Personalized Medicine in Oncology in the Developing World: Barriers and Concepts to Improve *Status Quo*

Adeoluwa Akeem Adeniji[a, d], Soniya Dulal[b], Mike G. Martin[c]

Abstract

Personalized medicine (PM) has revolutionized oncology management in high human development indexed countries. By interrogating both disease and host factors through a variety of tools, oncologists have been able to better target an individual's cancer, leading to improved outcomes. But both the tools used to define these variables, such as next generation sequencing, large immunohistochemical and fluorescence *in situ* hybridization (FISH) panels, and the weapons employed against each target are extremely expensive. The expenses have to be measured as not only the direct cost to the patient but also the cost to the system to develop and deploy the necessary infrastructure to optimally use them. However, the concepts of predictive, timely prevention and PM have demonstrated improvement in patient's satisfaction and cost effectiveness. In this paper we will summarize the relevant barriers and challenges that limit the implementation of PM in the developing world with an emphasis on the challenges in Nigeria and Nepal.

Keywords: Personalized medicine; Barriers; Oncology; Developing world; Patient stratification; Cost-efficacy; Individualized patient profiling

Introduction

Cancer is the second leading cause of death globally with about 70% of deaths from cancer occurring in low- and middle-income countries (LMICs) [1]. In Nigeria, some 100,000 new cases of cancer occur every year, with high case fatality ratio. With approximately 20% of the population of Africa and slightly more than half the population of West Africa, Nigeria contributed 15% to the estimated 681,000 new cases of cancer that occurred in Africa in 2008 [2].

Nigeria, Africa's largest economy with its biggest population of some 200 million people, only spent around 0.5% of its 2017 budget on healthcare. Public and private spending together in developing countries is on average less than 5% of that spent in developed countries; even if this money were spent as cost effectively as possible, it would probably be insufficient to meet critical health needs. The general budget stringency makes it difficult to argue for more public spending in countries like Nigeria and Nepal [3]. Health care financing in Nepal is not developed enough to protect the population from financial risk of utilizing health services in the case of chronic diseases like cancers. The partially implemented health insurance policy is with several limitations and is not readily available to everyone in Nepal.

Advances in oncology stand on the shoulders of population-based, large phase 3 clinical trials. These trials have allowed for some cancers to be cured and great improvements in duration of survival in others [4]. While these trials have inclusion and exclusion criteria, they are generally relatively broad and allow a diverse group of patients to be enrolled. These broad criteria allow the data to be generalizable, often without exhaustive testing of the patients' tumor, and the data and outcomes to be exported to developing countries.

Nigeria and Nepal are good examples of developing countries by any reasonable measure and as such can give true reflections of the state of personalized medicine (PM) in the developing nations and regions where they are located. The very low per capita gross domestic product (GDP), standard of living, poor economy and health care of Nigeria and Nepal showed that they are far from being developed. There is no doubt that the barriers to the practice of PM in oncology care in these two developing nations can be applied to other developing nations or the countries with them in the same region.

In the past two decades, the disciple of oncology in high-income countries has evolved from hematoxylin and eosin (H&E) stains to advanced diagnostic platforms. These basic science-driven advances have led to the advent of PM [5]. It is now realized that cancers, even those from the same tissue of origin that appear identical under the microscope, are not necessarily the same. Several oncolytics have been approved in the USA and the European Union based on biomarkers alone in a tissue of origin agnostic fashion [6-8]. These "targeted" agents are generally vastly more effective than conventional

Table 1. Response of Malignancies to TKI and IO Compared to Chemotherapy

Drugs	Cancer type	
Afatinib and erlotinib [9, 10]	Non-small cell lung cancer	Progression-free survival was significantly higher than with chemotherapy in patients with well differentiated adenocarcinoma of the lungs.
Imatinib [11]	Gastrointestinal stromal tumor	Overall and progression-free survival was significantly higher than with chemotherapy.
Cetuximab [12]	Colorectal cancer	Overall and disease progression survival is better with *RAS* wild type colorectal cancer.
Pembrolizumab [13, 14]	Colorectal and lung cancer	Pembrolizumab shows better overall and disease progression-free survival in colorectal and lung cancer with high tumor mutational burden than with chemotherapy.
Nivolumab and ipilimumab [15, 16]	Renal cell cancer and advanced non small cell lung cancer	This combination show better outcome compared to the conventional chemotherapy in renal cell cancer and advanced non-small cell lung cancer.
Atezolizumab [17, 18]	Triple-negative breast cancer and liver cancer	Shows better outcome compare to chemotherapy in triple-negative breast cancer with *PDL1* expression and liver cancer.

TKI: tyrosine kinase inhibitor; IO: immuno-oncology.

chemotherapy with less toxicity and a great chance of long-term survival (Table 1 [9-18]). All hosts are not the same either; the most rudimentary examples of this are in the metabolism of irinotecan, 5-fluorouracil (5-FU) and underlying autoimmune conditions [19-21]. Even the microbiome and the use of antibiotics may influence the effectiveness of immunotherapy [22-23]. By better understanding both cancer and host-related factors, and how these interplay, PM has revolutionized oncology improving both quantity and quality of life [24].

These advances have been achieved by the identification of driver mutations, resistance mutations and a dramatic improvement in the understanding of the interplay of cancer and the immune system [25]; but all of these are extremely expensive to deploy. For example one standard of care in the USA as endorsed by the Food and Drug Administration and the National Comprehensive Cancer Network (NCCN) for advanced non-small cell lung cancer (NSCLC) is two cycles of chemotherapy combined with the two immunotherapies ipilimumab and nivolumab. These immunotherapies are repeated every 3 and 6 weeks, respectively for 2 years. Ignoring the costs of identifying the correct patients for these drugs which would include complex pathology, serial imaging, serial laboratory work, and image-guided biopsies that in their own right could cost tens of thousands of dollars, the cost of 2 years of these immunotherapies would be $1,123,782 [26] for a single patient. Though the cost of the infrastructure would be spread over many patients this is a Sisyphean amount of money per patient for both developed and developing countries.

