiality, privacy, and the obligations of the physician. The scholars emphasize that the genomic data must be protected and needs security measures that protect the information that is stored within the HCO, but also the information that is exchanged among institutions, and with patients. They highly recommend that there is a fair balance between the need to improve healthcare and the need to reduce potential harm before genomics can be implemented into healthcare settings. Dale Fischer et al. have observed that HCOs has been focusing attention on the moral issues associated with the anticipated transformation required in the future implementation of PM in healthcare. They highlight community benefits should be construed as
a fundamental mission of the HCOs. The development of new therapies, technology, and societal expectations will open up the opportunity for more individuals to participate as information becomes more freely available, and inequality will be less acceptable. HCOs must recognize that the modern consumers will take control of their data and wellbeing and in the decision-making of treatment plans in the era of PM, shifting the way healthcare is delivered today. Thus, ethics and legislation will increasingly be a part of the healthcare delivery process. As pointed by Mary J. McDonough, the traditions of Catholic social teachings will continue to be critical of the market system for its failure of injustice, as the distribution of healthcare remain a critical issue with continued rising costs exacerbating equity issues.

Rivers and Glover note that quality of healthcare, in healthcare, is defined as the avoidance of death or increases in favorable outcomes. Satisfaction with healthcare is closely related to concepts of healthcare quality. According to Rivers and Glover, the organizational mission is what defines what the organization can do about the quality and costs; and also sets the basic values and principles to guide how services will be delivered. In the transformation process, the HCOs mission and goals will be critical since it will provide a general direction regarding the quality of health and costs that also reflects the overall organizational internal environment. Advancement of PM will lead to the powerful forces of change within the American healthcare system. As Baily et al. note, the transformation of healthcare management and delivery taking place through healthcare Quality Improvement (QI) raises ethical issues since QI attempts to improve the quality of care for patients may not be equal or equitable. QI in healthcare takes many forms, and while QI uses a wide variety of methods, they all involve deliberate actions to improve care, guided by data reflecting the effects.
According to Abouelmehdi et al., improved technology has had an impact already in HCOs. The advanced adoption of automation, for example, has led to improved patient care workflow and reduced costs in healthcare settings. However, the scholars note that it has also raised concerns for increased probability of security and privacy breaches in healthcare data. According to the CynergisTek’s Redspin, 2016, 7th Annual Breach Report: Protected Health Information (PHI), hacking attacks on healthcare providers had increased 320% in 2016, and 81% of records breached in 2016 resulted from hacking attacks alone. Additionally, ransomware - a type of malware that encrypts data and holds it hostage until a ransom demand is met - was “identified as the most prominent threat to hospitals.” Abouelmehdi et al. state that findings from this Report point to the pressing need for healthcare settings to take stronger, comprehensive approach to protect their information assets, and fight cyber-attacks that are a threat to healthcare.\textsuperscript{123}

According to Hollister and Bonham, EHRs are critical in PM research programs, since they contain all the essential data collected through patient’s visits. Considerable challenges arise due to inaccuracies in data recorded and inconsistencies across different EHRs, which limit the usefulness and applicability of PM research.\textsuperscript{124} The scholars also point out that PM research initiatives can also inadvertently cause harm unless they carefully consider the recording of data without variation throughout the EHR systems.\textsuperscript{125} As the scholars point out that the inadvertent inclusion or exclusion of data can limit the quality of the data, raising issues in PM research. However, they also add that processes are put in place to make sure the data are carefully collected from PM studies.\textsuperscript{126} Hollister and Bonham point out that potential harm of exclusion or inclusion can cause over representation or underrepresentation of populations, which can lead to misleading/inaccurate conclusion of research studies.\textsuperscript{127} The scholars recommend that
researchers should be mindful of the data and use it in such a way so as not widen the existing injustices in healthcare.  

Advances in automation technology and tools used in healthcare have raised many concerns. Abouelmehdi et al. lists the privacy and security concerns in big data as the most highlighted concern for HCOs. They state that healthcare organizations collect, store, maintain and share vast amounts of data in order to deliver the optimum care it promises its users - data that are sensitive information about personally identifiable healthcare information, that are entrusted by patients and must be protected by the HCO. Abouelmehdi et al. point out, while there are policies and governance in place that establish authorization required to ensure that patients' personal information is being collected, shared and utilized in the right ways - security for protecting these data had been identified as being insufficient. They argue that HCOs are still not adequately equipped with the necessary technical support to maintain the security of data, and remain one of the most vulnerable targets of cyber-attacks to publicly disclosed data breaches. Abouelmehdi et al. also noted that attackers used data mining methods and approaches to violate patient information, and therefore, HCOs should implement strong healthcare data security solutions that will protect important assets, and also satisfy healthcare compliance mandates.

Abouelmehdi et al. argue that security in big data should focus on three matters: data security, access control, and information security. The scholars recommend that healthcare organizations implement security measures and approaches to protect their big data, along with the associated hardware and software, and clinical and administrative information from internal and external risks. Abouelmehdi et al. have also noted several successful initiatives recommended by President Obama’s Counselor, John Podesta: 1. A policy should be
implemented to focus more on the actual uses of big data and less on its collection and analysis. 2. Policy concerning privacy protection should address the purpose. 3. Research on privacy protection needed, that can keep up with changes, and create appropriate balance among economic opportunities, national priorities, and privacy. 4. More education and training concerning privacy protection offered. 5. Privacy protections should be extended to non-US citizens since privacy is a worldwide concern.\textsuperscript{132} Creation of policies and mechanisms that address threats and attacks in each step of big data life cycle was also recommended.\textsuperscript{133}

In order for HCOs to address the critical issues of invasion of patient privacy due to emergent threats and targeted attacks, Abouelmehdi et al. recommend that HCOs must ensure that privacy of patient is secured and protected at every level of the processing model – ensure that personal information is kept private even in the events of changes in applications and/or privacy regulations. Because health-related data informatics varies by organizations and countries, there should be laws to protect data privacy that extends worldwide.\textsuperscript{134} They point out data protection regulations (De-identification, and Identity based anonymization) and laws in most of the countries along with salient features are, however, the same.\textsuperscript{135} Big data security and privacy continue to be considered as huge obstacles for researchers in this field.\textsuperscript{136} As a word of caution, the scholars add that even as costs for NGS diminish and confidence increases, population screening to detect disease susceptibility raises serious ethical concerns: overtreatment because of false positives; disparities in access to confirmatory follow-up, counseling, and insurance reimbursement; privacy and discrimination. They suggest that necessary public health education and intervention are put in place to educate people about the risks and benefits of utilizing PM and in turn, improve an underperforming U.S. healthcare system.\textsuperscript{137}
7.3.2. Institutional Solution – Maintaining Ethical Mission

According to Magill and Lawrence, there is an urgent need for OE to help nurture virtuous organizations, rich in stewardship and integrity. They argue that this will help with the ethical decision making and standards of conduct of all throughout the organization, which will be beneficial in regaining the lost trust, and also regain confidence with a renewed commitment to ethics.\(^{138}\) Lee and Mongan also add that in order to be defined as a well-organized healthcare, there needs to be a clear idea of what the greater organization means for hospitals, doctors, and patients themselves.\(^ {139}\) As Cornetta and Brown suggest that in order to communicate the goals and basis of this technology, it will be important to understand the underlying psychosocial and ethical challenges that may arise from this technology. They also suggest a societal dialogue between various community members from different fields, which will not only be educational, but also identify ethical and moral concerns and barriers.\(^ {140}\)

According to Magill and Lawrence, a slow erosion in HCOs results from loss of trust in areas of access, cost, and quality.\(^ {141}\) Therefore, ethics will play a critical role in HCOs in providing practical strategies that will guide healthcare leaders toward a better alignment between institutions and communities – strategies that will emphasize stewardship and integrity, as HCOs try to enhance patient care and improve healthcare services – that is embodied in its mission, vision, governance, and leadership. Magill and Lawrence further add that an organizational ethics strategy should be targeted toward compliance programs that focus on legal and regulatory requirements - seeking to foster a virtuous organization whose ethical principles inspire appropriate decision-making and moral behavior among all its personnel.\(^ {142}\) From research, it is evident that ethical companies actually have a higher probability of being profitable, and that is because of the trust that is developed through the ethics - making ethical
choices also result in lower stress for manager and employees since making decisions that conflict with personal integrity or beliefs can be highly stressful and unnerving. Overall, as Natcha Dolson highlight, ethical conduct builds trust among the team and business relationships which will ultimately validate and promote good business practices which will lead to success.\(^{143}\)

Gallagher and Goodstein view the preservation of institutional integrity as a central focus for organizational ethics. They highlight the need to align organizational decisions and actions with the organizational mission statement and core values.\(^{144}\) Moreover they add that successful organizations demonstrate strategies that reflect core ideology mission and values that motivate progress and change.\(^{145}\) Elizabeth D. Scott also mentions the need for strong leadership to rebuild community’s trust through processes that enhance the quality of care. Scott emphasizes organizational values as the driving force behind higher productivity, job satisfaction and organizational as well as individual outcomes.\(^{146}\) Values as Scott explains is everything (purposes) that is important for the organization’s survival and flourishing, and becomes embedded in routines as part of the organization culture. Scott highlights that HCOs have many purposes, but the most important purpose should be to provide good and just healthcare.\(^{147}\)

Magill and Lawrence views organizational ethics as fundamental for guiding leaders across the industry by encouraging a sense of stewardship and decision-making that fosters shared standards of ethical conduct. They highlight that there is a core concern with fulfilling critical responsibilities and ensuring that choices made on behalf of institutions are responsive to the market, financial, and legal realities.\(^{148}\) The American society, according to Fillerman, Gary L. eds., considers the provision of healthcare to all as a moral obligation, and it expects healthcare to be safe, effective, patient-centered, timely, efficient and equitable.\(^{149}\) They further add that HCO leaders have the ethical responsibilities to recognize and understand moral
complexities and consequences to the decisions they make, and they have the responsibility to nurture and maintain organizational culture. The authors emphasize that ethical leadership can make a significant impact - leaders need to ensure that the system they oversee function productively, that they change alignment with their purposes and goals, and that they have a framework in place that can identify, and address ethical or moral issues effectively.  

Jahn M. Buell writes that a framework that addresses ethical concerns in HCOs helps with making sure that the organization’s intentions – its vision, mission, values, strategy, and goals are represented in the daily works of the organization’s leadership and other staff. Buell states that all aspects of performance are reflected by how well the organization has embodied its ethical principles into action. Buell points out that it only takes a series of small, unnoticed acts to erode the ethical behavior that can lead to disastrous consequences for both the organization and as well as the staff. Buell further recommends that organizations should harness ethical wisdom, which is a collection of knowledge, experience and good sense to make good ethical decisions, and organizational leaders should take the necessary steps to ensure that an ethical culture is put in place.

