Editorial Article

Pharmacogenomics in Primary Care: A Crucial Entry Point for Global Personalized Medicine?

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1. PRIMARY HEALTHCARE AND PHARMACO-GENOMICS

Pharmacogenomics, the study of the influence of human genomic variation on drug efficacy and safety, is one of the cornerstones of personalized medicine and stands in contrast to the current "one size fits all" approach to drug prescription and dosing [1, 2]. Pharmacogenomics is among one of the first clinical applications in the field of genomics medicine and is most likely to represent the near-term payoff for this pioneering area of healthcare [2, 3]. Specifically, pharmacogenomics testing is expected to reduce the amount of trial and error that currently exists in prescribing and should ultimately lead to more efficient and safer drug therapies. Given that one in four primary care patients in North America is prescribed at least one medication that commonly causes adverse drug reactions due to genetic variability in drug metabolism, it is understandable that pharmacogenomics is expected to play a large role in personalized medicine. It is also increasingly being explored in the primary care context [4].

The emergence of this new and promising medical subspecialty, "pharmacogenomics-in-primary care", occurs at a time when global health care is struggling to contain costs while ensuring equitable access to treatment and healthcare. Escalating drug budgets, aging populations or expanding population size and limited healthcare resources are shared challenges across all countries regardless of the level of resources available.

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To be sure, provision of primary care has been acknowledged as having a major role to improve global health [5, 6]. The World Health Organization considers primary care to be a critical component of primary health care strategy as elucidated by the Alma Alta Declaration of 1978. Primary care involves the broadest scope of health care for patients of all ages and all stages of health. Based on this premise, we define primary care pharmacogenomics as "the study of the influence of human genomic variation on drug efficacy and safety within the context of patients engaged in preventative health measures as well as treatment for all types of acute or chronic physical and mental health issues".

The juxtaposition of pharmacogenomics and primary care in the context of global personalized medicine may provide insights for the appropriate applications of the new technology to avoid or minimize social conflict due to emerging contested genomics technologies, inappropriate translation of science into clinical practice, unrealistic and inappropriate expectations and potential harm. In what follows, we have chosen to select a brief synopsis of experiences with *primary care pharmacogenomics* from across the globe so as to inform and accelerate future progress in this new subspeciality of genomics-guided healthcare.

2. LESSONS FROM SRI LANKA

Sri Lanka, situated in the Indian Ocean, is a small tropical island with a population of 20 million. According to the Ministry of Health in a report focused on this topic in 2007, Sri Lanka has achieved relatively high standards of social and health care compared with countries of similar economic development and has some of the best health statistics among developing countries. The most important

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aspect of the country's health care system is its no-charge delivery to all citizens. Heavy government investment in the healthcare system since the end of the civil war in 2009 has resulted in access to primary healthcare by the majority of the population. Nevertheless, the social and economic toll of Sri Lanka's civil conflict, which spanned more than two decades, has kept the country's development markedly below its achievable potential.

The importance of new diagnostics and health research including personalized medicine as a strategy for improving health services has now been recognized in Sri Lanka. With the increasing realization of the positive contribution that pharmacogenomics research can make towards health development, research activities have been expanded during the last few years [7-9]. The potential role of pharmacogenomics is highlighted by the progression that has been seen with molecular diagnostics that were introduced in Sri Lanka in 2001 and grown steadily since then. Currently, the clinical applications of molecular methods are well established in infectious diseases, haematological diseases, human identity testing/forensics, tissue typing, oncology, and in well-characterized genetic disorders. Molecular diagnostics actually had its birth in detection of infectious diseases and has made rapid progress in viral and bacterial load testing and genotyping. Similarly, cancer diagnostics based on mutational analysis and gene expression profiling, though still at an embryonic stage, is likely to be the next major breakthrough in clinical practice. Further, molecular diagnostic tools have secured a firm place in haematology and prenatal testing in detecting coagulation disorders.

Based on this history, Sri Lanka warrants further healthcare and policy research in a context of pharmacogenomics in primary care, not only as a potential model for developing or resource limited countries but also as an example of the public health utility of pharmacogenomics and molecular diagnostics in northern, eastern and central provinces and post-war capacity building in healthcare. Just as the clinical application molecular diagnostics has been grounded in infectious disease diagnosis, primary care pharmacogenomics may also improve the effectiveness and safety of treatment for these important areas that are so key for post-war health care. These new technologies clearly demonstrate that capacity building is not only possible but also necessary for all other parts of the country although there must be sufficient government support. As Sri Lanka forges ahead in this new century, molecular diagnostics, pharmacogonomics and personalized medicine will continue to be of critical importance to public health [10].