To explore these issues, we will highlight barriers to PM in Nigeria and Nepal given the author's expertise. Nigeria, being the most populous country in Africa has increased in size continually and significantly over the decades with the current population of 205,808,201 as of 2020 [27]. The incidence and mortality of cancer are increasing in Nigeria, and cancer is responsible for 72,000 deaths every year, with an estimated 102,000 new cases of cancer annually [28]. In Nepal likewise, it has been predicted that in 2020, the incidence rate of cancer per 100,000 is estimated to increase to 41.4 in female and 38.5 in male [29].

Therefore, an unconventional way to achieve PM in these two countries and other developing nations must be established; otherwise, it may be impossible to practice PM in these nations considering the health care challenges which may be difficult to overcome. Considerations may be given to these two nations with significant discount for the supply of materials for advanced laboratory testing, novel drugs and trainings. The questions of how to ensure constant supply of these aforementioned factors and expertise may come to mind which of course would still require a lot of money that Nigeria and Nepal would not be able to afford. This financial implication will definitely need the help of the countries with High Human Development Index and the international bodies such as the World Health Organization (WHO) and World Bank. These countries would have to either embrace unconventional ways in order to enjoy PM any time soon or continue with the present non personalized method which is too generalized and ineffective.

Lack of Funds

Health system financing mechanisms are critical in ensuring Universal Health Coverage as they determine the availability, affordability, and acceptability of health services to the people. The public notices policy changes in health care and frequently bears new and unexpected costs or barriers to care unwillingly [30]. Both Nigeria and Nepal are increasingly concerned about the financial dimensions of the health sector as well. With lower national incomes (Table 2 [31]), health expenditure levels (Table 3 [32]), and health status, this concern may be particularly important for the two countries, where health sector efficiency differences may have a large impact on mortality [33].

The health status in Nigeria and Nepal, as evident by their respective high infant mortality rate of 59.1 and 33.2 per 1,000 birth when compared to that of New Zealand (4.3 per 1,000 births), USA (5.7 per 1,000 births) and UK (4.1 per 1,000 births), is poor. In these countries, the principal causes of poor health are inadequate prevention and lack of reasonable access

Table 2. Comparing Gross National Income per Capita ($) of Nepal and Nigeria With Some Developed Countries [31]

Year	Country					
	Nepal	**Nigeria**	**New Zealand**	**UK**	**Singapore**	**USA**
2016	770	2,470	39,390	42,980	53,020	57,180
2017	860	2,100	38,170	41,370	54,320	59,060
2018	970	1,970	41,100	41,730	57,900	63,200
2019	1,090	2,030	42,670	42,370	59,590	65,760

to basic health care together with health-related impoverishment results from a lack of risk pooling and insurance. Moreover, these countries compound the problems by making inefficient use of the resources they do have for health care and risk pooling [34]. The poor in the countries are even less likely than the better off to receive effective health care. In Nigeria, about 5,000 people immigrate annually to other countries to receive health care with 1.2 billion dollars lost to medical tourism annually [35]. Patients from Nepal mostly travel to India for foreign treatments and about 1,662 of them receiving treatment in India annually with estimated annual cost of $7,479,000 [36].

Measures are to be taken to redress the level and distribution of health in the two countries in the same way, and it is needed for every part of the developing world [37].

Medicine benefits through health insurance programs have the potential to improve access to and promote more effective use of affordable, high quality medicines. However, like other developing countries, out-of-pocket (OOP) expenditure is the dominant source of health financing in Nepal and Nigeria. More than 11% of Nepalese spend 10% of their total expenses for health [38], where 1.67% of the population is pushed below the poverty line of PPP$ 1.90 per capita per day [39]. Generally, 70% of the Nepalese use OOP payment for their health care [40]; however patients with cancer are beginning to receive help as the Nepalese government is currently providing financial assistance of up to NRs 100,000 (Euro 735.41, USD 830.17 exchange rate as of June 9, 2020) per person for cancer treatment under a scheme to support impoverished citizens [41]. In Nigeria, an average of 23% of individual income is spent on health care [42] while more than 90% use OOP health care expenditure. On an average, about 4% of households spend more than half of their total household expenditures on healthcare and 12% spend more than a

quarter [43]. As it stands today, Nigeria government has no financial assistance for the individuals who need cancer treatment. It therefore means that the Nigerians who cannot afford the cost of cancer treatment are likely to die of cancer quickly in addition to the higher chances of late presentation and high mortality when compared to the developed nations. This lack of funds has been found to be responsible for 85% of Nigerians who do self medications [44].

Health care financing is becoming more difficult for individuals, which is worse in the developing nations, where more than 60% of the world population live. These same nations are now battling with the mortality and morbidities that come with infectious disease and cancer [45]. Obviously, the mortality of cancer has become a huge burden in countries like Nigeria and Nepal, and the question of whether there will be a shift of the pool of funds made from foreign and local aids from the infectious disease to cancer soon, is still begging for answer.

Increasing prevalence of cancer is causing a significant impact on health and finance of individuals and state, more in low-income countries like Nepal and Nigeria. Most low-income countries do not have an effective financial protection mechanism, where over 50% of health care financing is from OOP payments, as compared with 30% in middle-income countries and 14% in high-income countries [46]. It is beyond doubt that PM in oncology requires a lot of funds which have been demonstrated in the developed countries. This has been the major reason that it is not usually practiced in Nigeria and Nepal even though there has been a strong focus on PM by large cancer centers and those who fund research.

Maximizing health benefits is also a major challenge in these two countries due to limited resources which in turn makes it difficult to purchase the costly high technology driven modern day equipment that are needed for the practice of PM

Table 3. Comparing Health Expenditure per Capita PPP ($) of Nepal and Nigeria With China, Singapore, UK and USA [32]

Year	Country					
	Nepal	**Nigeria**	**China**	**Singapore**	**UK**	**USA**
2011	137.42	192.85	438.56	2,404.66	3,255.07	8,523.83
2012	126.94	178.31	508.17	2,647.31	3,322.94	8,789.77
2013	127.47	208.46	574.7	3,068.61	3,374.14	8,987.9
2014	137.4	216.87	634.7	3,358.09	3,376.87	9,402.54
2015	151.32	215.62	705.56	3,696.38	4,125.03	9,507.62
2016	156.34	218.79	762.98	4,020.69	4,192.53	9,892.72
2017	150.07	221.1	841.11	4,269.96	4,126.3	10,212.7

Table 4. Comparing Health Expenditure Contributors in Nigeria and Nepal

Countries	Out-of-pocket payment	Government contribution	Health insurance contribution
Nigeria [48]	65%	30%	5%
Nepal [49]	23%	70%	7%

in oncology. The same also apply to the training and employment of adequate staff with the needed specialized skills for PM [47].