As Williams highlight, active engagement of institutional leaders from different areas is a critical attribute of the successful implementation of change in healthcare systems. According to Castlen et al., the transformation in healthcare delivery using genomics and PM warrants a great deal of change in conceptualizing patient/client management, which requires technology that will expedite interpretation of test results in a useful manner for clinicians. EHRs will have to be changed in order to accommodate the assessment of FH and other patient-reported symptoms that will be crucial in the care delivery. Castlen et al. further emphasizes the importance of dissemination and implementation of genomics information in the utilization of
clinicians to deliver care, stating that implementation process must include staff and organization in delivering the intervention, financial, and political implications as well as the extent to which systems are driven to improve population health. However, they note a tension between physicians and administrators that they stress must be resolved to achieve the most ethical outcomes for patients. They suggest increasing physician leadership in hospitals to promote good understanding and reduce the power struggle that exist between physicians and administrators.154

Scholars like Fassano emphasizes that money is still an issue in the implementation of PM into healthcare setting – stating that this is mainly due to the lack of proper infrastructure, and standardized process of data collection and interpretation, which creates an obstacle in ensuring that the shared data is accurate, up-to-date, accessible and secure.155 He adds that accurate data is vital for fewer medication errors, coordinated care, and customized treatments.156 In order to change the healthcare culture to become technologically savvy in the era of PM, a comprehensive culture change is necessary for technology values to be realized.157 Moreover, Fassano stresses that it will also be essential to convince doctors that PM is worth their time and money, and by giving them a system that is easy to use.158 He adds that ensuring that patient information remains private and secure will be critical, and privacy and security conversations are building a culture of shared responsibilities between payers, providers, and patients.159 Fasano highlights the role of funding in ushering in innovations, and that there will be a critical need to connect financing systems that use IT to enable the flow of payment, create innovative ways for providers to be paid based on performance and achievement of goals - making sure that the payment and outcomes are aligned.160 Dolson further highlights the importance of HCO’s need to fully understand ethics; and the organizations’ meeting the requirements of social responsibility, integrating it into the organization's culture in such a way that it is at the forefront
of all interactions and decisions. Dolson goes on to add that organizations do not need to decide between being successful or ethical, but instead become successful by being ethical.\textsuperscript{161}

7.4. Building an Ethical Foundation

Fillerman, Gary L., eds., note that our societal expectations of organizations have expanded so much that we now demand organizations, even for profits, to behave responsibly.\textsuperscript{162} This view is agreed by Sturmberg and Lanham, who adds that healthcare organizations are expected to operate ethically, and in order to build an ethical healthcare organization, it is important to understand the complex system of healthcare delivery - quality of care, financial viability, and intervention success rates, these are all emergent properties of healthcare delivery systems.\textsuperscript{163} We know that hospitals define themselves through their mission, and other documents, such as their codes of ethics.\textsuperscript{164} The overriding mission, per Craig E. Johnson, is to provide the best, most affordable healthcare ethically, with compassion, and empathy for its patients.\textsuperscript{165} Magill and Lawrence suggest that healthcare organizations need to embrace an organizational ethics strategy that recognizes the significance of fostering a virtuous organization to inspire the ethical conduct of its personnel. This section looks at simple guidelines that can help build an ethical organization.\textsuperscript{166}

7.4.1. Challenges and Principles for Integrating PM

Agarwal et al. state that technology has advanced faster than peoples' understanding of how it should be used. When medical technologies are expensive, and budgets are tight, it is difficult to decide whether to spend dollars on more sophisticated, and costly technologies that help only a selected few, or invest in the less costly preventive medicine, and health promotion that have the potential to help many. Agarwal et al. goes on and add that although health IT (HIT) has tremendous potential to improve the quality and reduce costs in healthcare, significant
challenges will need to be overcome in order to realize the full potential of HIT.\textsuperscript{167} It is crucial for HCO leaders to examine the ethical components of the many decisions, and choices encountered in order to develop a more comprehensive response or approach.\textsuperscript{168} HCOs have to maintain their quality of care, and remain faithful to their mission, while reducing their spending.\textsuperscript{169} Moeckel et al. note that research and innovation in PM are growing rapidly. However, its adoption into clinical practice has not kept pace with its advancement. In order for healthcare to transition into precision medicine, Moeckel et al. state that stakeholders will need to make a progression of strategies to create a momentum. Moreover, Moeckel et al. note that evidence indicates that in most cases PM is not even discussed at the point-of-care, and according to a recent public survey, only four out of ten consumers are aware of precision medicine, and only 11\% of patients say their doctor has discussed, or recommended precision medicine treatment options to them.\textsuperscript{170}

Moeckel et al. also state that practices and standards associated with the field of PM were cited as the lag in clinical adoption of PM. While there are many programs, such as the \textit{Personalized Medicine Coalition's (PMC) Healthcare Working Group (HWG)}, that has facilitated a dialogue about how to incorporate genomic information into healthcare practice, Moeckel et al. note that recent surveys showed that most healthcare organizations are not ready to implement PM. PMC's HWG has identified common challenges involved in developing precision medicine programs and the most promising strategies for addressing them.\textsuperscript{171} According to Moeckel et al., the following principles were recommended in order to integrate PM into healthcare practice: 1. Development and application of effective healthcare delivery infrastructure and data management systems so that it can be used to guide clinical decisions. 2.
Establishment and implementation of best practices for healthcare delivery approaches, processes and program operations that ensure access to PM.\textsuperscript{172}

Moeckel et al. write that overcoming challenges in integrating PM will require near-term strategies as well as long-term strategies. They suggest making progress in addressing challenges that are easier first, thereby clearing the path to address more difficult challenges later. They state that this will foster behavioral adaptation to PM as well.\textsuperscript{173} Magill and Lawrence emphasize the integration of stewardship and integrity with the decision-making processes, and ethical behavior for organizational ethics in healthcare. They point out that for HCOs to address ethical challenges, the decision-making process must emphasize the identification of \textit{a specific problem}; and \textit{resolution of the problem in an ethical manner}.

Moreover, Magill and Lawrence recommend that HCOs develop and adopt a standard of conduct that will enhance performance improvement throughout the organization, which will also be integrated with the guidelines for stewardship and integrity that fosters the ethical decision-making processes.\textsuperscript{174}

Scholars like Grigorean et al. argue that in order to make the applications of organizational ethics work, it is essential to set policies and procedures that include: (1) Ways of solving ethical dilemmas; (2) The framework for developing ethics-oriented trainings; (3) Ways of repaying ethical behaviors; (4) Consequences of violating ethical principles; (5) Ways to solve employee complaints; (6) The implementation of a hotline used to report anonymously suspicious unethical activities; (7) Activities to promote hospital organizational ethics contribute to the creation of an ethical climate.\textsuperscript{175} Moreover, Grigorean et al. add that it is evident that the HCOs will have to identify and address ethical issues related to the changes considering the advances in medical technology. They further highlight the need to establish ethics committees.
in healthcare organizations, as an integrative component of hospital operations, authorized to solve ethical issues wherever these might occur.\textsuperscript{176}

Ethics committees within HCOs are noted by Grigorean et al., to be beneficial not only in influencing the quality of care but also in aiding with the transformation, and addressing any issues that may arise in the process. The scholars add that ethics committees in the US have grown significantly from 1\% in 1983 to 60\% in 1989, and this percentage stepped over 90\% in 1998. In 1992, the \textit{Commission on Accreditation of Healthcare Organizations} (CAHO) of the United States of America demanded from institutions to implement specific mechanisms dedicated to ethical issues. Scholars highlight two main functions of the ethical committee:

- Acts in order to be compatible with the official regulations of the state and connected agencies;
- Offers a consultancy environment for ethically complicated situations which may occur either during patient treatment or medical research.\textsuperscript{177} The scholars further goes on the explain that the aim of the ethical committees all over the nation is to elaborate clinical healthcare policies is higher than estimated, as they have an important role in debating and solving medical and clinical policies and cases. They add that many of the EC policies refer to important aspects of medical policies, which apply not only to institutions but also to taxpayers, patients, and society. The scholars assert that ECs play an important part in the medical system and are an essential feature of hospital efforts to control complex ethical problems.\textsuperscript{178}

As Sahini et al. point out that previously the adoption and management of healthcare IT was left on the organization's chief information officer and other technical personnel, which in their opinion were not successful. They cite that Boston Medical Center, Geisinger Health System in Pennsylvania, Intermountain, Mayo Clinic, and New York University (NYU) Langone Health, are all examples of organizations that had successful healthcare IT implementation by
allowing all members to work in the implementation process. The scholars further add that senior leaders and clinicians are essential constituents in the successful implementation; and organizations should make pledges to improve quality that are more than words and are visible.\textsuperscript{179} Sahini et al. suggests that senior leaders should not only encourage the development of the necessary data infrastructure but also help establish a vision for how the collected data will be used to improve productivity.\textsuperscript{180} The scholars point out that HIT systems also offer HCOs the use of predictive analytics to guide future decision making in clinical operations. Predictive models in precision medicine, according to the scholars, will be used to correlate particular genetic mutations with specific forms of treatment.\textsuperscript{181} They also highlight the need for specialized teams of clinical personnel to give meaning to the insights from the analyses to delivering improved care.\textsuperscript{182}

Castlen et al. argue that HCOs are continuously faced with the daunting task to reduce costs and maximize efficiency. Administrators try to identify factors that can reduce spending without adversely affecting patient care – which the scholars observed leads to physicians feeling their role as caregivers being curtailed, and often leads to attempts to obstruct or resist changes. They argue that physicians, administrators, and society at large desire just and excellent care for patients, therefore, implementation of new procedures and policies and well-developed guidelines will be needed to helpfully standardize the procedures, without impacting the doctor-patient decision-making process.\textsuperscript{183} According to scholars like White et al., there will also be a critical need for the integration between informatics and interprofessional practice and interprofessional education (IPE/IPP) that will be needed in the implementation process of PM.\textsuperscript{184} In their opinion, the biggest challenge in developing solutions will be fostering collaboration between the actors, processes and the context.\textsuperscript{185}
7.4.2. Building the Infrastructure to Support PM

Lee and Mongam note, for PM to work effectively, all the components of the US healthcare system need to move from a fragmented system into a system that collaborates to work together.\textsuperscript{186} There are a lot of complexities and costs associated with the operation of our healthcare delivery system. In the era of PM, where genetics information will be crucial for clinical decision-making, foundational changes in the infrastructure and mechanism for the collection, management and sharing of the data will be necessary. As scholars like Samuel J. Aronson and Heidi L. Rehm add, even though understanding of the genetic makeup is critical in PM for providing care, clinicians will have the support of tests and tools that will match genetic determinants to the patients. They also add that, simply matching variants will not be sufficient; clinicians will need to determine the implications associated with the clinical indications, and cross checked with other data to determine the best treatment plan for the patient.\textsuperscript{187} A policy must be put in place in order to avoid convoluted procedures and undesirable consequences on individuals and institutes.\textsuperscript{188}

An optimized infrastructure designed to support the precision medicine ecosystem efficiently will manage and integrate the flow of material, knowledge, and data needed to generate, validate, store, refine and apply clinical interpretations. EHRs and associated systems will enable clinicians to apply results, both when they are received and as the patient’s condition and knowledge of the variants evolve. At present, much of this infrastructure is at a very early stage of development. However, the infrastructural foundation for precision medicine is beginning to emerge.\textsuperscript{189} EHRs should serve as the clinician’s gateway to all of the patient’s information, including any genetic data. Information should be organized and displayed in a way that integrates with the clinician’s workflow and facilitates diagnostic and treatment decisions.
Creating these interfaces often involves establishing electronic connections that span multiple organizations and integrate systems from competing vendors. At this stage, only a few interfaces exist due to costs associated with creating them. Clinical knowledge-sharing infrastructure and case repositories, especially when combined with EHR-derived content, can provide clinicians and clinical laboratories not only with unprecedented access to clinical data, but also make this information accessible to researchers. Improved infrastructure to capture both test results and patient outcomes should enable the measurement of such benefits.

Moeckel et al. point out that effective strategies are needed in order to manage the large volumes of information associated with PM. They add that strategies that combine efforts to understand the different perspective of stakeholders and structured collaborations among healthcare organizations can be a good starting point. Although health systems are challenged with managing performance, the scholars observed that most organizations do not have a clear understanding of how to address them. They highlight that HCOs must recognize the need for increased use of data and analytics to improve strategic decision making in the era of PM. They noted that 90 percent of CFOs and other senior finance executives in a survey in 2018 stated a need for improved analytics and reporting for strategic decision making. 96 percent of the senior finance executives, in the same survey, also acknowledged that cost transformation would be significant for their organization. According to Sargeant and Spence: “leveraging data and analytics to know where to focus cost efforts was the most commonly cited impediment to achieving cost-reduction goals” - thereby “identifying and managing cost-reduction initiatives” have been identified as “the most important performance management activity.”

Sargeant and Spence further note the importance of having cost benchmarking processes in HCOs. The scholars state that benchmark-rich databases and analytic tools are essential in the
successful operation of a HCO, since these tools can help assess strategic performance that will drive the required transformation of care, quality, costs, and patient experience. They further highlight that benchmark-based reports and scorecards can help leadership observe: “patterns of performance that impact utilization, cost, quality, outcomes, and patient experience based on factors such as diagnosis, comorbidities, treatment type, department, and physician.” They add that other areas can also be targeted for improvement, and best practices can be developed from areas of outstanding performance. Seargent and Spence noted from a survey that about: “18 percent did not perform any cost benchmarking.” However, they recommend all HCOs should benchmark quality and cost performance to understand their competitive position. They also recommended the redesigning of HCO’s financial planning process to identify appropriate strategies that will move forward their organizations’ missions and other objectives. Seargent and Spence suggest a “continuous measurement of performance” to ensure that the strategies meet the expectations.