3. LESSONS FROM CHINA AND AUSTRALIA

Australia and China, the two largest countries in the Asia-Pacific region, have very different healthcare systems. As a developed country, Australia is well known for its healthcare system and general practitioner network, while as a developing country, China has made significant progress in its healthcare reform by establishing community-based primary care [11, 12]. To date, although there are no solid examples of pharmacogenomics use in primary care in either of these two countries, the establishment in 2001 of the Office of Population Health Genomics as the Genomics Directorate in Western Australia is a unique example of how to allow healthcare to respond to the advances in genomics technologies by monitoring genetic service delivery and engaging the community to develop evidence-based policies, and evaluating advances in genetic technologies for implementation into clinical practice.

Research and development in pharmacogenomics is rapidly increasing in China with anticipated investments from the pharmaceutical industry. This has resulted in China becoming one of the more important pharmacogenomics global centers. The strategic collaboration combining genomic sequencing and data analytic capabilities in China with academic and pharmaceutical industries' expertise and experience will provide a platform well-suited for next-generation sequencing solutions to develop important primary care pharmacogenomics tools to aid drug development and enable effective tailoring of medicines in China. Some of the current breakthrough areas for primary care pharmacogenomics in Australia and China include cancer screening and personalized therapy in oncology, drug resistance in cancer, ultra violet-induced skin damage treatment, molecular mechanisms of the tumour microenvironment and traditional Chinese medicine [11-13]. The two contrasting health care systems in Australia and China with a strong emphasis on primary care will provide interesting insights for future developments in global personalized medicine.

4. LESSONS FROM TURKEY

Turkey is a country of more than 80 million people bridging the eastern and the western hemispheres. In the authors' expert opinion, this represents a "postmodern transition zone" among the developed countries and the low to moderate income countries (LMICs). Lessons learned in Turkey regarding emerging genomics technologies and diagnostics medicine thus offer a "translation" promise relating to both developed and developing countries.

An inaugural personalized medicine conference was held in Istanbul in 2009 [14]. The growing interest in pharmacogenomics and personalized medicine should be contextualized further in light of current restructuring of the Turkish healthcare system with greater emphasis in primary care, although this is not always warmly embraced by tertiary care physicians who are accustomed to have a greater personal control and power in healthcare. That is, primary care being the focus of public health and the family physician being the primary contact point for patients both provide a unique opportunity for responsible integration of pharmacogenomics and other health technologies in a manner that takes into account the needs of population health and health systems and services. In the authors' expert opinion, family physicians in Turkey are influential in shaping healthcare policy as well as health technology assessment. Still, the transition of pharmacogenomics from tertiary care use (*e.g.*, in oncology) to a broader focus in primary care will demand not only education primary care physicians but also effective policies and reward systems to enable and encourage these physicians to take interest in and utilize pharmacogenomics tests. This and regional capacity building efforts in primary care pharmacogenomics and

personalized medicine, together with its integration with genetic counseling, as well as education of scientists, health-care professionals and publics are the central focus at academic centers such as the Personalized Genomics Health-care Center, Pharmvation-BIGEM at Anadolu University in Eskişehir, Turkey

Turkey, as with many other resource-limited global regions, is seriously in need of developing scientific merit and health technology assessment resources so as to independently evaluate the emerging genomics technologies and determine the public health utility of pharmacogenomics testing. There is also a need for well-trained staff for interpreting pharmacogenomics test results. For optimal selection of tests, pharmacogenomics case studies must be carefully examined with a view to their putative impacts on population health. Notably, we submit that the application of pharmacogenomic testing will be more successful and efficient if integrated with routine therapeutic drug monitoring. Primary care, emphasizing pharmacogenomics, should play an important role for entry of most healthcare innovations into the public health system. Use of technology that is not grounded on solid evidence, particularly as seen in the pharmaceutical field, is a big challenge in primary care. Yet, Turkey is keen on evidence-based evaluation and use of new technologies. Besides their efficacy and safety, pharmacogenomic outcomes can provide long-term cost-effectiveness, but the current system is focusing on short-term results and tends to give pharmacogenomic testing less priority.

Turkey currently has a universal health insurance system, which has been strengthened to overcome issues of accessibility and equality. Turkey now needs a new governance approach in order to deal with all these difficult issues and develop genomics-relevant legislation and policies. A major demand is an adaptation of regulatory processes to the promising new technologies. Turkey needs to incorporate a sound public health evidentiary framework in response to emerging research and development efforts for personalized healthcare, providing opportunities to generate new collaborations and insights for global policies. Regional capacity building efforts in primary care pharmacogenomics and personalized medicine will continue to be a central focus in Turkey across universities and academic centers.

5. LESSONS FROM LEBANON

Lebanon is a country situated on the Eastern coast of the Mediterranean Sea and has a population of 4.1 million. Historically, its strategic and geo-political location within diverse populations including the Phoenicians, Egyptians, Persians, Greeks, Arabs, and Ottomans contributed to its heterogeneous demography and high level of genetic/ genomic diversity. To the best of our knowledge, no pharma-cogenomics tests are currently available in Lebanese clinical practice, except for the breast cancer tissue *HER-2* expression performed in referral medical centers such as the American University of Beirut Medical Center (AUBMC). A recent study conducted on the effect of *VKORC1* and *CYP2C9* genetic polymorphisms on oral anticoagulants dosing in a sample of Lebanese patients from AUBMC showed an association between the genetic polymorphisms of these genes and the maintenance doses of oral anti-coagulants [15]. Based on these results, the institution is considering offering these two tests for patients who may be initiated on oral anticoagulants. Yet, many existing challenges ought to be addressed before their adoption.