The current level of health care funding from government tax revenue is relatively low in most African countries where Nigeria stands out as the largest population. Most times in Nigeria, the health sector share of total government expenditure is below 10%. One of the single largest sources of financing is that of OOP payments which is about 65% of total health care expenditure in Nigeria (Table 4 [48, 49]) and many other sub-Saharan African countries [50].

Despite the availability of a growing menu of personalized cancer treatments, actually matching patients up to the right therapy can be difficult. Investment in genomic testing is vital to quickly get patients on the best treatment course, but financial and operational barriers remain. The foremost among these is the cost associated with genomic sequencing and the use of companion diagnostic devices, cited by 28% of Definitive Healthcare's respondents as the biggest challenge for already-established precision medicine schemes [51]. This challenge is obviously one of the big obstacles which lead to delay in presentation, diagnosis and treatment as seen in many patients from Nepal [47].

Absence of Advanced Genetic Testing Facilities

Advanced molecular biology including genetic testing has been seen to be an integral part of PM [52] as distinct molecular biomarkers are identified which invariably form the basis of the targets use in PM. Research in the "omic" sciences has resulted in improved understanding of the relationships between genes, proteins and disease, providing more tools for PM [53]. High-throughput technology has revolutionized the area of translational research, confirming the high complexity and heterogeneity of common diseases, particularly cancer. Therefore, moving from "classic" single-gene-based molecular investigation to molecular network research might result in discovering clinical implications faster and more efficiently [54].

Many cancers are driven by mutations. Over the last quarter of a century, several sequencing strategies have identified multiple mutations in approximately 400 cancer genes [55]. Genomic databases are important and contribute to knowledge of genetics on human health, as well as a basic understanding of genetic differences between human beings [56]. It is interesting to know that most of the studies that contributed to this knowledge are based on populations of European ancestry, providing reasonable genetic representation of individuals of European ancestry in databases but poorer representation of other ethnic populations including the developing world [57].

This underrepresentation of Nigeria and Nepal populations is likely to be a problem because it may miss gene-disease relationships for which the exposure or outcome is rare in European populations. It limits the generalizability of the findings, and the translation of these findings into clinical care in diverse populations [58]. Greater genetic diversity is associated with greater ancestral heterogeneity; this higher level of understudied diversity in the developing world can yield novel genetic findings, but some methods that assume homogeneous population structure and work well in European populations may work less well in the presence of greater heterogeneity in the developing world [59]. Hence, there is the need for accelerated genome-based studies in the developing world.

Human genome variations, including hair color, skin color and face shapes, have been described in Mexico, India, Thailand, and South Africa. Such investments into science and technology will enable these countries to embark on the path to the medical and health applications of genomics, and to benefit economically [60]; and this needs to be done in all the regions of Nigeria and Nepal as it is presently far from the reality till now. Also, ethical concerns, such as platforms for sharing biosamples, genomic and phenotype data regarding the use of genetic information call for a cautious approach to the implementation of public health initiatives that involve widespread genetic testing [61]. The limitation to access to genetic testing may include problems of few genetic counsellors, limited primary care genetics knowledge and unequal testing access based on region, age and race, all of which are obviously amplified in Nigeria and Nepal. Individuals may also forego testing for fear of discrimination by employers or insurance companies or the effect a positive test might have on families and relationships [62]. The lack of equipment such as biobank facilities and electricity to power it will continue to limit the reality of practicing advanced genetic testing in Nigeria and Nepal, thereby limiting the possibility PM in the management of diseases including oncology.

Lack of Needed Expertise

Lack of expertise is another obstacle, as many physicians may struggle to accurately interpret test results without specialist's assistance, which is another major cost driver for clinics and hospital departments trying to build pathology teams that are up-to-date with the newest tests. These are major hurdles to PM in Nigeria and Nepal, which are not unique to these two countries as developed countries like USA also has challenges in this aspect. A 2018 survey of 160 oncologists in the USA by Cardinal Health found that 60% of physicians who do not use genomic tests avoid them because of the difficulty of interpreting the data. In clinical research and development, too, there

are growing pains associated with moving the pharmaceutical pipeline towards drugs targeting smaller patient sub-groups. Again, cost is a central issue, companion diagnostics do not come cheap, finding and validating biomarkers to guide targeted therapies is a lengthy task, and analysing vast amounts of data often requires new teams with specialized knowledge. This is most clearly seen in the eye-watering prices of some of the world's first truly individualized cancer treatments, chimeric antigen receptor T-cell (CAR-T) therapies.

There have been reported significant "brain drain" in the health care systems of Nigeria and Nepal among its health care professionals and knowledge, as health workers migrate to wealthier countries such as Australia, Canada, USA, and the UK. This has reduced the available number of health care workers. Nepal has only 0.67 doctors and nurses per 1,000 population, which is significantly less than the WHO's recommendation of 2.3 doctors, nurses, and midwives per 1,000 population. Nigeria, on the other hand has 0.4 doctors and nurses per 1,000 population.

Clinical Trials/Precision Medicine Barriers in Drug Development

Research and healthcare will only progress when patients have access to, and participate at much higher rates in clinical trials. The big challenge increasingly facing patients is their ability to access and afford these new and innovative therapies. In order for precision medicine to truly succeed, we need to ensure ready access to appropriate diagnostic and genetic tests, coupled with easy access to optimal personalized treatment regimens. With unwavering determination, advocates throughout the country must champion clinical decision and payment models that support precision medicine.