Seargent and Spence further notes that the current healthcare environment addresses multiple challenges related to changing payment and delivery models. There is a need for robust performance management in order for organizational transformation. Per Seargent and Spence, “finance leaders have a pivotal role to play” in the reduction of risks and centers on building organizational agility in order to prepare the organization for changes. They also add that: “Agility is enhanced through high-quality enterprise performance management processes and tools that enable finance professionals to develop scenarios, set targets, track and communicate progress towards goals.” Additionally, Seargent and Spence specify the need for significant new talent with expertise in areas that can keep up with the organizational agility and value-based care delivery, as well as data analytics and technology to transform costs.
Research has demonstrated that there is a clear need for a dominant organizational culture and ethical leadership in the era of precision medicine, especially in the adoption of the technology. Manion et al. views ethical leadership as an essential component in organizations, because leaders who strive for ethical conduct motivate followers to pursue ethical ways, and also involves strategic planning process so that policies, decision-making processes, consultation, accountability, ethical standards are put in place for guidance. They also add that ethical leadership includes communication, collaboration, quality, succession planning, and tenure. Lepore et al. note that organizational culture will be a crucial factor in understanding the ability of any organization to perform and compete. Davies et al. explain that cultural transformation must employ strategies that are highly selective, aims for a balance between continuity and renewal, and identifies those cultural aspects to keep and reinforce, and those that need to be reworked. They point out that the organizational culture cannot be tackled in isolation from such issues as the organizational structure, financial arrangements, lines of control and accountability, strategy formulation, or human resource management initiatives. Davies et al. emphasizes that the organizational culture must have a bearing on the clinical performance and healthcare quality, and identify interventions and management strategies that can be predictive of cultural attributable impacts in performance improvements.

Scholars like Berkman et al. and Mackert et al., state that HCOs must take into account the importance of literacy of the technology and tools used in the era of PM, and that health literacy is tied to the acceptance of the technologies and tools, and is an essential factor in patient health outcomes and results in health care costs. Hennemann et al. add that HCOs need to understand that employees, staff and other stakeholders need to have adequate familiarity with the meaning of language surrounding new technologies. They note that common disadvantages
reported for such technologies in healthcare by providers are lack of guidance through a therapeutic relationship, limitation of communication, and control or concerns about data security. Moreover, they add that healthcare professional attitudes towards the technology were also identified as indicators whether the tool would be used or not. Thy pointed out that different healthcare professionals such as nurses and physicians also have roles as educators and patient advocates and will need to be properly educated and trained in genomics and informatics tools employed in PM to be able to understand the genomic language used in the practice innovation. With the completion of the HGP, healthcare professionals face the challenges of enormous change in practice, and may not be adequately prepared to address the challenges. Given the psycho-social, and familial implications of genetic tests and screenings in PM, scholars like Ishveen and Kelly argue that healthcare professionals will need education in genomics and also ethics for the proper delivery of care in PM. Williams et al. also add that the implementation process will not be optimal unless the participants as well as the institutional leaders are aware of the PM approach and the benefits and the harms associated with the tests involved.

**Conclusion**

In healthcare, there are a lot of ethical issues that are dealt with every day, which must be addressed in a well-reasoned way. Conflicts might arise among the mission, vision and patient right statements due to many reasons, and may have ethical ramifications if the ethical standards are undermined. Protecting patient information will be at the core of an ethical healthcare organization. However, a well-organized healthcare system will ensure that the staff is well educated about the needs of the organization, and ensure that both clinical and nonclinical staffs are knowledgeable and involved in ethics and ethical decision-making without fear of reprisals.
for contrary opinion. As Sahini et al. writes that there will be constant challenges to revamp the organization with new technologies in the era of PM. However, the top executives, the board of trustees, physicians, and nurses will all have to work together to support these drive to improve care.
Chapter 8: Education and Competency Rich in Genomics and Ethics is a Necessity for Healthcare Professionals in the Era of PM

8.1. Introduction

Advances in genomics are anticipated to contribute to the development of more effective, personalized approaches to the prevention and treatment of infectious diseases.\(^1\) Such potential tailored interventions for particular individuals, populations or subpopulations, raises ethical, legal and social implications (ELSIs) that requires good understanding of genomics as well as ethical principles in order to address issues and utilize this translation of genomic information into practice to provide patients, families, and communities with competent, safe, effective healthcare.\(^2\) Recent studies that compare trends in the genetic curricula in the U.S. and Canadian medical schools have demonstrated inadequate incorporation of genomics material into the curriculum; as a result, the health care workforce is not adequately prepared to incorporate genomics into regular practice in the era of PM. From studies, it has been identified that there is a need for health provider education and competency rich in genomics and ethics. The purpose of this Chapter is to look at existing educational standards and outline the specific needs and challenges associated with advances of genomics and PM. This Chapter also proposes potential approaches for educators to keep pace with this rapid advancement.

8.1.1 Era of PM - Knowledge of Genomics and Healthcare Professionals

Precision medicine (PM) uses various genomic, biomarker and drug metabolism information to guide care for an individual patient in a precise manner.\(^3\) It encompasses various diagnostic tools that measure drug metabolism, genetic risk for disease development, and tumor type/markers that can guide better oncology treatments.\(^4\) As scholars like Terri A. Manolio et al. and Adam C. Berger have pointed out in their respective studies, that the knowledge of this
information and utilizing of this information has not kept pace in clinical practice; thereby resulting in a substantial delay in the translation of genetic research findings into patient care within the healthcare system.\textsuperscript{5, 6} In an era of PM, it is important to make sure our healthcare workforce is adequately prepared to serve its population. This section looks at the knowledge and confidence levels of healthcare professionals in genomics and PM, especially those who will be in the first phase of interaction to initiate the process.

Despite the promises of PM, it faces several challenges, one of which has to do with the human factor, and the lack of preparedness of the workforce.\textsuperscript{7} As Scholars like Dhar et al. point, with the advances of genetic testing and genomic technology, it is now possible to have high throughput sequencing of human genomes fast and at a low cost. Allowing it to be used to target therapeutics, determine better prognosis by utilizing probabilistic risk assessment for many conditions. It is not far away that practicing physicians will be utilizing these technologies and making decisions based on the results generated for their patients in their practice.\textsuperscript{8} However, training and education of genomics and genomic technologies used in PM have not kept pace with the growing use of the application in clinical practice. Lack of provider awareness and knowledge of genomic medicine has been reported by Plunkett-Rondeau et al. as a barrier to the implementation of PM. A survey utilized in their study on primary care physicians (PCPs), reported PCPs “lack knowledge of genetics relevant for daily practice, lack oversight of genetic testing, and feel inadequate to deliver genetic services.”\textsuperscript{9} Paneque et al. also emphasized the need for education around genetics and genomics - particularly, when and how to use genetic/genomic testing – that this education extends across “continuing medical education programs, residency and medical school levels, and all healthcare professions.” They also indicated that medical students approaching graduation may not have appropriate mastery of critical genetics concepts,
and that current physicians do not feel adequately trained in genetics and genomics, and few PCPs are “comfortable ordering genomic tests or explaining test results to patients.”  

As the tools used in medicine is changing, so is the practice – making it difficult for healthcare professionals to keep pace with the changes. As pointed out by Dhar et al., many patients approach their primary care physicians (PCPs) for more information about the various direct-to-consumer (DTC) genetic tests, and some even go to their PCP just to seek help in “interpreting their test results.” However, Dhar et al. noted that PCPs felt they lacked the knowledge or training to answer questions about DTC tests. Based on their study in 2012 on 2,402 primary care and internal medicine providers in North Carolina, of whom 382 responded, only 38.7% were aware of DTC tests and of those, only 15 % felt prepared to answer questions about DTC results. Dhar et al. suggest that this lack of knowledge may perhaps be due to the misconception that genetic tests are only of concern to specific specialties, “such as pediatrics and prenatal obstetrics.” Regardless, Dhar et al. feel, PCPs need to be equipped with the knowledge to critically assess and explain genetic test results to their patients, and need to know when to refer patients for specialty care in medical genetics, and counseling.  

As Plunkett-Rondeau et al. pointed out that a large percentage of U.S. medical schools in the past did not even offer a course in human genetics - in 1981, only 28% and in 1988, about 18% offered a course. However, Plunkett-Rondeau et al. also noted that studies from 2005 demonstrated that the numbers have vastly changed with the genetics education being incorporated into the curriculum with the majority of medical genetics (about 77%) being taught in the first year; with 47% incorporating aspects of medical genetics training into the third and fourth years of study. Plunkett-Rondeau et al. also added that education in genetics has not kept up with the various advances such as DNA sequencing, DTC personal genome testing, and the
use of exome sequencing. And they report that, in order to help medical genetics education to evolve with the changing scientific and educational landscapes the Association of Professors in Human and Medical Genetics (APHMG) updated its medical school core curriculum in genetics, using “the Accreditation Council for Graduate Medical Education competency domains,” as a framework of principles that can be incorporated into a wide variety of curricular formats.12

According to studies, at least 10% of patients seen in primary care had conditions with genetic influence. However, due to PCP's lack of knowledge of genomics and genetics, patients at risk of genetic disease may not be recognized, while those who seek advice may not be referred, or managed appropriately. As Paneque et al. pointed out that serious consequence can result from undetected genetic risks, such as increased morbidity, mortality, family burden, and healthcare costs. With the advancement and availability of genomic technologies in clinic as well as individual DTC genomic tests, educators need to ensure appropriate coverage of genetics and genomics topics in training future healthcare providers.13,14 Lack of PCP’s knowledge in ordering genomic tests has been an indicator in lack of PCP’s confidence in ordering genomic tests for patients. The next section looks at the confidence level of the workforce.

8.1.2. Confidence Level of the Work Force?

In the age of genomics, PCPs will be increasingly involved in preventive care and management of relevant surveillance processes, creating pathways to deal with patient requests regarding genetic tests. Primary care can be provided by a range of health professionals and is defined by the World Health Organization (WHO) as healthcare: “that is directly accessible by patients as the first point of contact, as well as being comprehensive and ongoing. It involves prevention, and pre-symptomatic detection of disease, as well as early diagnosis, all of which are relevant to patients at risk of genetic disease.” According to studies by Paneque et al., it was
identified that PCPs had three main responsibilities in relation to genetics: “being able to identify patients at risk of a condition; contributing to medical management; and appropriate communication of genetic information to patients.” However, they voice their concern that genetics education is only very slowly starting to become a common part of medical curricula, and research demonstrates that PCPs are not ready for precision medicine in the clinical setting.¹⁵

According to scholars like Allison A. Vorderstrasse et al., personalized and precision medicine will require the appropriate interpretation and clinical “use of novel and personalized information” by healthcare professionals; and providing the adequate support for patient decision-making while being attentive to family may raise ethical implications in the approach to care.¹⁶ They add that given the amount and types of data that will be collected in EHRs with PM strategies, healthcare professionals will need to look at ways to optimize the use of personal patient data of multiple types in patient care.¹⁷ Suther and Goodson identified key areas that PCPs lacked confidence in: lack of genetic knowledge, lack of interpreting family history, lack of referral guidelines.¹⁸ With the recent cost reduction and availability of DTC genetic test kits that enable people to receive a list of genetic illnesses and whole-genome testing for markers thought to be predictive of traits and disorders and chronic illnesses - dilemmas arise when consumers face ambiguous or alarming results needing expert interpretation from their PCPs.¹⁹

Per Keyan Salari, data suggests that the American public will turn to their PCPs when faced with a dilemma. Salari adds that according to a study on 1000 individuals in the U.S., 72% indicated they were ready to go to their PCPs with questions. However, evidence indicated that although some physicians are equipped to interpret such reports, the majority of physicians lack training to deal with these issues, and that patients were likely to be disappointed and misinformed. Salari furthermore adds that another study showed that 64% of patients with
genetic conditions received no genetics education materials from the healthcare provider, even though that was the most important part in the management of their condition. Salari also noted that educational materials mailed by genetic testing companies to practicing physicians, as indicated in a study, proved ineffective, since over half of the physicians answered basic questions related to genetic testing incorrectly. This is an indicator that more fundamental training is required to enhance physician's knowledge about basic genetic testing, and their ability to provide the counseling needed. And as Salari noted that it was indeed reported, 68% of physicians in the study acknowledged an increased desire to learn more about genetic testing. Moreover, physicians spend little or no time to elicit detailed or any patient family history, which according to several studies was credited to hinder the effective utilization of genetic testing and counseling. Salari asserts that these studies together suggest that many physicians need the fundamental education and training in order to be adequately trained to appropriately order simple single-gene tests or to interpret simple results, and also communicate the results to the patients who requested the tests. Salari emphasizes that in order to utilize genomics in medicine, physicians must be able to effectively use, evaluate and interpret the results.  