LMICs – such as Lebanon - are characterized by distinct economic, social and cultural norms; it is anticipated that extant efforts for the clinical applications of personalized medicine will be faced with different challenges and barriers when compared to those in high-income countries. These include cost and availability of the test as well as a lack of technology, infrastructure and expertise. Additional factors related to the prescribing physicians are mainly skepticism and inadequate knowledge [16].

Lack of physician knowledge is probably the most important barrier against the implementation of personalized medicine in LMICs. For instance, we have shown that although Middle Eastern primary care physicians perceive clinical pharmacogenomics as potentially relevant and important in their practice, very few actually perform and/or refer patients to genetic testing or genetic counseling. Primary care physicians were willing to be more involved, provided that they receive adequate training first [17]. Furthermore, we recently evaluated the attitudes of a group of medical students at AUBMC toward pharmacogenomics testing, which reinforced the need for further education [18].

Other pharmacogenomics-related projects in the fields of cardiology and oncology are currently ongoing at AUBMC. Several educational efforts are planned in order to bridge the gap between patients' high expectations of health care and information on one hand, and the healthcare professionals' insufficient knowledge and reluctance to apply personalized medicine on the other hand.

6. LESSONS FROM CANADA

In Canada, 70% to 80% of all prescriptions are written by primary care physicians and two out of five primary care patients in North America currently take prescription medication [19, 20]. In recent years, commercially available pharmacogenomics tests have been approved by the Food and Drug Administration in the US but at this time, Health Canada does not require pharmacogenomic testing for new drug approval or in the prescription process. As a result, pharmacogenomics testing in patients remains very limited and is used mostly in settings such as oncology treatment and anti-coagulation clinics.

The consequences of future anticipated widespread use of pharmacogenomics in primary care remain unknown with the potential for harm as well as benefit. In a feasibility study of warfarin testing in a family practice clinic, the ethical and legal issues that most ethicists and researchers have assumed will be the greatest barriers did not emerge and testing was successfully completed with comparable times for return of other laboratory results (about 24 hours). However, in public consultations on the use of pharmacogenomics testing in primary care, patients and health care providers were mostly concerned about communication of results and how this might impact treatment or more particularly, access to treatment [21]. While patients and providers easily grasped

the potential for pharmacogenomics testing to save money by avoiding non-effective treatments and improve safety by minimizing adverse side effects, they felt that pharmacogenomics needed to be implemented judiciously and not just in the context of cost-effectiveness [21]. Management of expectations was seen as a critical element. As implementation of pharmacogenomics testing in primary care lags behind the acute care settings, we have an opportunity to develop best practices and education for primary care health professionals and patients in a way that is transparent and accountable.

CONCLUSIONS AND FUTURE OUTLOOK

The countries represented here were selected in order to provide breadth of experience rather than full representativeness, resulting in a diverse blend of geographical and population sizes, at different points in health care development. The brief glimpses provided by each country into the state of primary care pharmacogenomics provides insight into some interesting trends.

First, the emphasis on the importance of primary care in the provision of quality health care is striking, as is the recognition that it is a suitable target for developing global personalized medicine. Second, all the countries included seem to recognize the potential of personalized medicine, whether it is pharmacogenomics or molecular diagnostics, in tackling difficult health issues and have allocated resources and even developed centers to support this critical topic. The priority for pharmacogenomics varies among the different locations but is continuing to gain in significance, even in LMICs. Third, the importance of providing education and training programs at the same time as research and implementation of any form of personalized medicine, particularly for primary care, has emerged as a consistent theme for all countries. In addition to training programs for health professionals that might be implicated in the use or implementation of the tests, there was also an identified need for adequately trained scientific personnel and the associated services such as genetic counseling. Fourth, the necessity of genomics relevant legislation and policy to structure and prioritize the implementation and research agendas within health care systems as related to primary and public health care. Finally, the value of transparency and accountability to patients in the context of primary care pharmacogenomics was noted.

It is our belief that personalized medicine, highlighted by the subspeciality of pharmacogenomics in primary care, will be strengthened by pooling of international experiences to obtain best practice recommendations, improve patient safety and quality of healthcare, and assist in the optimal allocation of resources for all settings. By borrowing from, and working together with our "neighbours" in the best possible way, we may accelerate the convergence of primary care and pharmacogenomics in the context of global health, resulting in the ultimate goal of maximizing benefit and minimizing harm in 21st century medicine and health care.

ABBREVIATIONS

AUBMC = American University of Beirut Medical Center

LMICs = Low and middle income countries

CONFLICT OF INTERESTS

None declared/applicable.

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