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**Genomic medicine without borders: which strategies should developing countries employ to invest in precision medicine? A New "Fast-Second Winner" Strategy**

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3 **Genomic medicine without borders: Which strategies should developing**  
4 **countries employ to invest in precision medicine? A New “Fast-Second**  
5 **Winner” Strategy**  
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**Short title:** *Fast-Second Winner strategy for global development*

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## Abstract

Genomic medicine has greatly matured in terms of its technical capabilities but the diffusion of genomic innovations worldwide faces significant barriers beyond mere access to technology. New global development strategies are sorely needed for biotechnologies such as genomics and their applications towards precision medicine without borders. Moreover, diffusion of genomic medicine globally cannot adhere to a “one-size-fits-all-countries” development strategy, in the same way that drug treatments should be customized. This begs a timely, difficult but crucial question: how should developing countries, and the resource-limited regions of developed countries, invest in genomic medicine? While a full-scale investment in infrastructure from discovery to the translational implementation of genomic science is ideal, this may not always be feasible in all countries at all times. A simple “transplantation of genomics” from developed to developing countries is unlikely to be feasible. Nor should developing countries be seen as simple recipients and beneficiaries of genomic medicine developed elsewhere because important advances in genomic medicine have materialized in developing countries as well. There are several noteworthy examples of genomic medicine success stories involving resource-limited settings which are contextualized and described in this global genomic medicine innovation analysis. Additionally, we outline here a new long-term development strategy for global genomic medicine in a way that recognizes the individual country’s pressing public health priorities and disease burdens. We term this approach the “Fast-Second Winner” model of innovation that supports innovation commencing not only “upstream” of discovery science but also “mid-stream”, building upon emerging highly promising biomarker and diagnostic candidates from the global science discovery pipeline, based on the unique needs of each country. A mid-stream entry into innovation can

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3 enhance collective learning from other innovators' mistakes upstream in discovery science  
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5 and boost the probability of success for translation and implementation when resources are  
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7 limited. This *à la carte* model of global innovation and development strategy offers  
8  
9 multiple entry points into the global genomics innovation ecosystem for developing  
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11 countries, whether or not extensive and expensive discovery infrastructures are already in  
12  
13 place. Ultimately, broadening our thinking beyond the linear model of innovation will help  
14  
15 us to enable the vision and practice of genomics without borders in both developed and  
16  
17 resource-limited settings.  
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29 **Key words:** Strategy for global biotechnology development, precision medicine,  
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31 developing countries, public health genomic, fast-second winner.  
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## Introduction

Genomic medicine is inherently a “science without borders”, aiming to advance therapeutic and diagnostic medicine worldwide. The field has greatly matured over the last decade in terms of its technical capabilities. On the other hand, the vision and practice of genomics without borders face formidable challenges and opportunities beyond simply access to technology (McCarthy et al., 2013). For example, an astute global and yet customized strategy for the diffusion of global genomics across nation state borders is lacking.

Diffusion of genomic medicine globally cannot adhere to a “one-size-fits-all” model, in the same way as drug treatments should be customized. This begs a timely, difficult but crucial question: how should developing countries, and the resource-limited regions of the developed countries, invest in genomic medicine?

One might argue that a full-scale infrastructure investment from discovery to the translational implementation of genomic science is ideal and should be in place in all countries worldwide. However, this may not always be feasible, with resource limitations; or, if achieved, scientific capacity building may not be real-time and commensurate with global innovative breakthroughs, thereby resulting in time lags and inequities in global science.

A simple transfer of genomic services from developed to developing countries is unlikely to be feasible. Developing countries should not be seen simply as recipients and beneficiaries of genomic medicine developed elsewhere because important advances in genomic medicine have been (and will continue to be) materializing in developing countries as well.