According to research, the majority of underutilization of genetic services by PCPs was due to lack of adequate genetics information and knowledge. According to Jeanette J. McCarthy, recent reports indicate that medical students approaching graduation may not have appropriate mastery of critical genetics concepts, and that current physicians do not feel adequately trained in genetics and genomics, and that few PCPs are comfortable ordering genomic tests or explaining test results to patients. In fact, lack of provider awareness and knowledge of genomic medicine has been reported as a barrier to PM’s implementation. According to the Centers for Disease Control and Prevention (CDC), genomics plays a role in
“nine of the ten leading causes of death.” Katherine Johansen Taber points out that heart disease and cancer are at the top of this list. She adds that although many physicians understand the importance of correctly collected and interpreted family history in the revelation of risk for these diseases, some do not realize that genomic applications beyond the family history are recommended, and usually assist in the diagnosis and treatment of many disease areas. Currently, Taber adds, there are more than 26,000 genetic tests that are available for over 5400 conditions, many of which are for rare diseases. However, PCPs either lack the knowledge, or are not adequately trained to utilize these tests.

Studies have also reported that PCPs have been inconsistent with the use of FH. Suther and Goodson add that insufficient time and lack of confidence have acted as barriers in the proper elicitation and utilization of FH in the clinical settings, leading to the failure of appropriate referrals. Accurate FH is important in the proper diagnosis and determination of risks of genetic diseases. It has been identified that PCPs have difficulty with genetic referral decisions unless the risk is either very low or very high. Moreover, Suther and Goodson add that assessing and counseling about genetic risks requires knowing which choices are available, and PCPs lacked information about genetic services and options available to patients. According to scholars like Guttmacher et al., “genomics-based knowledge and tools promise the ability to approach each patient as the biological individual he or she is, thereby radically changing our paradigms and improving efficacy.” Paneque et al. add that by raising PCPs' confidence through education that includes genetics, they would be able to apply this into practice, implement personalized genetic risk assessment for patients, and potentially increase receptiveness to additional genetics education and training. Nonetheless Paneque et al. point out that it has been identified by research that the self-confidence of PCPs in their ability to provide
genetic healthcare are generally low. According to data, although primary care pediatricians in the U.S. reported that they frequently managed children with genetic conditions - they did not feel competent with the issues either. Paneque et al. also add that many had ordered genetic tests and referred patients to a genetic specialist mainly because of parental queries, and because they wanted to obtain information to better manage the conditions they were unsure of. As Paneque et al. highlight, if PCPs stay “genetically uneducated and incompetent” related to the use of genomic information in general practice, individual genetic medical care is likely to be unhelpful, and may possibly be even harmful.

8.2. Education of Healthcare Professionals

Elizabeth A. Nelson and Amy L. McGuire state that even though good medicine has always been personalized, where physicians use their medical expertise based on applying known data on lifestyle and health of individual patients; patients today are mostly interested in the concept of "personalized" - that is based on individualized genetic and epigenetic profiles, without the population-based benchmarks and generic side effects. Given the unprecedented technological advances, especially with the completion of the HGP, it is only a matter of time when genomics will be integrated into the regular clinical practice. Nonetheless, according to Nelson and McGuire, studies suggest that most physicians are not adequately prepared for this technology, and lack the knowledge to interpret even the simplest of genetic tests, and as a result underutilize/or not utilize the resources. In order to prepare physicians for this new technology, studies suggest courses in genetics be integrated throughout the entire medical school curriculum. In anticipation of the impact genomics will have on the future of healthcare, all actors need to be educated and trained in genomics. Collaboration between different actors from across different specialties - their work integrated towards the delivery of safe and effective
treatment - is critical. This section looks at the existing education curriculum, the gaps, and the importance of ethics education in preparing healthcare professionals in genomics and precision medicine.

8.2.1. Looking at the Existing Education Curriculum

As Hyland et al. note, because of the completion of HGP and the development of genomic-based technologies, many of the disciplines previously viewed as rare are no longer viewed as that. However, a comprehensive understanding of the principles of genetics and genomics, from basic science to clinical application will indeed be critical to preparing physicians with the skills necessary to make informed decisions.\textsuperscript{30} PGx is a major constituent in PM, where the genetic variations of human individuals can guide the selection of drugs in order to maximize useful effects, and to minimize harmful side effects.\textsuperscript{31} C. Carlberg adds that the application of PM is anticipated to allow earlier detection, and more effective treatment of diseases. The basics of pharmacogenomics are included in most pharmacology curricula for students in medicine, pharmacology, and other health sciences. However, Carlsberg adds that the current medical students need to be trained to understand and use this information appropriately and responsibly. They add that this adaptation of biomedical education will enable future health workers with the knowledge, skills, and attitudes required to practice PM. In spite of the importance of genomics, studies show the majority of medical schools have yet to incorporate genetic or genomic courses into their curricula.\textsuperscript{32}

Taber notes that the perception of clinical value of genetic tests and genomic technologies also plays a critical role in the uptake of PM in the aftermath of the lack of a prepared workforce. Since the new genomic technologies are supposed to empower physicians with the best possible treatments for the individual patients, physicians need to see evidence and demonstrations that
using these new tools will indeed improve the care and health of their patients, and indeed is worth the time. PGx is a good example. As Grace M. Kuo et al. add, although PGx has the potential to provide safe and effective drug management to provide personalized care “using the right drug at the right dose to the right patient,” there are also uncertainties about its application in clinical practice by providers, because of which PCPs do not take the time to train themselves in using PGx – thus PGx remains underutilized. Moreover, as Katherine Johansen Taber highlight findings from a survey of PCPs who did not order PGx testing - more than half responded, that was because they were not sure what tests to order. She adds that it is not that the lack of genomics knowledge equates to poor provider care, it only implies that the adequate knowledge and training would have empowered them to deliver the best possible treatment. This shows that the gap in genetics knowledge results in the inability to order and interpret genetic testing, and referral to specialists and counseling.

As McCarthy highlight, although genetics contents have increased in the undergraduate curriculum, studies show that current educational approaches do not prepare students to practice in a healthcare environment. A literature review identified a lack of knowledge and confidence in addressing issues related to genetics in the clinical setting as impeding the progress of primary care services. As McCarthy point out, it was found that fewer than 25% healthcare professionals felt prepared or competent to order genetic tests even though they recognize the clinical importance of genetic tests. Similar gaps in genetics knowledge among “internists and primary care physicians,” and among both medical students and practicing physicians were also identified in published studies. Moreover, Guttmacher et al. also noted that deficiencies in genetics knowledge among medical personnel were not limited to students and practitioners, but was also identified among senior medical officers in major health plans in the United States,
which they say, will likely act as an impediment to the integration and reimbursement of genetics services.\textsuperscript{38}

According to Dr. Michael F. Murray, Director of Clinical Genomics at the Genomic Medicine Institute of Geisinger Health System in Danville, Pennsylvania - there is no standardized approach in the United States to genomic education for physicians. Even as of today, most healthcare professionals, feel inadequately prepared for any large-scale application of genomic medicine. It is true that medical schools have increased the amount of genomics they incorporate into the curriculum, and more recent graduates have a more extensive educational exposure to genomics. However, he adds that the educational programs vary widely for residents and fellows in graduate medical education (GME) training, and are not consistent, and the level of genomics education also differ among clinical specialties. Dr. Murray also add that generally, providers are usually quick at grasping the working knowledge of laboratory test with use, but with genomics and genetics most physicians do not order testing for patients - and surveys show that a significant percentage of physicians admitted to not having adequate understanding of the testing menu, or the specific indications for the tests. Without the inclusion of genomic medicine in medical education, physicians will not be able to meet their patient’s demands.\textsuperscript{39}

Carlberg adds that medical schools can supplement their curricula with learning objectives that contain deeper understanding in the concepts of genetics and genomics (and PGx), and training for their practical applications, such as translating the family genetic history of a patient into choosing the most appropriate out of more than 2200 available genetic tests. He adds that the students should learn how to interpret the statistical significance of such test results in the context of the individual patient’s medical profile, select the best-suited drug, and to calculate the adequate dose, respectively.\textsuperscript{40} As highlighted by Plunkett-Rondeau et al., data
suggests that even though medical schools are integrating genetics and genomics into their curriculum it is not occurring uniformly across all institutions, and because genetics typically does not have a heavy weight on pre-clerkship hours, most institutions only have a small fraction of genetics in the integrated examinations. As a result, they add that some graduates of medical schools may be able to pass and move forward without meeting basic competencies in medical genetics, and this is one of the reasons why most health care providers do not feel competent utilizing genomics in their everyday practice.\textsuperscript{41}

8.2.2. Ethics Education and its Applications in Medicine – Identifying Gaps

Precision medicine brings with it many ethical issues pertaining to individual as well as familial issues. Physicians need to consider the ethical principles of autonomy, non-maleficence, beneficence, and justice in the decision making process. With the dramatic effects of risk predicting, genetic counselors will play a big role in the era of personalized medicine. As J. Ryan et al. point out the philosophical underpinnings of genetic counseling practice are founded on care-based and feminist ethics according to the \textit{National Society of Genetic Counselors Code of Ethics}. They add that counselors recognize the importance of the individual patient, or client factors in providing care, and counseling; as well as the importance of broader-based contextual relationships and factors that influence a person's needs, decision making and approach, keeping in mind the genetic information and its impact on relatives. Ryan et al. also add that genetic counselors understand the familial implications of genetic tests, and therefore consider both the personal and familial aspects of such information. When appropriate and necessary, genetic counselors encourage family members to be present during counseling appointments.\textsuperscript{42}

In looking at the different areas of ethics, autonomy is a core concept embodied in the code of Ethics by the \textit{National Society of Genetic Counselors}. Autonomy relates to respecting
individual's right and information that enables patients to make informed decisions. In genetic counseling, it has a broader, relational approach as it takes into consideration familial values and other relationships, while also recognizing the social and historical context. The principle of avoiding harms - non-maleficence - relates to ensuring actions or services do not harm the individual client. As J. Ryan et al. note, in personalized medicine, there are several potential harms - the harm associated with the possibility of lacking adequate information may result in the inability to make a fully informed choice regarding counseling. This can result in decreased autonomy and potential emotional and psychological consequences. Ryan et al. also add that these potential harms may be mitigated by the implementation of a “carefully considered service model, grounded in the principles of care-based or feminist ethics.” Other harms cited are consequences of psychiatric genetic counseling, that relate to increased fatalism or stigma that could be associated with attributing illness to genetics.43

Moreover, Ryan et al. add that for genetic counselors the principle of beneficence need to promote positive outcomes as well - through alleviating guilt by modifying clients’ understanding of cause of illness. Carefully implemented genetic counseling services, embody beneficence by respecting and accommodating an individual's right to accurate information. Attributing an illness to either genetics or the environment can have serious negative consequences such as experiencing self-blame.44 They add that overestimating and underestimating risks can be problematic; this is where genetic counselors play a role in helping clients make more fully informed decisions. The principle of justice in personalized medicine relates to making genetic counseling services available equally to all, and making allocation of resources within a health care system to all in a fair and just way.45
There were gaps identified in the education of healthcare providers in genomics. Although extensive genomic curricula have been developed for PhD students, nurses, and pharmacists, a gap in genomic education in medical school curricula has been identified and acknowledged that extends into many training areas. Scholars like Laudadio et al., have noted the eight subject areas which were initially identified that can be used to address the gaps: “basic genetics and genomic principles; ethical, legal, and social issues; sample acquisition; quality assurance and validation; regulatory and compliance; testing and interpretation; reporting; and patient management”. However, with the field of genomics evolving, one challenge will be in keeping the educational material, as well as the educators of this curriculum up-to-date. They add that the curriculum should be considered dynamic and should be reevaluated as needs change.