Clinical pathways, trials, and reimbursement models must be structured in a way that accommodates precision medicine by allowing physicians to pursue treatment options that hold the greatest promise for personalized treatments from the very start of a patient's deeply personal care journey. Barriers to conducting clinical trials in developing countries including Nigeria and Nepal were also identified as lack of financial and human capacity, ethical and regulatory system obstacles, lack of research environment, operational barriers and competing demands [63].

The cost of new drugs is the most significant factor. Precision medicine relies upon individual patient genetic profiling, biomarker identification and validation, and big data research that require significant investments.

The use of PM for cancer prevention rather than treatment therefore needs to be emphasized. This rise in incidence is accompanied by a sharp increase in cancer mortality, which disproportionately affects patients in low-middle income countries [64].

Nigeria and Nepal also lack good quality evidence that characterises the molecular landscape of cancers just like many other low-middle income countries. As cancer medicine becomes increasingly driven by molecular alterations in high-income settings, low-income settings may become left behind.

Further efforts on an international scale must be made by researchers, funders, and policymakers to ensure cancer research addresses disease across the world, so models are not limited to subtypes of disease found in high-income countries.

It is very obvious that Nigeria and Nepal together with the other developing countries contend with barriers, such as delays in accessing healthcare, advanced disease at presentation, and limited access to treatment; research and clinical practice in developed countries are aimed toward developing treatment strategies tailored to individual patient characteristics and tumor biology [65].

Conducting high-quality cancer trials is challenging in low-income settings which are predominant in Nigeria and Nepal. These challenges are further amplified even in small expectations resulting in lack of postal address systems, patient records and the infrastructure to process clinical specimens. Furthermore, a supply of clinical trial lists is short in these two countries. Training and exchange programmes with developed countries partners may help provide solutions in the short term, however, long-term infrastructure building must be given priority.

One example of where this is changing is Rwanda, where electronic patient record systems are being introduced [66]. Nigeria is also beginning to experience electronic record-based activities which are more pronounced in the private sectors. The Nigerian public health sector is still not able to demonstrate a good effort in this regard. Integrating clinical systems into research in such settings would enable efficient research to be undertaken. In high-income countries (HICs), registry-based trials provide an efficient means of producing follow-up data, and this approach could be emulated in Nigeria and Nepal, where electronic records exist [64]. To achieve an effective PM adoption in these two countries, it is imperative to balance equity issues across diverse populations while improving efficiency in healthcare.

In developed countries, molecular testing is already being used to target therapies to specific alterations in tumors. At present, in Nigeria and Nepal, implementing effective national programmes for precision cancer therapy and prevention following similar models to examples within developed countries is unlikely to be feasible.

A lack of trained laboratory medicine workforce, instruments, transportation, finances, and evidence to support the applicability of clinical response are all key factors. Access to pathology and laboratory medicine services in their current format is a major issue, with some developing countries having no workforce at all [67-69].

Barriers to conducting clinical trials in developing countries which include the two countries in focus were: lack of financial and human capacity, ethical and regulatory system obstacles, lack of research environment, operational barriers and competing demands [70]. Nigeria and Nepal have not experienced any major clinical trial till date. Recently, clinical trials on prostate cancer (CAPTC), Herceptin use in HER-2 positive breast cancer (ARETA) and the use of imatinib in gastrointestinal stromal tumor (GISTIMAB) were commenced and all these trials are still in the very early phase. Although clinical trials are important to address sustained inequity that

results from high burden of disease in developing countries, these countries are grossly under-represented in global clinical trial platforms.

Medical schools and teaching hospitals in developing countries have poorly prepared their graduates to conduct scientific trials and clinical research. In India for example, though there are half a million physicians with 50 - 60 physicians per 100,000 people, fewer than 200 have been trained in good clinical practice (GCP).

Lack of Adequate Health Insurance Coverage

These healthcare systems are striving towards universal health coverage (UHC) to ensure everyone has access to needed health services, without undue financial hardship; and financial constraint remains as one of the main challenges in attaining and maintaining UHC [71].

Primarily, both economic challenges and operational issues present the most significant obstacles to the development of PM adoption and implementation [70, 72].

To harness PM in South-East Asia (SEA), changes at multilevel in the healthcare systems are essential to improve the quality of patient care and health system productivity. The major challenge observed in oncology service in Nepal is the high cost of the treatment; and because of the lack of insurance, and a proper health policy, people have to bear all burden by themselves. Most low-income countries do not have an effective financial protection mechanism where 50% of health care financing is from OOP payments, as compared with 30% in middle-income countries and 14% in high-income countries [73].

The high cost of new biotechnologies can exacerbate health inequalities and become a problem for health services' sustainability, especially in these two countries. The emphasis on personalized or precision medicine may shift funds away from less costly interventions that have greater public health impact.

One of the great promises of precision medicine is to reduce the cost of medical care, based on greater efficiency in the use of drugs, avoiding their use in patients in which they would be ineffective or avoiding side effects.

To the contrary, the high cost of targeted drugs produces inequalities in access to the drugs' benefits and challenges for health systems' sustainability. The cost of new cancer drugs has grown rapidly and continuously [74], and their average cost per patient often exceeds $100,000 a year [75].

The high cost of targeted drugs will entail inequalities in access to the benefits within these two countries, between populations from different social strata. For Nigeria and Nepal that often experience difficulties in accessing basic health technologies for their populations, the costs of the new treatments are prohibitive such as it applies to most LMICs which are unable to provide their populations with all the drugs that are considered essential by the WHO [76].

Thus, PM may concentrate resources in the part of the population that already has higher purchasing power and better access to health services.

For the incorporation of new technologies in PM, it is essential to undertake a cost-benefit assessment from an ethical perspective that considers whether they will be accessible for everyone to benefit and will not exacerbate the existing health disparities.

The central focus on the individual and on high-cost technologies that benefit a small portion of the population not only will fail to reduce the main health problems affecting the world, but may also increase the inequalities, with concentration of resources and technologies in the population strata that already have the best access to health, thereby exacerbating health inequalities and hampering health services' sustainability, especially in LMICs [77].