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3 There are several noteworthy examples of genomic medicine success stories  
4 involving resource-limited settings, some of which will be contextualized and described in  
5 this global genomic medicine innovation analysis. Additionally, we outline here a new  
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10 long-term development strategy for global genomic medicine in a way that recognizes the  
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12 pressing public health priorities and disease burdens of the individual countries concerned.  
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14 We term this approach “Fast-Second Winner” model of biotechnology innovation without  
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16 borders which broadens our approach to global innovation beyond a narrow linear model  
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18 that invariably commences upstream from discovery science.  
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### 23 **Where do we stand currently in global genomics?**

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28 Recent advances in genomics, other related multi-omics biotechnologies  
29 (transcriptomics, proteomics, metabolomics, glycomics) and study designs such as  
30 genome-wide association studies, next-generation sequencing and the companion big-data  
31  
32 technologies for genomics data translation, have served to change our past perceptions of  
33  
34 traditional medical practice and have served to herald a new era, that of Genomic  
35  
36 Medicine. These new technologies are gradually being adopted by diagnostic laboratories  
37  
38 and hospitals in the United States and Western Europe, while several regulatory bodies,  
39  
40 such as the United States Food and Drug Administration (FDA; <http://www.fda.gov>) and  
41  
42 the European Medicines Agency (EMA; <http://www.ema.europa.eu>) are issuing guidelines  
43  
44 to facilitate, and at the same time rationalize, the translation of genomic and precision  
45  
46 medicine interventions into the clinic. In principle, genomic and precision medicine are  
47  
48 two separate but highly complementary disciplines, the former comprising an integral part  
49  
50 of the latter. In other words, genomic medicine guides customization of healthcare, with  
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52 medical decisions, practices or products being tailored to the individual patient mainly by  
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3 means of molecular and cellular-based approaches but also in conjunction with imaging  
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5 and other analytical approaches.  
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8 However, the pace of implementation of genomic medicine varies from country to  
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10 country, depending upon a number of different parameters. These parameters include  
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12 barriers, arising mainly from the lack of resources and infrastructure, poor technology and  
13  
14 knowledge transfer, the limited genomics education of healthcare professionals and  
15  
16 occasionally misplaced skepticism regarding the potential benefits that this new discipline  
17  
18 has to offer medicine (Forero et al., 2016). Additionally, most advances in human and  
19  
20 medical genomics stem from resource-rich developed countries. Therefore, they can  
21  
22 generally not be translated directly into the settings frequently found in resource-limited  
23  
24 emerging countries. As such, the potential of genomic medicine is often not fully  
25  
26 appreciated, whether by biomedical scientists and healthcare professionals, or by the  
27  
28 general public and policymakers. When one takes into account that around 85% of the  
29  
30 world's population lives in developing/resource-limited countries, it becomes apparent that  
31  
32 the issue of providing access to genomic medicine in these settings is crucial.  
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35  
36 Despite these barriers, there have been several notable examples of the successful  
37  
38 implementation of genomic medicine projects in resource-limited settings across different  
39  
40 continents that pertain either to population pharmacogenomics or public health genomics.  
41  
42 Moreover, there have been various successful efforts to build research networks with  
43  
44 common interests in genomic medicine. Some of these are summarized below, and we  
45  
46 believe that they can serve as model cases for the implementation of genomic medicine in  
47  
48 other resource-limited environments. Herein, the notions “developing country” and  
49  
50 “resource-limited settings” will be used to denote an environment in which: (a) resources  
51  
52 assigned for genomics research are scarce, (b) access to genomics knowledge and  
53  
54 information is restricted, (c) genomic implementation is limited, (d) genomics education is  
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3 relatively poor, and/or (e) collaborative opportunities for genomics research with renowned  
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5 institutions are rare for various reasons, such as geographical, societal, economic or  
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7 political.  
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### 10 11 12 **Capacity building in genomic medicine**

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14 One of the most important reasons that genomics research is lagging behind in  
15  
16 resource-limited settings, as compared to developed countries, is the lack of dedicated  
17  
18 resources and research centers that help to spearhead the generation of new knowledge by  
19  
20 training and educating young scientists, medical students, clinicians etc.  
21  
22