The genetics education that physicians-in-training typically receives in medical school and graduate medical education is ill-suited for practicing PM. Laudadio et al. add that medical schools should include in their curricula more basic science concepts in genetics and genomics, as well as, practical training for the applications. Surprisingly, a recent study reported that only 11% of U.S. and Canadian medical schools had practical training as part of their curricula.

According to the NIH, medical education should include the principles of genetic variation, and how to conduct and analyze genome-wide studies of complex diseases in the human population. A set of core competencies in genetics were also identified by the National Coalition for Health Professional Education in Genetics that all health professionals should possess. Both these organizations offer valuable strategies that will serve as a strong starting place for medical school, and graduate medical education reform. However, along with fundamental training needs it has been identified that medical schools need to identify and implement the most effective education models that will enable trainees with the required
knowledge. According to a novel hands-on genomics course developed by Stanford University in 2010, it was demonstrated that medical students should also have the option to undergo personal genome testing (PGT) as part of the course curriculum. Results from research on this training demonstrated that students improved their understanding of genomics, and concepts of clinical genomic testing. Salari et al. state that in order to realize the potential of genetics and genomics in healthcare it is evident that medical trainees be provided with the proper educational foundation that is continued throughout clinical training; and should include ethics education in order to address the ethical, legal and psychosocial issues.\textsuperscript{50} Cornetta and Gunther also add that medical curricula that actively combine holistic care (such as psychological, and spiritual) and precision medicine will help create more empathic physicians, who will not only know when to order genetic tests, but also know when their patients' need to be referred to counselors for guidance and support. This combined approach will be ideal for the era of PM which will require knowledge of PM and delivery of personalized care.\textsuperscript{51}

8.3. Delivering Personalized Medicine on a Regular Basis

Advances in genetic knowledge and technologies are moving genetic issues into the basic healthcare of every patient, accompanied by numerous ethical and professional challenges. As noted by Matthew A. Bower et al., PCPs will be utilizing genetic services in providing and referring patients to appropriate genetic tests and other services. Genetic counselors will likely be called upon to educate PCPs about recognizing and resolving ethical dilemmas when patients have genetic concerns. As the demand for genetic testing grows and expands into primary care, Bower et al. add that it is highly likely that genetic counselors will run into more complex cases, and they will need more training and readily available resources to address the ethical issues inherent in these complex cases.\textsuperscript{52} Facilitating and supporting patient's informed decision making
in PM involves understanding and delivering results specific to disease risk - which will be a major challenge of genomic medicine in the clinical setting. The healthcare professional needs to be prepared with advances of genomics as they arise on a constant basis. Genetic counseling with the unique skills and roles will also be an important part in the healthcare delivery because of the ethical and professional challenges related to application of genetic testing and treatment. The next section looks at genetic counseling and its role in delivering genomics in healthcare.

8.3.1. Comparing Genetic Counseling, and Delivering Genomics in Healthcare

As Heather Skirton et al. note The National Society of Genetic Counselors has defined genetic counseling as a “process in aiding people to comprehend and adapt to the medical, psychological and familial implications of genetic contribution to diseases.” Genetic counseling is effective in enhancing healthcare systems and in coordinating genetics knowledge in public health policies. Recent findings also conclude genetic counseling as an important tool for the implementation of genetic disorders prevention strategies. Genetic counselors have become an integral part of medical teams in many hospitals and clinics throughout the world due to the ethical dilemmas associated with the provision of the services. Didactic preparation in ethical reasoning and applied experience influences the ways in which genetic counselors address challenging ethical dilemmas. Being responsive to client emotion, and enabling cognitive processing, are both necessary to enable clients to process information and enable them to use it effectively in decision making.

According to Ormond, there are debates about what “genomic counseling” will include and who will practice it in the era of full genomic medicine approach – the incorporation of genomic medicine will create differences in the scope and approach of genetic counseling. Amongst the many challenges, one crucial challenge for counselors will be discussing which
incidental findings (if any) should be determined and returned to patients. It is important to remember that patients will most likely not be familiar with the wide range of conditions, making it more challenging to make informed decisions in this area.\textsuperscript{61} Ormond adds that genetic counselor roles have expanded vastly from the original prenatal and pediatric genetic counselor roles to specialty areas such as oncology, cardiology, neurology, as well as working as experts with the non-geneticist specialist physician.\textsuperscript{62} As Bereshneh et al. point out that diagnosis in medical genetics is vital because at least 10\% of sperm and 25\% of mature oocytes have chromosome abnormality and about 20\% of all known pregnancies end in spontaneous abortion. Moreover they add, about 2-3\% of infants have congenital malformations where genetic factors are evident in more than half of them; and 5-10\% of common cancers are genetically based. They also add that there are over 21,000 diseases and single-gene traits registered up to now in OMIM (Online Mendelian Inheritance in Man); and over 500 metabolic disorders with genetic origin have been reported as of today. Diagnosis of medical genetics is becoming critical in the early diagnosis of such inherited diseases.\textsuperscript{63}

Counseling persons or families with genetic concerns frequently pose challenges to the involved professionals who have to deal with often complex ethical situations. According to Brigitte Gschmeidler & Magdalena Flatscher-Thoeni, a focus group study identified 16 ethical/professional domains encountered by genetic counselors in the United States: “informed consent, withholding information, facing uncertainty, resource allocation, value conflicts, directiveness/non-directiveness, determining the primary patient, professional identity issues, emotional responses, diversity issues, confidentiality, attaining/maintaining proficiency, professional misconduct, discrimination, colleague error, and documentation.” \textsuperscript{64} As noted by Alliman et al., although general healthcare goals may be similar across countries, practitioners’
decisions regarding patient care may vary due to differences in their cultural, religious, spiritual, and ethical values. The scholars add, as clinical genetic services evolve worldwide, genetic counselors are playing an integral role in helping patients receive the necessary information to make appropriate decisions.65

Alliman et al. also highlighted the areas of challenges and stated that, Informed Consent issues raised ethical dilemmas concerning the patient’s ability to make voluntary decisions since not all the information can be provided in some cases. They also noted that counselors also questioned their own ability to present relevant material to those patients in an understandable fashion. Issues involving consent in presymptomatic testing were also critical issues.66 Facing Uncertainty was another domain that consisted ambiguity due to insufficient information about the clinical utility of a genetic test result, interpretation regarding severity and unclear patient care standards.67 Withholding Information raised question about whether to reveal unanticipated information. This domain also includes situations in which a patient declines a genetic test result that provides clinically valuable information. Diversity presented challenges to patient care arising from differences in cultural, socioeconomic, religious, and/or spiritual beliefs between the patient and the counselor. Alliman et al. also pointed that in the area of Professional Identity Issue, there were challenges regarding the professional role and the ambiguity that can result from feeling “caught in the middle”, and a lack of appreciation for the unique skill set that counselors bring to the clinical practice was often voiced in surveys.68 Directiveness/nondirectiveness involved situations in which genetic counselors questioned the extent to which they should guide the patient in decision-making.69

According to Veach et al., Informed Consent will continue to be problematic as more genetic tests and technologies enter the marketplace, and as companies begin to more
aggressively market their products. According to a study on the scope of ethical and professional issues that genetic counselors, physicians, and nurses faced, *Informed Consent* was the most prevalent issue for all three professional groups - since it took on some unique aspects with respect to genetic information. Informed Consent is usually equated with the information provided, usually with regards to invasive procedures, in the present context it has to do with information provision, which is complex with genetics and makes information provision a critical issue. Moreover, Veach et al. noted that sometimes this information can have negative emotional impact that the professional can do nothing about (such as no cure/treatment); and the interpretation of genetic test results is not always black and white. Informed consent also raised issues due to the fact genetic information was not always enough information and patients did not always have the ability to understand the implications of the information. Bower et al. also added that this was particularly challenging when it involved cases of presymptomatic testing and genetic testing of minors. Results from a survey of 177 cases of APC (adenomatous polyposis coli) gene testing indicated that only 16.9% of cases had obtained written informed consent. Today, they added, brochures are provided by many companies and clinics to promote and describe genetic testing. However, Bower et al. noted that only 10% of the examined pamphlets from 125 organizations discussed the risks and benefits of genetic testing; very few discussed the rights of patients or the intended use of the test; and only one pamphlet mentioned insurance discrimination; and none mentioned the need for written informed consent prior to testing. This clearly demonstrates the issues of patients not being fully informed about the genetic tests prior to making decisions.

According to Groepper et al., genetic counselors’ roles are expanding rapidly beyond the clinical context due to the advancement of complex genetics and genetic testing, and as a result a
A growing percentage of genetic counselors are working in laboratory settings as well.⁷³ According to Alliman et al., the extensive role of genetic testing in clinical setting will need a reevaluation of the direction for counselors. Currently, the National Human Genome Research Institute recommends informing the individual about the purpose and medical implications of the test, before any genetic test is performed/ordered. The most prevalent strategies recommended were “Further discussion with patient, Consult with professional, and Referral to a professional.”⁷⁴ As Cornetta and Brown point out that not all genetic tests will require counseling of patients, neither will it be practical. There will be a need for best practices for counseling and for creating appropriate curriculum, and that can be accomplished by gathering input from PCPs.⁷⁵

8.3.2. Existing Gaps between Genetic Counseling and Genomics in Future

In the era of PM there will be a critical need for appropriately educated genetic counselors. Alarmingly, as Hazin et al. point out, there are only 3,026 board-certified genetic counselors in the United States, with little effort to expand genetic counseling programs. This lack of counselors will hinder the application of genomic testing in clinical practice.⁷⁶ As Michael L. Begleiter point out, only handful countries provide formal courses in genetic counseling, while others leave genetic counseling in the hands of medical practitioners or medical geneticists. Genetic counselors are uniquely trained to provide support, explanations and guidance to individuals or families who have been diagnosed with a genetic disorder. The completion of the HGP has resulted in the identification and amplification of testing for a variety of genetic conditions, as a result of which there is a need for appropriately trained genetics professionals to deliver this information to families, and to assist them in adjusting to the implications of their diagnosis.⁷⁷ Scott McGrath and Dario Ghersi point out that although there are trained specialists to help interpret genetic test results, their number in the U.S. and globally
is low compared to the future needs in the era of PM. 3,021 genetic counselors were employed in the U.S. in 2015, with an additional 135 practicing outside of the U.S. The American Board of Medical Genetics and Genomics (ABMGG) lists only 1,286 certified clinical geneticist in the world as of July 2014. McGrath and Gbersi also point out that only 1,194 of the 1,286 clinical geneticists work in the U.S, which is equivalent to 0.18% of the total physicians in the U.S.\(^{78}\)

Michael L. Begleiter also points out that genetics services worldwide are provided to families through a team approach, consisting of clinical geneticists, nurses, genetic counselors and other medical professionals, who are supported by cytogeneticists, biochemical geneticists and molecular geneticists, who provide laboratory expertise that aids the diagnosis and management of individuals with genetic conditions. Begleiter highlight, although genetic counselors identify risks of genetic conditions for patients and families, they are also important partners in the decision making process for patients and families. Counselors need to be trained to appreciate the entirety of humanness taking into consideration the social, ethical and legal issues.\(^{79}\) According to Elisabeth Pain, some of the essential skills identified as necessary for genetic counselors are: “Communication skills, Critical thinking skills, Interpersonal counseling and psychosocial assessment skills, Professional ethics and values.” As Elisabeth Pain notes, a career in genetic counseling requires a thorough understanding of genetics, extensive medical experience, and excellent communication and counseling skills.\(^{80}\) As Roy C. Ziegelstein notes, genetics differs from other areas of medicine in that it so often involves families, rather than only individuals. While providing accurate information to family members is important, Ziegelstein adds that it can also be ethically challenging in terms of ownership of medical information, and privacy issues, for counselors. He emphasizes that in order to deliver personalized medicine it
has to be remembered to connect the ‘omics’ and see each patient and each person, as an individual at the same time.\textsuperscript{81}