The Physicians Resistance and Patients Unawareness

In many countries where physicians and patients have access to the latest information on the treatment of care for cancer, there is not usually a problem with adopting the new guidelines on the part of the physicians and awareness of the new cancer care by the patients. However, this is not the same in Nigeria and Nepal, as many physicians may not be aware of the new guidelines approved for the cancer care and some of those that know may find it difficult to adopt it immediately. Also, patients in Nigeria and Nepal may find it difficult to get up-to-date information as regards their cancer care. Customized patient care provided on the basis of biomarker status is an important component of precision medicine, a care model whereby medical decisions and treatments are tailored to the individual patient's genetics, environment, and lifestyle. Biomarkers have become part of modern clinical practice, but an in-depth understanding of how patients experience personalized care and how physicians implement it in their routine practice is not yet available.

Providing timely information to patients to fully inform them about their treatment and biomarker screening options will allow them to appreciate the value of personalized treatment options. The willingness of patients to undergo additional diagnostic procedures and manage consequent delays in the initiation of treatment may also be a key factor in the success of such approaches. Improved understanding of the challenges that physicians and patients face regarding biomarker testing may enable physicians to better align their treatment plans with practice guidelines.

There is still a clear need for patients to have access to additional sources of information that will allow them to more fully understand their treatment options and better engage in decision-making. Furthermore, patients with a better understanding of their disease, available treatment options, and ongoing research may be more likely to participate in clinical trials, thus paving the way for future identification of additional biomarkers, more effective treatment options, and more cost-effective therapies.

The efforts to increase access and control costs may encourage doctors to participate in testing more effectively compared with efforts targeted toward patient or physician educa-

tion.

Data demonstrate wide global use of biomarker testing but with regional variations reflecting cultural and local practice. Self-reported and physician-assessed cancer literacy, although generally high, highlighted important regional variations and the need to provide patients with additional information [78].

The rising cancer burden in the two countries stresses already weak health care and economic infrastructures and poses unique challenges. Also, extrapolation of the experiences of cancer control programs in HICs to LMICs is often inappropriate.

Policymakers, healthcare professionals, industry groups and researchers recognize health information exchange (HIE) as a vital component of the solution to the problems posed by disparate and fragmented health systems and non-interoperable technologies [79, 80].

Lack of information obstructs the delivery of healthcare that results in many preventable deaths in LMICs [81]. However, although the available resources to tackle barriers (e.g., infrastructure organizational, technical, and data management) vary in each of the LMICs, there is benefit in LMICs sharing their resources (experts, workforce, technology, and interventions) and learning to develop HIE.

Lack of Immediate Availability of Novel Drugs in Developing Nations

Access to new cancer medicines is an essential part of the healthcare, but remains a challenge to all LMIC [82]. This is significantly amplified in Nigeria that has the largest black population in the world. The same thing also applies to Nepal. Although some countries can have an access to a new drug themselves, based on the scientific dossier provided by the manufacturer (usually high-income countries), middle-income countries with varying levels of development and drug regulatory capabilities, or low-income countries with very limited or no drug regulatory capability cannot undertake full assessments of new pharmaceutical products. Nigeria and Nepal will not likely have immediate access to new innovative drugs until many years after the initial approval, which is usually due to the high cost of the drugs, which many people in the two countries cannot afford and other logistics issues for making it available. For example, drugs like bevacizumab, Herceptin were not readily available in Nigeria about 5 years after it was approved, which is already in use in the Europe and USA. Drugs like pembrolizumab, atezolizumab and pertuzumab that were approved between 2016 and 2017 are still not readily available in Nigeria and Nepal. Interestingly, the recently approved tucatinib is not likely to be readily available in these two countries till about next 5 - 7 years.

In terms of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) success story at Bir, oral gefitinib is available under $8426.92 government fund at Bir Hospital, Kathmandu, Nepal. This targeted drug cost around 67.42 USD for 30 tablets, which is also affordable to most of the Nepalese cancer patients, if they have to buy after completion of 8,426.92 USD fund.

This trend must be changed if PM would be a constant practice in these two countries knowing that these barriers have become perennial with the present methods.

Non-communicable diseases are now recognized by the United Nations and WHO as a major public health crisis, and cancer care in LMICs is now acknowledged as a global health priority [83]. Evidence proves that high prices of branded originator medicines and no legal production of generics increase the catastrophic costs, as well as morbidity/mortality of medication in lower income countries [84]. The problem has arisen in many developing countries where the population not only have lower economic status, but also lower health status and higher needs for medicines. Many of the imported novel medicines are priced for the markets of high-income countries, and are not publicly funded in most of LMICs including Nigeria and Nepal, presenting a huge burden to health system.

In the rural areas, the weak health service delivery system and human health resources, as well as the limited capacity of supply and distribution may also block patients' physical access to novel medicines. As these medicines are mostly specialty prescription medicines, many of them are targeted therapies, which need genetic testing and careful monitoring to guide the personalized medication. All these need well-trained specialists and laboratory assistants to deliver. However, these resources are not always available in the resource-limited contexts, especially in remote poor rural areas. Such situation is common in the developing countries where there are generally weak health systems, especially in rural areas [85].

Achieving broader and better access to modern medicines will require multiple and coordinated government efforts, which would need to target the whole lifecycle regulation of novel medicines with a health system perspective, from balancing intellectual property (IP) protection, strengthening research and development (R&D) and public health, to appropriate regulatory approach and financing mechanism, and to supply chain management, as well as smart use.

Overcoming Barriers to Implementing PM

There are evidences that integrating PM into patient care practice holds significant promise for enhancing health care quality while reducing its cost. While PM holds much promise, overcoming these discussed barriers could prove challenging with regard to differential reimbursement schemes, the expected need for rapid and reliable genomic information on acutely ill patients in hospital settings, and the need for a framework to enable consistent and coherent communication of information between community health services and hospitals.

To address the lack of needed expertise, the knowledge gap among available health care professionals can be bridged by introducing, updating and training them regarding PM. Incorporating the basics of PM in medical student's curriculum will also provide the needed foundation moving forward in their clinical practice.