23 Research in Africa has revealed insufficient genetic knowledge at the level of  
24  
25 medical education, while international genetics research on Africa has consistently failed  
26  
27 to build capacity in the two-decade post-initiation of the Human Genome Project (Wonkam  
28  
29 et al., 2006, Wonkam et al., 2011, Matovu et al., 2014). Since then, the latter trend is  
30  
31 rapidly changing with initiatives such as the H3Africa Consortium that is fully engaging  
32  
33 young Africa Sciences in Genomics Research (Consortium, 2014, Matovu et al., 2014) and  
34  
35 providing new hope to accelerate Precision Medicine in Africa. For example, the  
36  
37 Department of Science and Technology, South Africa, has recently launched the South  
38  
39 African Precision Medicine Initiative.  
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42 Also, in Latin America, there are very few research centers that have the capability  
43  
44 to facilitate genomics research and education. Yachay Tech University  
45  
46 (<http://www.yachaytech.edu.ec/en>) is the first research-intensive University in Ecuador. It  
47  
48 was inaugurated in March 2014 in one of the most biodiverse countries to be found  
49  
50 anywhere in the world, as part of a long-term national plan towards a knowledge-based  
51  
52 economy. As part of this initiative, Yachay Tech is planning to establish the Ecuadorian  
53  
54 Center for Genomics and Bioinformatics. Such a research center would act as a magnet not  
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3 only within Ecuador, but also for the entire South American region. The new Institute will  
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5 be established in cooperation with the Golden Helix Foundation ([www.goldenhelix.org](http://www.goldenhelix.org)), a  
6  
7 UK-based non-profit research organization active in research and education in genomics  
8  
9 and translational research, with a special interest in disseminating an understanding of  
10  
11 human genetics and genomics and promoting, in tandem with research organizations, the  
12  
13 clinical application of pharmacogenomics in medical practice.  
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15

16 The two institutions are committed to carrying out research in the area of Genomics  
17  
18 and Bioinformatics related particularly to the following fields: Systems Biology,  
19  
20 Bioinformatics, Biotechnology, Biodiversity, Conservation Biology, Ecology,  
21  
22 Evolutionary Biology, and, last but not least Population Genetics, Pharmacogenomics and  
23  
24 Genomics and Translational Medicine. In the field of human genomics education, the new  
25  
26 Institute, in conjunction with the Golden Helix Academy, will organize graduate courses in  
27  
28 human genomics, genome informatics and public health genomics, while it will also  
29  
30 provide academic certificates and diplomas in the aforementioned disciplines. Overall, the  
31  
32 envisaged Ecuadorian Institute of Genomics and Bioinformatics at Yachay Tech aspires to  
33  
34 be a recognized center of reference for Genomics in South America for the analysis of data  
35  
36 on genetic disease incidence and to guide research and public health policies of relevance  
37  
38 to various populations and ethnic groups. In addition, this Institute promises to be a key  
39  
40 partner in research projects addressing the tremendous wealth of the continent's  
41  
42 biodiversity and its sustainable management.  
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47 Apart from Latin America, there are also similar efforts in other parts of the world.  
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49 In the UAE, the Zayed Bin Sultan Center for Health Sciences  
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51 (<http://www.cmhs.uaeu.ac.ae/en/zchs>) has been established in the United Arab Emirates  
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53 University, with the generous support of the Zayed Foundation, and aims to become the  
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55 flagship research center of the College of Medicine and Health Sciences for population  
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3 health. The center was established to support and contribute to the United Arab Emirates  
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5 University mission of becoming a world-class center for applied research, with national  
6  
7 and international outreach and innovation whilst preserving the unique values of the UAE.  
8  
9 The center intends to forge formal links with other universities and institutions through  
10  
11 equitable memoranda of understanding. In the field of Genomic Medicine, the first project  
12  
13 focusing on Public Health Genomics was designed and already started, in an effort to  
14  
15 canvass the genomic medicine environment in the UAE with the prospect of extending this  
16  
17 project into neighboring countries in the region (see below).  
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### 20 21 22 23 **Population pharmacogenomics**