Family history has been identified as the key to determining the mode of inheritance and that is why it is recommended that basic health information be appropriately recorded across three generations. The healthcare professional must be clear about why the genetic test is needed or requested, and must make sure that the patient is involved in the decision-making process with full knowledge of the implications of such requests/tests.\textsuperscript{82} According to Tarja-Brita Robins Wahlin, counselors need to report findings about specific genes that seem to contribute to specific disorders, and be able to explain about the clinical significance of the reports. For starters, healthcare providers must be knowledgeable about the differences between abnormal genotype and phenotype, and must have the basic wisdom about genotypic tests, and the implications associated with it. Wahlin further adds that Predictive testing programs are complex and raises challenges since it gives the applicants a choice to know or not to know their carrier status, some of these choices can have emotional toll, and potential candidates need to decide what they want to do - to know or not to know?\textsuperscript{83}

There are also challenges associated with incidental findings (IFs), with respect to the design of electronic health record (EHR) systems for reporting IFs, since there are currently no standardized protocols for handling and disclosing IFs in a manner that is consistent with the aims of routine patient care.\textsuperscript{84} As Hazin et al. point out that patient privacy will be a critical consideration in the adoption of EHRs. Although there is the \textit{Health Insurance Portability and Accountability Act (HIPAA)} and the \textit{Genetic Information Nondiscrimination Act (GINA)} that are supposedly put in place to protect patients, neither prohibit genetic discrimination. As a result there are fears that lead to the controversial practice of opting out of documenting sensitive
information into medical records. As Hazin et al. highlights that predictive testing is associated with rising risks of suicide, putting emphasis on counselors to address the emotional, ethical issues that arise with this application. It is the counselors’ uttermost duty to help the applicants to make informed decisions based on their individual circumstances, ethical, and religious values.

Currently, genetic counselors provide a majority of formal genetic counseling services in this country. However, with the advances of genomics, physicians and nurses in primary care will practice the majority of individualized, genetically based preventive medicine. Scholars argue that this will prompt dramatic changes in the patient–primary care provider. With the frequent utilization of genomics, there will be advances of more complex cases, as a result, primary care providers will have to make determinations about appropriate referrals and be able to prepare patients accordingly. As noted by Veach et al., that there will likely be a number of ethical and professional dilemmas; and most likely not enough information will be available for guidance and support. Since a great deal of genetic screening and counseling will move into the realm of primary care, more research into the anticipated dilemmas are critical for the future of PM, especially it is important to look into primary care providers’ perceptions of the anticipated ethical issues. The next section looks at the educational needs and challenges, and looks into recommendations.

8.4. Educational Needs and Challenges

As previously highlighted by scholars, there is a shortage of adequately trained workforce, and documented low confidence levels within primary care physicians on the topic of genomics. Failing to address these needs could slow or even prevent precision medicine from becoming successfully integrated into healthcare. The current exposure received by healthcare professionals across different specialties has been deemed inadequate and inconsistent. As
highlighted by scholars like Lauddaio et al., the availability and declining costs of single-gene
tests are making the applications of genomics clinically useful for diagnosing and classifying
disease, determining disease risk, generating prognostic information, and predicting response to
therapy - as a result, healthcare professionals need to be able to utilize these applications. It has
become of utmost importance to address the educational needs and challenges that span didactic,
laboratory, and experiential teaching environments for professional, postgraduate, and continuing
pharmacy education (CPE). The next section looks at the educational approaches and strategies
that can be undertaken in order to address these challenges and needs.

8.4.1. Educational Approaches and Strategies

According to Walt et al., there is a need for better literacy in genomics in order for
physicians, and other healthcare providers to utilize the potential of genomics into clinical
practice. However, incorporating the essential education and training into medical education is a
complex process, and requires adequate discussion and planning within the community
academics. Previous research recognized that short-term educational initiatives alone were not
likely to cause significant changes in areas of genetic risk, assessment of risk and appropriate
management of patients in patient care. As Paneque et al. note that better objectives may be
aiming at changes in genetic awareness and the ability to locate relevant information instead of
only aiming at changes in knowledge. As observed by Walt et al., a study at Tufts University
School of Medicine to examine ways to improve genomic education, noted that medical curricula
needed to include “technology, genome-wide association studies, ethics, statistics, and data
quality.” Moreover, practitioners who were not genetic specialists also identified risk
assessment as an important topic; and scholars also identified other strategies to provide practical
change - such as use of support/resources/tools at a policy level, and provision of clinical decision aids. 

According to Laudadio et al., in order to identify better educational initiatives, a comparison was done on the different healthcare related schools (such as pharmacy and pathology) curricula in order to come up with better strategies to incorporate knowledge and skills that will enhance the future healthcare professionals’ ability to incorporate genomics into their clinical practices. It has been suggested that professionals with adequate knowledge in molecular genetics and genomics will be able to fulfill the role of the expert. Kuo et al. state, even though pharmacy professionals are assumed to take the leadership role in precision medicine initiative, it was observed that they also lack confidence in pharmacogenomics, and are not confident to apply this information into practice yet. According to a survey on 377 pharmacists working in community pharmacies, more than 70% indicated a score below 50% for level of confidence in pharmacogenomics topics. Another study on 303 pharmacists reported that 85% of pharmacists agreed that pharmacists should be knowledgeable about pharmacogenomics. However, 63% felt they were not confident in applying the results of pharmacogenomics tests to the selection, dosing or monitoring of drug therapies. Kuo et al. note that even though pharmacogenetics/genomics didactic teaching is increasing in schools of medicine, evidence-based educational materials about pharmacogenomics have been reported as not readily available to healthcare professionals or the public. Educational campaigns toward bridging this gap between pharmacogenomics, and practices of medicine, and pharmacy amidst clinicians is needed. Another growing emphasis, as pointed out by Weitzel et al., is on the need for strategies to advance PM and clinical use of PGx data. However, challenges remain in the
implementation and incorporation of genomic data into the EHR, ethical concerns, and challenges in the areas of reimbursement and practitioner education.  

Many similar strategies and guidelines to assist educators in overcoming these challenges are emerging. The National Coalition for Health Professional Education (NCHPEG) in the United States have developed guidelines for genetics education, and defined core competencies in genetics for health-care providers. According to Wylie Burke and Jon Emery, various strategies to promote genetics education have been used, which include problem-based medical school curricula, continuing medical education for practicing physicians and innovative approaches for delivering genetics information to practitioners. They point out that three U.S. federal agencies also funded a program to develop medical faculty skills in genetics - Genetics for Primary Care (GPC). The GPC project utilizes dialogue between experts in genetics and primary care to develop goals for genetics education for PCPs. These include a case-based curriculum, and educational interventions, in the form of workshops, lectures and interactive case discussions, by genetics/primary-care teams in 20 participating institutions. As Burke and Emery note, the GPC curriculum emphasizes the clinical problems commonly seen in primary care practice and uses an evidence-based approach, which incorporates information about rare genetic diseases and basic genetics concepts in this context. As highlighted by Weitzel et al., the National Coalition for Health Professional Education in Genetics updated the guidelines in 2012 for competencies in genomics. Pharmacists, Pathologists, Nurses as well as PCPs should be able to order, interpret and report test results; and for Pharmacists it is essential that they have the knowledge to guide optimal drug selection and dosing based on those results.  

Because nurses are usually at the forefront of providing care, according to the members of the National Nursing Organizations in the U.S, Williams et al. emphasize that there is an
urgent need for genomic content across basic and continuing nursing education programs that will allow students to apply this knowledge in the clinical setting with people across the lifespan throughout the spectrum of health and illness; and provide resources to prepare faculty. Training the workforce with the adequate genomic knowledge has been highlighted as critical in order to close the gap.\textsuperscript{102} However, all health care providers, not just nurses, should be trained in genomics - otherwise, nurses will bear the heavy burden of delivering and consoling patients.\textsuperscript{103} However, Burke and Emery state that genetic information can be a double-edged sword – it has the potential to provide important clinical benefits but is not always clinically useful, and can sometimes cause harm – which is why healthcare providers need to be prepared in genomics. Given the variety of healthcare settings in which primary care occurs, Burke and Emery add there is a need for collaborative approaches between the various providers. PCPs, and all frontline healthcare providers, and geneticists and genetic counselors should be encouraged to continue a range of educational experiments, and an ongoing discussion of the lessons that are learned from them.\textsuperscript{104}

Scholars like Weitzel et al. suggests that gaps be addressed by implementing course curriculum that offers pharmacogenomics or genomics-based primer courses during the first year so that students will get the foundation of basic genetics knowledge that will be built upon and integrated into second- and third-year courses in the curriculum. They have also emphasized that practice-based patient care applications be included, so that patients can feel better prepared to apply the knowledge and skills to patient care decisions in the third year and beyond of experiential training.\textsuperscript{105} As explained by Scott McGrath and Dario Ghersi, PM offers the potential to integrate big data analytics into healthcare, which offers great advantages, such as R&D acceleration, expanded genomic analysis, and public health insights. However, they add
that the adoption of the EHR will be a major component of PM, and will not be obstacle-free to attain due to a lack of experts with the skillset to incorporate, and utilize this technology, in addition to the under preparedness of the healthcare workforce. However, they add that the promise of PM is a desirable goal, and will have a positive impact on human health at large if implemented properly. According to the American Association of Medical Colleges (AAMC), strategies should aim to provide tools for life-long learning. Genetics should not be viewed as a specialized field that is needed by a small set of specialists – but rather as a field, that has an overarching influence in health and disease of all in the future. Additionally, AAMC states that because it is still unclear as to how soon PM will take effect, and in what manner it will be integrated into the medical practice, creates a special educational challenge. The AAMC adds that it is difficult to motivate students to learn things on the promise that they will be important in the future, and it is also difficult to find current case examples and role models. However, three domains were identified by AAMC for the integration of genetics into medical practice - prevention, diagnosis, and treatment. Three-time horizons were also identified – during clinical rotations, start of residency, and beginning of practice.

As Korf et al. note, due to the volume, sensitivity and complexity of genomic information (related to privacy, and handling of IFs, and testing of children, for example), it will likely exceed the capacity of physicians to review the information on such a brief clinical encounter, and surpass the clinician’s expertise in genetics, that genetic tests (even PGx testing) may very well be deflected to trained professionals in medical genetics. Other concepts recommended in the education are application of models for evaluating genetic tests and consideration of ELSIs of genomic testing. According to Williams et al., numerous barriers identified in the framework developed for genomics education include limited curricular time, access to
education opportunities, and resources within the educational institution to sustain inclusion of genomic content into the primary care curricula (medicine, nursing, pharmacy and so on). Additionally, limited genomic knowledge by faculty was also highlighted in studies.\textsuperscript{110}

Weitzel et al. recommends collaboration among other colleges and schools and shared teaching resources. They have also identified patient-centered, team-based approach to experiential education as key to the education process. According to Weitzel et al., the NIH is another valuable resource that works closely with health professionals to support sharing of resources through the Genetics/Genomics Competency Center (G2C2) and the Global Genetics and Genomics Community (G3C). G2C2 is a peer-reviewed resource that puts together existing educational resources and aligns them with professional educational competencies; G3C provides use-case scenarios for genetics and genomics.\textsuperscript{111} Moreover, Weitzel et al. note that patient-centered, team-based approach to experiential education has been identified as key to providing students with the needed training. They add that, practice-based experiences are critical in the clinical practices, especially with training on how to use the EHR resources, and problem-solving and communication skills. The also add that complementary education roles of medical geneticists and genetic counselors should be emphasized.\textsuperscript{112} The next section looks at quality improvements and competencies.