Drawing associations between clinical medicine, genetics and molecular mechanisms and pharmacogenomics hold the promise of guiding therapy based on a multidimensional

appreciation of disease pathogenesis and opportunities to intervene. The choice of therapeutics also has the potential to be personalized using pharmacogenetics, acknowledging that patients react, respond and metabolize medications in a varying and hopefully predictable manner. To make these testing facilities readily available, professional collaborations should be established among the nation's health ministry and providers of these services to convene up-to-date and promote the use of all valid and available technology to improve ability to tailor care to patient needs.

For the increasing demand for more research and clinical trials, there should be a collaborative system to support national scientific network for analysing, integrating and updating molecular and "omics" data to be integrated in the electronic health records and data bank.

Conclusions

PM is now the recommended standard of care in many developed nations for oncology care. However, PM is yet to become a significant practice in Nigeria and Nepal as there are still many native barriers which majorly are lack of funds, necessary facilities, expertise, clinical trials, novel drugs availability, physicians and patients factors. These barriers therefore limit the implementation of PM in these two countries which are good examples of developing nations. Unconventional methods should be considered to make PM a full reality in Nigeria and Nepal. Such method may include significantly subsidized supply of novel drugs, trainings, materials and equipment for advanced testing and a responses evaluation to single dose check point inhibitors without testing.

Acknowledgments

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Author Contributions

Conception and design: Adeoluwa A. Adeniji, Soniya Dulal, Mike G. Martin. Financial support: Adeoluwa A. Adeniji, Mike G. Martin. Administrative support: Adeoluwa A. Adeniji, Mike G. Martin. Provision of study materials: Adeoluwa A. Adeniji, Soniya Dulal, Mike G. Martin. Collection and assembly of data: Adeoluwa A. Adeniji, Soniya Dulal. Data analysis and interpretation: Adeoluwa A. Adeniji, Soniya Dulal, Mike G. Martin. Manuscript writing: all authors. Final approval of manuscript: all authors. Accountable for all aspects of the work: all authors.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

References

1. You W, Henneberg M. Cancer incidence increasing globally: The role of relaxed natural selection. Evol Appl. 2018;11(2):140-152.
2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010;127(12):2893-2917.
3. Akin J, Birdsall N, de Ferranti D. Financing Health Services in Developing Countries. The Policy and Research Division of the World Bank's Population, Health, and Nutrition Department.
4. Unger JM, Cook E, Tai E, Bleyer A. The role of clinical trial participation in cancer research: barriers, evidence, and strategies. Am Soc Clin Oncol Educ Book. 2016;35:185-198.
5. Hood L, Friend SH. Predictive, personalized, preventive, participatory (P4) cancer medicine. Nat Rev Clin Oncol. 2011;8(3):184-187.
6. Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. Nat Rev Clin Oncol. 2018;15(12):731-747.
7. Marcus L, Lemery SJ, Keegan P, Pazdur R. FDA Approval summary: pembrolizumab for the treatment of microsatellite instability-high solid tumors. Clin Cancer Res. 2019;25(13):3753-3758.
8. Herbst RS, Lopes G, Kowalski DM, Nishio M, Wu Y-L, de Castro Junior G, et al. LBA79 - Association between tissue TMB (tTMB) and clinical outcomes with pembrolizumab monotherapy (pembro) in PD-L1-positive advanced NSCLC in the KEYNOTE-010 and -042 trials. Ann Oncol. 2019;30(5):v916-v917.
9. Pottier C, Fresnais M, Gilon M, Jerusalem G, Longuespee R, Sounni NE. Tyrosine kinase inhibitors in cancer: breakthrough and challenges of targeted therapy. Cancers (Basel). 2020;12(3):731.
10. Ahn MJ, Sun JM, Lee SH, Ahn JS, Park K. EGFR TKI combination with immunotherapy in non-small cell lung cancer. Expert Opin Drug Saf. 2017;16(4):465-469.
11. Almaazmi H, Stem M, Lo BD, Taylor JP, Fang SH, Safar B, Efron JE, et al. The Impact of Imatinib on Survival and Treatment Trends for Small Bowel and Colorectal Gastrointestinal Stromal Tumors. J Gastrointest Surg. 2020;24(1):98-108.
12. Laurent-Puig P, Grisoni ML, Heinemann V, Liebaert F,

Neureiter D, Jung A, Montestruc F, et al. Validation of miR-31-3p expression to predict cetuximab efficacy when used as first-line treatment in RAS wild-type metastatic colorectal cancer. Clin Cancer Res. 2019;25(1):134-141.

13. Meiri E, Garrett-Mayer E, Halabi S, Mangat PK, Shrestha S, Ahn ER, et al. Pembrolizumab (P) in patients (Pts) with colorectal cancer (CRC) with high tumor mutational burden (HTMB): Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) Study. Journal of Clinical Oncology. 2020;38(4):133-133.

14. Ott PA, Bang YJ, Piha-Paul SA, Razak ARA, Bennouna J, Soria JC, Rugo HS, et al. T-cell-inflamed gene-expression profile, programmed death ligand 1 expression, and tumor mutational burden predict efficacy in patients treated with pembrolizumab across 20 cancers: KEYNOTE-028. J Clin Oncol. 2019;37(4):318-327.

15. Hellmann MD, Paz-Ares L, Bernabe Caro R, Zurawski B, Kim SW, Carcereny Costa E, Park K, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. N Engl J Med. 2019;381(21):2020-2031.

16. Watanabe K, Sugiyama T, Otsuka A, Miyake H. Complete response to combination therapy with nivolumab and ipilimumab for metastatic collecting duct carcinoma of the kidney. Int Cancer Conf J. 2020;9(1):32-35.

17. Mavratzas A, Seitz J, Smetanay K, Schneeweiss A, Jager D, Fremd C. Atezolizumab for use in PD-L1-positive unresectable, locally advanced or metastatic triple-negative breast cancer. Future Oncol. 2020;16(3):4439-4453.

18. Chang Lee R, Tebbutt N. Systemic treatment of advanced hepatocellular cancer: new hope on the horizon. Expert Rev Anticancer Ther. 2019;19(4):343-353.