24  
25 Pharmacogenomics is steadily being implemented in the world's health systems  
26  
27 albeit at a rather heterogeneous pace. The pace of implementation is significantly faster in  
28  
29 the United States and western European countries, whereas other countries in Europe and  
30  
31 elsewhere are currently lagging behind. The landscape is heterogeneous even within  
32  
33 Europe mostly due to the lack of harmonization of the national guidelines in Europe and  
34  
35 most importantly, differences in resource availability (Mitropoulos et al., 2011). Another  
36  
37 important parameter is the variable prevalence of pharmacogenomic biomarkers in  
38  
39 different ethnicities around the world; these have scarcely been documented. Given that the  
40  
41 cost-effectiveness of genome-guided interventions relies upon our knowledge of the  
42  
43 prevalence of certain biomarkers in different ethnic groups, it becomes challenging to  
44  
45 define those actionable pharmacogenomic biomarkers on which drug-dose  
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47 recommendations will be set.  
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52 The *Euro-PGx project*, launched in 2010 by the Golden Helix Foundation and  
53  
54 forming an integral part of the Pharmacogenomics for Every Nation Initiative (PGENI),  
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56 (<http://www.goldenhelix.org/activities/research/pharmacogenomics>), aims to determine the  
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3 spectrum and the variation of pharmacogenomic biomarker allele frequencies across a  
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5 large number of European countries, many of which are characterized by limited resources,  
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7 in an effort to provide the basis for deriving country-specific drug-dose recommendations.  
8  
9 In addition, a project that aims to raise pharmacogenomics awareness among biomedical  
10  
11 scientists and healthcare professionals has been initiated by organizing several single-day  
12  
13 educational events (the Golden Helix Pharmacogenomics days;  
14  
15 <http://pharmacogenomicsdays.goldenhelix.org>) in various European countries.  
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19 As expected, the findings from this large-scale genotyping effort in 18 European  
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21 countries, using the DMET+ microarray (Affymetrix, Santa Clara, CA, USA) and  
22  
23 conventional genotyping methods, suggested that the prevalence of individual  
24  
25 pharmacogenomic biomarkers varies significantly, despite the strong Caucasian genetic  
26  
27 component in all of the European populations analyzed (Mizzi et al., 2016). In particular,  
28  
29 data from the analysis of 36 clinically actionable pharmacogenomic variants in all 18  
30  
31 European populations revealed significant differences in the prevalence of 7  
32  
33 pharmacogenomic biomarkers in at least 7 European populations, which are implicated in  
34  
35 the efficacy and toxicity of 51 drugs. As far as warfarin dose recommendation is  
36  
37 concerned, it is evident that there are marked differences in the predicted average warfarin  
38  
39 dose in different European populations analyzed (Mizzi et al., 2016). These data may help  
40  
41 in amending existing treatment recommendations, and rationalizing treatment modalities  
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43 for these drugs in the respective countries.  
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47 As of mid-2017, this project is being replicated, with a special focus on South East  
48  
49 Asian populations, under the umbrella of the Global Genomic Medicine Collaborative  
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51 (G2MC) Pharmacogenomics Working group and includes 8 South East Asian populations,  
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53 mostly from developing countries (**Table 1**). The *100 Pharmacogene Resequencing*  
54  
55 *Project* will focus on the resequencing of 100 pharmacogenes in a large number of healthy  
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3 donors of South East Asian descent. Genotyping will be performed at the RIKEN Institute  
4 in Japan, using the whole pharmacogene resequencing panel and will include genotyping  
5 of the HLA genes and *CYP2D6* gene amplification. Healthy donors from Europe and the  
6 Gulf Cooperation Council (GCC) countries will be analyzed as controls. This project is  
7 anticipated to yield important benefits for the participating countries, including (a) capacity  
8 building, (b) harmonizing education activities, (c) performing economic evaluations to  
9 determine whether certain genome-guided treatment modalities are cost-effective, (d)  
10 motivating the replication of these studies in these populations using a much larger  
11 population sample, and (e) making people aware of the clinical value of  
12 pharmacogenomics.  
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25 In addition to the burden of Communicable disease such as HIV and malaria, nearly  
26  $\frac{3}{4}$  of newborns with Sickle Cell Disease (SCD) are born in Africa (Piel et al., 2013)  
27 indicating the urgent need in this setting to further accelerate research on  
28 pharmacogenomics, that could ultimately improve the prevention of disease and patient  
29 care. Fortunately, emerging genomics research involving African scientists are improving  
30 our knowledge of genomic modifiers of SCD, that will be useful for anticipatory guidance  
31 in clinical practice (Makani et al., 2011, Wonkam and Hurst, 2014, Geard et al., 2017).  
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## 43 **Rethinking the linear model of innovation for genomics without borders**