\textbf{8.4.2. Quality Improvement and Developing Competencies}

Surveys of both primary care and specialist physicians reveal unease, and even unwillingness to use genomic data. The increasing use of genomics in caring for cancer patients and for some pediatric patients will likely extend to other areas of healthcare. According to Korf et al., studies reported that the age of nearly half of the practicing U.S. clinicians are more than 50. Which, according to the scholars, means their medical school and residency training occurred before the
advances in genomic medicine – which is why they are less confident or hesitant in using genomics. As Korf et al point out, given the rate and evolving nature of genomics data, current trainees are also faced with the challenges of keeping pace with the progress, which makes their education out of date by the time they start to practice. With the increasing utilization of these tools, it is critical that these challenges are overcome in order to implement PM into healthcare setting. Misuse of genomics due to a lack of training can also result in harm to patient based on inaccurate or unnecessary tests.¹¹³

In order to improve quality in the era of PM it is important that healthcare professionals at the frontline of patient care be prepared to utilize this technology, especially in the use of EHR technology. Hazin et al. add that appropriately designed EHR systems will be needed to optimally utilize the genomic information. They also add that, given the sensitivity of the genomic information, inclusion of this data into the EHR is anticipated to raise ethical, social and legal issues.¹¹⁴ Frontline healthcare professionals will need to know how to collect FH, obtain informed consent for genetic testing, and administer gene-based therapies. They also have the role of: advocating for, educating, counseling and supporting patients and families making genomic-based health care decisions. D. Lea adds that frontline health professionals will also need to have a good understanding of the ethical and social issues associated with these decisions, and how to address them appropriately.¹¹⁵ Understanding the appropriate way to deliver information and getting consent in the decision-making and consent process for the patient and family will be critical for healthcare professionals. Lea also adds that there are a lot of procedures associated with the utilization of PM that may need results to be shared with family members who may be affected. Multiple ethical issues may arise with each patient that has to be resolved, that may include privacy and confidentiality of genomic data, and fear of
discrimination. GINA, as D. Lea states, is designed to prohibit improper use of genetic information in insurance and employment decisions.

According to Korf et al. the Genomic Medicine Competencies Working Group was tasked with the development of a framework for competencies in genomic medicine for physicians in various fields. The Working Group formulated a set of competencies, given the different medical disciplines of physicians can be utilized as a starter for developing competencies geared to their areas of practice. Moreover, Korf et al. add that The National Human Genome Research Institute and the Inter-Society Coordinating Committee for Physician Education in Genomics (ISCC) took up the initiative to develop best practices that they call “entrustable professional activities” (EPAs), which have embedded competencies designed to guide residency training and postgraduate medical education - eight in total: "Patient care, Knowledge for practice, Practice-based learning and improvement, Interpersonal and communication skills, Professionalism, Systems-based practice, Inter-professional collaboration, Personal and professional development.”

The five EPAs as elaborated by Korf et al. are listed below:

1. Family History: Healthcare professionals need to be able to elicit, document, and act on relevant family history pertinent to the patient’s clinical status, includes conducting patient interviews, use of standard pedigree symbols, recognizing patterns of Mendelian inheritance and calculating simple and complex risks, and providing information to patients and family as appropriate. Make appropriate referrals based on results of family history (Korf et al., 2014).

2. Genomic Testing: Healthcare professionals must be able to order, interpret, and communicate the results of appropriate genomic tests, and be able to provide referral to appropriate specialist for genomic testing of a condition outside the physician's scope of practice. Korf et al. add that
the professional must be competent to use genomic testing to guide patient management of the benefits, risks, and alternatives, be able to address issues of incidental findings, and also direct patients to relevant clinical trials if applicable (Korf et al., 2014).

3. **Patient Treatment Based on Genomic Results**: Use genomic information to make treatment decisions for patients and family such as clinical conditions and drug responses. Make relevant information readily available to other healthcare professionals following proper protocols. Be knowledgeable about databases available and relevant resources such as ongoing clinical trials, pharmacogenomics, and patient-oriented Internet resources from reliable organizations (Korf et al., 2014).

4. **Somatic Genomics**: utilized to guide the diagnosis and management of cancers/conditions related to somatic genetic changes. Korf et al. also added, be able to explain the benefits and limitations, including implications regarding treatment of the condition and clarification of prognosis, guide choice of therapy and adjust drug dosage in patients with cancer. Ensure that specialists and laboratory involved in a patient's care are communicating with one another and with the patient; Stay up to date on progress, especially related to new cancer treatments, or other tissue-based disorders (Korf et al., 2014).

5. **Microbial Genomic Information**: use genetic testing to guide treatment in infectious diseases using the knowledge of microbes in human health and diseases. Korf et al. highlights, be able to order, interpret and explain results to patients and families especially if there is "a risk for contagion," and take the appropriate containment steps. The scholars also add, keep an open communication with appropriate healthcare professionals and specialists in order to make certain that appropriate tests are ordered.
Without the proper education, training and incorporation of the technology, it will not be possible to realize the anticipated potential benefits of precision medicine. As Mazmanian et al. note, it will be essential to provide the continuing education to physicians to improve the care provided to patients. This education includes instruction designed to help physicians acquire and apply scientific knowledge, demonstrate skill, and perform effectively as caregivers. However, there is no single standardized model apparent for evaluating the effects of individual Continuing Medical Education (CME) activities, and no single standardized model appears to exist for evaluating clinical outcomes in healthcare. Clinical outcomes of care may include health-related quality of life (HRQL), and Mazmanian et al. suggested multiple exposures to information in variety of educational activities in the clinical setting can be necessary to affect outcomes and performances. Frequency exposure was also looked at and it was found that multiple exposures to content to meet instructional objectives intended to improved clinical outcomes. Although CME interventions have always been linked to improved clinical outcomes, and many studies have applied quality improvement (QI) efforts, Mazmanian et al. recommend additional studies to decide whether the methods are clinically beneficial. According to Katherine Johansen Taber, the two educational programs that stood out were The City of Hope Comprehensive Cancer Center 14-month CME program, and El Camino Hospital in Mountain View, CA 10-module course. These programs incorporated basic genomics skills and knowledge, such as collecting FH, learning to utilize genetic tests, learning to interpret validity of the result; and also employed distance pedagogical learning, comprehensive face-to-face training and other continuing professional development training.

Proponents of PM argue that educational barriers/lack of preparedness by healthcare workforce is not a barrier that cannot be overcome, as long as there is a strategy put in place to
prepare them. It has been suggested by Olle ten Cate and Fedde Scheele that deficiencies can be easily overcome by teaching concepts with clinical relevance. Competency-based training frameworks, although not new in medical education, have only recently been introduced into postgraduate training on a nationwide scale, and their impact has been unprecedented. This shift may be justified, but many scholars involved in medical training, worry that the competency-based movement will create new obstacles for sound training: focusing on competency rather than expertise. Nonetheless, Cate and Scheele point out that competency framework for postgraduate training are usually read as logical sets of general qualities that every medical specialist should acquire, and have been reviewed by many individuals and committees for their relevance and comprehensiveness. Scholars also recommend using EPAs, as the central focus of curriculum building, in combination with general competencies – arguing this combination will do justice to both educational theory and clinical teaching practice.

Conclusion

It is evident that opportunities for genetic testing, and other applications of genetic technology, such as PGx and gene-based therapies, are opening up to more utilization of applications of PM, having important implications on primary care practice. If PM is to be incorporated into clinical settings, PCPs and all healthcare providers at the frontline will need to be adequately prepared in a rapidly evolving field. The challenges highlighted in this Chapter points to the urgent need for educating PCPs and other healthcare professionals about genetics, and the various ethical principles in delivering results. However, the best approaches to educating healthcare providers in a way that produces meaningful changes in clinical practice are not clear - especially given the competing coursework, and training needs that exist in today’s increasingly complex healthcare settings. Incorporating ethics education into the curriculum has
also been emphasized in order to provide healthcare professionals with the background to navigate through the ethical, legal and social issues associated with the genomics testing and delivering of results. It is evident from research that the most effective education process involves the systematic collaboration between different specialties, and continuous training, and education that starts from early on.\textsuperscript{132}
Chapter 9: Concluding Thoughts

9.1. Thoughts on the Potential of PM as the New Paradigm for Healthcare

Scholars like J.D. Prince emphasizes that PM has been anticipated as the new paradigm for healthcare delivery, because of its potential ability to lower the cost of healthcare by shifting from the “one-size-fits-all” approach (thought as wasteful, and inefficient) to a more “personalized” or “individualized” care that is aligned with the genetic variants of the person, the environment and lifestyle. PM is anticipated to improve and speed up diagnostics and treatment of diseases, by offering more targeted therapeutic care – nationally, as well as globally.¹ The inception of PM started from the launch of the Precision Medicine Initiative (PMI) by the Obama Administration in 2015, an ambitious project that aimed at developing individualized treatment and prevention strategies for diseases such as cancer and other chronic, infectious and rare diseases. As Spencer H. Nam and Clayton M. Christensen point out, PM would be ideal for diseases such as cancer since some of the best-in-class drugs are reported to be ineffective in twenty to thirty percent of all cases, and a five-year survival rate for most metastasized cases are less than ten percent – therefore, cancer could significantly benefit from the personalized treatment and prevention offered by PM.²

Helen K. Brittain explains that almost all medical specialties are virtually impacted by genetic diseases, and the enhanced understanding of the role of genetic variants, in combination with rapid advancements in sequencing technologies through PM is already transforming the speed of diagnosis and providing increased opportunity for tailored management of diseases.³ The PMI push from the US federal government has led PM to become an important concept for health researchers, practitioners, as well as biomedical organizations. However, PM has a
lot to prove, and has a long way to go in order to be successfully integrated, and smoothly adopted into the healthcare system.

9.1.1. What We Know About PM So Far?

Sharon F. Terry points that PM aims to move away from the current treatment based on the average patient – which is successful for some, but not all. The Precision Medicine Initiative (PMI) launched by President Barack Obama in his State of the Union address before both chambers in 2015, aimed at enabling PM as the new era of medicine, that has the capacity “to empower patients, researchers, and providers to work together toward the development of individualized care through research, technology, and policies.” President Obama also called for increased investment in US infrastructure and research, and the 2016 budget submitted to Congress, asked for $213M to fund the PMI.4

According to Francis S Collins, director of the NIH, and Harold Varmus, director of the National Cancer Institute, the PMI would have two main components: a near term focus on cancer and a longer term focus on the application of PM to healthcare in general. Moreover, Michael McCarthy adds that an allocated budget of $130M was also dedicated for the creation of a “national research cohort” of a million or more volunteers - whose genetic, medical, and lifestyle data would be collected for research purposes, with the promise that these participants would be able to help design this program.5 The anticipation is that PM will make more effective prevention, diagnosis and treatment, by developing a deep understanding of patients' genetic and genomic information – making it easier for doctors to select the most efficient drugs, optimal dose for medication usage and the least side effect. 6

9.1.2 Highlighting PM’s Impact
Cancer is a potential area of focus for PM. Garrido et al. states that PM has already become a reality in oncology. They argue that PM’s implementation is not only an ethical mandate and obligation of policy, efficacy in the treatment of patients and prevention of diseases, but because it has proven in certain cases that it fosters the ability to select the patients who will likely better respond to the treatment, not putting them through the torments of suffering from lack of benefits, toxicity or effects of adverse reactions. Additionally, Jill Kolesar & M. Lynn Crismon agrees that PM is anticipated to have an impact on the therapeutic innovation in the future, with targeted therapies as the major drivers of oncology therapeutic innovation. They add that recent forecast predicts that immune checkpoint inhibitors and targeted therapies will constitute more than 95% of the lung cancer market by 2024. Patients getting the precise drug will be critical, given the high cost of targeted therapies; these drugs are exclusively confined to the treatment of specific subset of patients. In favor of PM, Solomon M. Adams et al. add that cardiac pharmacogenomics is another rapidly growing field that offers the potential for improved treatment outcomes, as well as prevention of adverse drug reactions. PM is also employed in diabetic research – although the current knowledge is not sufficient for the prediction of diabetes risk, or for decisions regarding specific prevention or treatment measures using genomics.