19. Gilad Y, Eliaz Y, Yu Y, Han SJ, O'Malley BW, Lonard DM. Drug-induced PD-L1 expression and cell stress response in breast cancer cells can be balanced by drug combination. Sci Rep. 2019;9(1):15099.

20. Steiner M, Seule M, Steiner B, Bauer I, Freund M, Kohne CH, Schuff-Werner P. 5-Fluorouracil/irinotecan induced lethal toxicity as a result of a combined pharmacogenetic syndrome: report of a case. J Clin Pathol. 2005;58(5):553-555.

21. Wen F, Li Q. Treatment dilemmas of cetuximab combined with chemotherapy for metastatic colorectal cancer. World J Gastroenterol. 2016;22(23):5332-5341.

22. Serpas V, Rogers JE, Xiao L, Mola-Rudd K, Dasari A, Kee BK, et al. Impact of antibiotic exposure on the efficacy of immune checkpoint blockade in MSI-H metastatic CRC. J Clin Oncol. 2020;38(4_suppl):161-161.

23. Shaikh FY, Gills JJ, Sears CL. Impact of the microbiome on checkpoint inhibitor treatment in patients with non-small cell lung cancer and melanoma. EBioMedicine. 2019;48:642-647.

24. Horgan D, Lal JA. Making the Most of Innovation in Personalised Medicine: An EU Strategy for a Faster Bench to Bedside and Beyond Process. Public Health Genomics. 2018;21(3-4):101-120.

25. Lal JA, Sudbrak R, Lehrach H, Brand A. Functional dynamics: from biological complexity to translation and impact in healthcare systems. J ComputSciSyst Biol. 2013;6(2):88-92.

26. Yang T, Liang L, Wang MD, Shen F. FGFR inhibitors for advanced cholangiocarcinoma. Lancet Oncol. 2020;21(5):610-612.

27. Worldometer elaboration of the latest United Nations data. https://www.worldometers.info/world-population/nigeria-population/.

28. Nigeria Cancer Control Plan 2018-2022. https://www.iccp-portal.org/system/files/plans/NCCP_Final%20%5B1%5D.pdf.

29. Poudel KK, Huang Z, Neupane PR, Steel R. Prediction of the cancer incidence in Nepal. Asian Pac J Cancer Prev. 2017;18(1):165-168.

30. Donelan K, Blendon RJ, Schoen C, Davis K, Binns K. The cost of health system change: public discontent in five nations. Health Aff (Millwood). 1999;18(3):206-216.

31. Source: www.macrotrends.net.

32. Source: data.worldbank.org.

33. Berman P. National health accounts in developing countries: appropriate methods and recent applications.

34. Hsiao W, Shaw RP. 2007. elibrary.worldbank.org.

35. Facts and Figures about Nigeria health care system. International Medical Travel Journal. https://www.imtj.com/country/NG/#horizontalTab1.

36. The Rising Nepal: support for medical treatment abroad. Himosh Sharma. https://risingnepaldaily.com/.

37. O'Donnell O. Access to health care in developing countries: breaking down demand side barriers. Cad Saude Publica. 2007;23(12):2820-2834.

38. Dulal S, Paudel BD, Wood LA, Neupane P, Shah A, Acharya B, Shilpakar R, et al. Reliance on self-medication increase delays in diagnosis and management of GI cancers: results from Nepal. JCO Glob Oncol. 2020;6:1258-1263.

39. Health Financing Profile 2017. World Health Organization (WHO). 2017. Available online at: https://apps.who.int/iris/bitstream/handle/10665/259643/HFP-NEP.pdf?sequence=1&isAllowed=y (Accessed June 9, 2020).

40. Saito E, Gilmour S, Rahman MM, Gautam GS, Shrestha PK, Shibuya K. Catastrophic household expenditure on health in Nepal: a cross-sectional survey. Bull World Health Organ. 2014;92(10):760-767.

41. Uzochukwu BS, Ughasoro MD, Etiaba E, Okwuosa C, Envuladu E, Onwujekwe OE. Health care financing in Nigeria: Implications for achieving universal health coverage. Niger J Clin Pract. 2015;18(4):437-444.

42. Aregbeshola BS, Khan SM. Out-of-pocket health-care spending and its determinants among households in Nigeria: a national study. J Public Health (Berl.). 2020.

43. Onwujekwe O, Hanson K, Uzochukwu B. Examining inequities in incidence of catastrophic health expenditures on different healthcare services and health facilities in Nigeria. PLoS One. 2012;7(7):e40811.

44. Omolase CO, Adeleke OE, Afolabi AO, Afolabi OT. Self medication amongst general outpatients in a nigerian community hospital. Ann Ib Postgrad Med. 2007;5(2):64-67.

45. Islam SM, Purnat TD, Phuong NT, Mwingira U, Schacht K, Froschl G. Non-communicable diseases (NCDs) in developing countries: a symposium report. Global Health. 2014;10:81.

46. Leive A, Xu K. Coping with out-of-pocket health payments: empirical evidence from 15 African countries. Bull World Health Organ. 2008;86(11):849-856.

47. Mosadeghrad AM. Factors affecting medical service quality. Iran J Public Health. 2014;43(2):210-220.

48. Onwujekwe O, Ezumah N, Mbachu C, Obi F, Ichoku H, Uzochukwu B, Wang H. Exploring effectiveness of different health financing mechanisms in Nigeria; what needs to change and how can it happen? BMC Health Serv Res. 2019;19(1):661.

49. World Health Organization, Health Financing profile in Nepal. 2017.

50. McIntyre D, Gilson L. Redressing dis-advantage: promoting vertical equity within South Africa. Health Care Anal. 2000;8(3):235-258.

51. Waldman SA, Terzic A. Companion diagnostics at the intersection of personalized medicine and healthcare delivery. Biomark Med. 2015;9(1):1-3.

52. President's Council of Advisors on Science and Technology (PCAST). Priorities for Personalized Medicine. http://www.whitehouse.gov/files/documents/ostp/PCAST/pcast_report_v2.pdf.

53. Ku CS, Loy EY, Salim A, Pawitan Y, Chia KS. The discovery of human genetic variations and their use as disease markers: past, present and future. J Hum Genet. 2010;55(7):403-415.