Public health genomics has evolved to responsibly integrate advancements in genomics and according to Caron M. Molster et al., is anticipated to contribute to individual differences in immunological responses to vaccines, infections and drug therapies in populations. To top off all these advances in PM, the WHO's Human Genomics in Global Health Initiative has been created “to provide information and raise awareness within the health sector, governments and the wider public on the health challenges and opportunities” presented by genomics.
9.2. Implementing a New Technology Is Not Simple

As J. Larry Jameson & Dan L. Longo point out, PM has raised many high expectations – to improve care and speed up the development of new targeted treatment – and these expectations have only begun to be realized. With every new technology, there are daunting challenges. Jameson & Longo add that as PM develops, the most daunting challenge for providers will be to manage the complexity associated with implementing the sequencing algorithms, especially at a time when most providers feel inadequately prepared in the area of genetics. Additionally they add that much work remains to be done in order to prove whether this approach will actually improve care, and reduce costs to healthcare - since in many areas the implementation of PM will undoubtedly increase costs.\textsuperscript{12}

J. Larry Jameson & Dan L. Longo also states that bioinformatics technology will be increasingly applied to interpret results and apply interventions in PM. The opportunities are tremendous for PM to improve health and health outcomes, but the challenges for the PCPs, on the frontlines of patient care will also be tremendous.\textsuperscript{13} Opponents fear that the personalization approach of PM may lead to the de-personalization of the patient-centered care it promises to deliver - therefore, it is important to make sure that does not happen.\textsuperscript{14} Kathrin M. Cresswell et al. states that integrating the needed technology and developing regulations and guidelines in order to ensure that the massive amount of data is protected and secure will be the greatest challenge in implementing this new technology.\textsuperscript{15} Also, making sure that the ethical, legal and social issues are identified and addressed will be critical in order to ensure PM’s potential.

9.2.1 Barriers to Overcome

From studies it was noted that one important challenge is managing the interests of the various stakeholders: patient, physician, health system, payer, and the industry. This is because
everyone has a different interest. Although patient and physicians may have the same interest in understanding and treatment of the diseases; physicians will also have the challenge of finding the best treatment plan, with the least cost to the patient, and payers and also meet the industry interests – related to cost of new diagnostics and profitable therapies. As Haslem et al. point out, PM as a cost-saving approach has been debated for a long time. However, they add that from studies it was found that precision medicine approach may be a feasible option in patients with refractory cancer. Nonetheless, they also state that the impact of PM compared with standard therapies on survival and the effect of implementing sophisticated diagnostic technologies such as Next Generation Sequencing (NGS) on the costs of cancer care still remain unknown.

Scholars have argued that cost analysis of the effectiveness versus implementation will be critical for the sustainability of novel therapies. However, Haslem et al. point out that due to limited availability of data and limitations on data sharing, the cost associated with implementing novel medical treatment approaches has always been difficult to measure. Similarly, the cost associated with precision cancer medicine remains a primary question for both payers and providers alike. They agree that given the increasing health care costs, and limited resources, measuring the value of treatment will be critical to sustainability. Alexander P. Cole et al. also add that comparing the cost to survival benefits of the different care settings with anticancer agents has been difficult. With the ongoing debate regarding the costs of cancer therapies, investments in simple systems-based changes to improve cancer care delivery can be an important and likely cost-effective strategy which can be used to improve the survival of cancer patients.
Another critical challenge is organizing the wealth of growing information in the era of PM as pointed out by scholars like Arsia Amir-Aslani & V. Mangematin; and J. Larry Jameson & Dan L. Longo. The enormous amount of information, which continues to grow, has created a situation where handling the existing information, making use of it, and absorbing the information from a wide range of areas - has become an extremely daunting task. With the increased complexity in diseases PCPs will need to utilize bioinformatics tools with clinical navigation and specialized referral pathways. 22,23

9.2.2. Need for Addressing the Ethical and Social Implications

The fast sequencing of data is generating vast amounts of genetic variants - some of unknown clinical applications - raising issues of disclosing (or not) information to patients and family members, who may be directly or indirectly affected. According to Marilyn J. Hammer, although technological advances are allowing for faster and more accurate data leading to more precise medicine - false positives, false negatives, and conflicting results by varying analytic approaches make determination of disease risk less precise. To address these issues, she adds that protocols for standardization are being implemented along with centralized resources that can verify findings using “pooled information for accurate determination” of clinically relevant genetic variants. 24

Moreover, Hammer adds that the generation of vast amount of genetic variants raises issues of incidental findings (IFs), and return of results (issues of what to disclose and what not to disclose by physicians) – leading to moral and ethical dilemmas of physicians involved. However, Hammer adds that there are no clear guidelines as to how to answer these questions yet, and decisions are often made on the specific case. 25 With the promise of integrating new genetic technologies into clinical settings come promises as well as technical and clinical
challenges, which are similar to but qualitatively different from those that are usually dealt with
in traditional medical genetics. Ormond and Cho add that it will be important to implement core
ethical principles to address the ethical and social issues associated with PM, particularly as new
technology is integrated into clinical practice, and issues of potential stigma and impact on
perceptions of disability arise.26

According to NIH, genetic discrimination, emotional consequences, risk of behavior
changes, and confidentiality of test results are possible risks associated with genetic testing.27
Wolf et al. point out, although both ethics and law (HIPAA and GINA) protect the privacy and
confidentiality of health information about patients and research participants, mapping the
pathways by which this information may currently reach relatives, as well as the reasons that this
information may not be shared, helps illuminate the core question: whether relatives should be
granted broader access.28 Despite GINA, legal fear persists because GINA does not provide
protection against discrimination in life, disability, or long-term care insurance.29

In order to reduce the existing gaps in health in developing countries, developing
countries need to keep up in the race, and start putting more effort in the building of capacity
(research, technical skills and infrastructure). This is a pressing requirement for countries
wishing to develop their own pathogen genome projects directed at the communicable diseases
which are particularly common in their populations.30 According to the WHO, there is a crucial
need for all Member States to improve awareness and understanding of genetics, and the medical
potential of genomics in particular, through educational programs at all level to communicate
these concepts effectively. The WHO could play a major role in providing technical assistance to
Member States to aid them in establishing centers for clinical genetics, and genetic research
programs targeted to their particular health problems - through supporting regional meetings, the
establishment of collaborative training programs between developed and developing countries, and the development of local networking.\textsuperscript{31}

\textbf{9.3. Implementing PM into Healthcare}

Per Carrie Anna McGinn et al., implementing the information technology is the most critical challenge in the implementation of PM in healthcare. She adds that the EHR is an important data repository for HCOs, as it contains sensitive information, and can be purposeful in addressing many of the healthcare system challenges – such as better quality of care - and benefits of its implementation are expected for patients (such as relevant, timely and up-to-date information), healthcare professionals, organizations and the general public (citizen empowerment and participation in decision making).\textsuperscript{32} McGinn et al. add that the most frequently mentioned issue in the implementation of EHRs were issues related to the technical aspects, such as technical limitations related to software or hardware and other system problems – that were always considered as a barrier. Overall ease of use was also perceived as a barrier, and was closely associated with the design and technical issues – more user-friendly, and easy to use tools were desired.\textsuperscript{33} According to McGinn et al., “Interoperability, Privacy and security, Cost, Productivity, Familiarity and ability with EHR, Motivation to use EHR, Patient and health professional interaction, Lack of time and workload,” were also cited as perceived barriers to the implementation and use of EHRs in HCOs.\textsuperscript{34}

According to scholars like Payne et al., it would be more convenient to utilize genetic tests and genetically targeted therapies if payers opted to cover them. Therefore, collaboration among payers, scientists, and clinicians is essential for accelerating uptake and value creation – since collaboration with payers would create a unique opportunity to more rapidly develop the information required for evidence-based decision making.\textsuperscript{35} Jane Null Kogan adds that a well-
designed real-world observational basis in collaboration with payers could also strengthen the evidence base for PM, which does not exist today and as a result slowing the implementation process.  

9.3.1. Ethical Foundation Is the Cornerstone

HCOs are expected to provide healthcare to the sick and vulnerable individuals, and this represents a profoundly moral practice. The American society considers provision of healthcare to all as a moral obligation, and it expects healthcare to be safe, effective, patient-centered, timely, efficient and equitable. As Garrido et al. note, to enable the management and sharing of the vast amount of data generated by the new sequencing tools, there will be need for improved and secure information technology systems. More professional roles in the field of bioinformatics and other research areas will be needed to facilitate the transformation of PM. Substantial investment and multidisciplinary approaches will be needed to evaluate the implementation of PM into healthcare.

PM’s greatest promise was, and still is, PM’s assumed beneficial economic impact, especially through cost effective targeted treatments. Per Brett Doble, PM has not been able to prove its promise in this area as of today - prices for such therapies have been quoted as high as US $150,000 per patient per year, and if used as part of combination therapy or in sequence as much as US $300,000 for the treatment of one patient. Identifying areas where PM will accrue meaningful benefits at an affordable cost is a challenging endeavor. We can agree with Doble that the application of economic evaluation to assess the value of PM and consideration of its opportunity cost will be an essential first step.

As pointed out by Jacques S. Beckmann, and Daniel Lew, healthcare is laced with complexities due to the continuing developments in the organization and delivery of care. HCO
leaders should be more focused in creating an ethical organization that will provide the care. Although profit is also important, Beckmann and Lew add that it should not be the only important goal. The goal should be focused on providing quality and ethical care. They add that ethics and legislation will increasingly influence the processes that facilitate healthcare delivery. The traditions of catholic social teachings continue to be critical of the market system for its failure in justice, as distribution of healthcare remain a critical issue with continued rising costs exacerbating equity issues. Beckmann and Lew add that in the era of PM, citizens will have an increased role in managing their own health – warranting for the availability of adequate resources to promote the people’s awareness of the approach and its benefits to their health. They add that this will also create the trust needed, and incentivize them to participate in this medical revolution.  

9.3.2. Making Sure the Workforce is Ready

Genomics is the cornerstone of the cutting-edge PM programs – genomic sequencing in PM is largely used as a screening tool. However, Jessica Santos argues that sequencing genomes of healthy people will raise many concerns, such as the potential harm associate with the probabilistic results, which can be uncertain as well as ambiguous. She adds that Direct-To-Consumer (DTC) testing companies have resulted from the commercialization of data generated by sequencing technologies, and findings show that the application of these tools is controversial because a person could carry about 54 so-called lethal genetic mutations, that do not seem to harm their health. She states that this can cause dilemmas in physicians, since they do not know what to tell healthy people with these variants. Research shows that >98% of DTC participants buy these tests because of curiosity and personal interest in knowing about their health. 
Research also shows that primary health teams in particular are likely to face increased demands for genetic information about genetic disorders from their patients because of DTC.

Scholars like Sandy M. Thomas reports that from research it was identified that medical education gives a low priority to genetics, and will need to include more education in genetics, genomics, bioinformatics and ethics in the era of PM. A range of strategies and initiatives have been made to correct this issue. However, given the fast advancement of genetics technologies and their application in healthcare, there is an urgent need to provide the basic fundamental training in genetics to all healthcare professionals including nurses. Thomas also adds that more genetic counselors will be needed in the era of PM. Although the current ethical standards employed in genetic counseling is widely accepted, counselors have to remember they have defined responsibilities that ensure that patients know that counseling is voluntarily undertaken and that it provides accurate information. Although, previously much of the demand had been driven by reproductive issues, Thomas explains that predisposition for common diseases are likely to play an expanding role today. Strategies to deal with the increased demand for information and advice about rare disorders and predisposition to common diseases at the primary care level will require the integration of different healthcare professionals into local teams. Genetic counselors, specialist nurses and practice nurses will be needed to support the genetic practitioners.
End Notes

Chapter 1
3 Colleen M McBride, "Blazing a trail: a public health research agenda in genomics and chronic disease," Preventing Chronic Disease, 2, no. 2(2005).

Chapter 2
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