54. Roukos DH. Novel clinico-genome network modeling for revolutionizing genotype-phenotype-based personalized cancer care. Expert Rev Mol Diagn. 2010;10(1):33-48.

55. Cancer Gene Census. www.sanger.ac.uk/genetics/CGP/Census/Google Scholar.

56. Bustamante CD, Burchard EG, De la Vega FM. Genomics for the world. Nature. 2011;475(7355):163-165.

57. Popejoy AB, Fullerton SM. Genomics is failing on diversity. Nature. 2016;538(7624):161-164.

58. Manrai AK, Funke BH, Rehm HL, Olesen MS, Maron BA, Szolovits P, Margulies DM, et al. Genetic misdiagnoses and the potential for health disparities. N Engl J Med. 2016;375(7):655-665.

59. Martin AR, Teferra S, Moller M, Hoal EG, Daly MJ. The critical needs and challenges for genetic architecture studies in Africa. Curr Opin Genet Dev. 2018;53:113-120.

60. Hardy BJ, Seguin B, Goodsaid F, Jimenez-Sanchez G, Singer PA, Daar AS. The next steps for genomic medicine: challenges and opportunities for the developing world. Nat Rev Genet. 2008;9(Suppl 1):S23-27.

61. Aleksandr Ivanov. Barriers to the introduction of new medical diagnostic tests. Laboratory Medicine. 2013;44(4):e132-e136.

62. Ahmed S, Tate J, Thrift-Perry M, Wait S. Barriers and opportunities in genetic testing for BRCA gene mutations in Europe: a strategic policy response to support women and families at risk for breast cancer. J Glob Oncol. 2018;4(2):141s-141s.

63. Alemayehu C, Mitchell G, Nikles J. Barriers for conducting clinical trials in developing countries- a systematic review. Int J Equity Health. 2018;17(1):37.

64. Wang H, Naghavi M, Allen C, Barber RM, Bhutta ZA, Carter A, Casey DC, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet. 2016;388(10053):1459-1544.

65. Drake TM, Knight SR, Harrison EM, Soreide K. Global inequities in precision medicine and molecular cancer research. Front Oncol. 2018;8:346.

66. Amoroso CL, Akimana B, Wise B, Fraser HS. Using electronic medical records for HIV care in rural Rwanda. Stud Health Technol Inform. 2010;160(Pt 1):337-341.

67. Horton S, Sullivan R, Flanigan J, Fleming KA, Kuti MA, Looi LM, Pai SA, et al. Delivering modern, high-quality, affordable pathology and laboratory medicine to low-income and middle-income countries: a call to action. Lancet. 2018;391(10133):1953-1964.

68. Wilson ML, Fleming KA, Kuti MA, Looi LM, Lago N, Ru K. Access to pathology and laboratory medicine services: a crucial gap. Lancet. 2018;391(10133):1927-1938.

69. Sayed S, Cherniak W, Lawler M, Tan SY, El Sadr W, Wolf N, Silkensen S, et al. Improving pathology and laboratory medicine in low-income and middle-income countries: roadmap to solutions. Lancet. 2018;391(10133):1939-1952.

70. Jakka S, Rossbach M. An economic perspective on personalized medicine. HUGO J. 2013;7(1):1.

71. World Health Organization (WHO). Universal health coverage: moving towards better health - action framework for the Western Pacific region. Geneva: WHO; 2016.

72. Davis JC, Furstenthal L, Desai AA, Norris T, Sutaria S, Fleming E, Ma P. The microeconomics of personalized medicine: today's challenge and tomorrow's promise. Nat Rev Drug Discov. 2009;8(4):279-286.

73. Mills A. Health care systems in low- and middle-income countries. N Engl J Med. 2014;370(6):552-557.

74. Fojo T, Mailankody S, Lo A. Unintended consequences of expensive cancer therapeutics-the pursuit of marginal indications and a me-too mentality that stifles innovation and creativity: the John Conley Lecture. JAMA Otolaryngol Head Neck Surg. 2014;140(12):1225-1236.

75. Workman P, Draetta GF, Schellens JHM, Bernards R. How much longer will we put up with $100,000 cancer drugs? Cell. 2017;168(4):579-583.

76. Gyawali B, Sullivan R. Economics of cancer medicines: for whose benefit? New Bioeth. 2017;23(1):95-104.

77. Iriart JAB. Precision medicine/personalized medicine: a critical analysis of movements in the transformation of biomedicine in the early 21st century. Cad Saude Publica. 2019;35(3):e00153118.

78. Ciardiello F, Adams R, Tabernero J, Seufferlein T, Taieb J, Moiseyenko V, Ma B, et al. Awareness, understanding, and adoption of precision medicine to deliver personalized treatment for patients with cancer: a multinational survey comparison of physicians and patients. Oncologist. 2016;21(3):292-300.

79. Brailer DJ. Interoperability: the key to the future health care system. Health Aff (Millwood). 2005;24(Suppl1):W5-19-W5-21.

80. Hripcsak G, Kaushal R, Johnson KB, Ash JS, Bates DW,

Block R, Frisse ME, et al. The United Hospital Fund meeting on evaluating health information exchange. J Biomed Inform. 2007;40(6 Suppl):S3-10.

81. Chatterjee P, Biswas T, Datta A, Sriganesh V. Healthcare information and the rural primary care doctor. S Afr Med J. 2012;102(3 Pt 1):138-139.

82. Wilking Nils, Bengt Jonsson. A pan-European comparison regarding patient access to cancer drugs. 2005:472-485.

83. World Health Organization United Nations high-level meeting on noncommunicable disease prevention and control. http://www.who.int/nmh/events/un_ncd_summit2011/en/.

84. Ahmadiani S, Nikfar S. Challenges of access to medicine and the responsibility of pharmaceutical companies: a legal perspective. Daru. 2016;24(1):13.

85. Diao Y, Li M, Huang Z, Sun J, Chee YL, Liu Y. Unlocking access to novel medicines in china-a review from a health system perspective. Risk Manag Healthc Policy. 2019;12:357-367.