### 44 **A Fast-Second Winner development strategy**

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48 The linear model of innovation has been a dominant framework that has guided and  
49 shaped scientists' and innovators' approach to scientific breakthroughs. The linear  
50 innovation model commences from discovery science and proceeds in a linear fashion  
51 toward translational research, in its various phases, then on to implementation science  
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3 followed by innovation diffusion and capacity building. This model does not take into  
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5 account that innovations may, sometimes if not always, arise out of user needs. More  
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7 importantly, the linear model creates a tendency to commence innovations from discovery  
8  
9 science which in some cases may not be feasible with limited resources. Innovations by  
10  
11 definition are unprecedented practices and products and as such, innovators often fail and  
12  
13 their mistakes can inform other innovators who may have fewer resources or who cannot  
14  
15 afford to fail because they have limited financial or technical resources.  
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18  
19 Building on the above context, and the fact that innovations and innovators can  
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21 commence “innovating” not only upstream but also “midstream”, we propose here a new  
22  
23 long-term development strategy termed the “Fast-Second Winner” mode of innovation  
24  
25 **(Fig. 1)**.  
26

27  
28 The Fast-Second Winner model recognizes the pressing public health priorities and  
29  
30 disease burdens of individual countries and supports midstream innovations that build  
31  
32 upon emerging highly promising biomarker and diagnostic candidates from global science.  
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34 Importantly, a mid-stream entry into innovation can enhance collective learning from other  
35  
36 innovators’ mistakes upstream in discovery science and boost the probability of success for  
37  
38 translational and implementation science when resources are limited. Hence, this *à la carte*  
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40 model of global innovation offers multiple entry points into global genomics innovation  
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42 ecosystem for developing countries, whether or not extensive discovery infrastructure is  
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44 already in place.  
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48 This is contrary to investing in ALL aspects of innovation horizontally from  
49  
50 discovery infrastructure to translation to implementation science in a given country, which  
51  
52 is not only expensive but also does not serve well the unique needs of each country. Lastly,  
53  
54 to be able to apply a second rapid model of innovation, one needs some kind of an  
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56 innovation observatory, which can best identify the emerging candidate markers or drug  
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3 and marker combinations and suggest them to various countries, filtering and distilling  
4  
5 them through a given country's own public health needs.  
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## 10 11 **Other capacities necessary for genomics without borders**

### 12 13 **Raising genomics awareness among healthcare professionals**

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19 One of the key elements to ensure efficient integration of genomics into clinical  
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21 practice is to enrich health professionals' genomics knowledge. At present, a typical  
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23 practicing physician has only very limited training in genetics. Healthcare professionals'  
24  
25 lack of genetics knowledge coupled with the lack of awareness on the part of patients and  
26  
27 the general public about the benefits of genetic information, leaves individuals confused as  
28  
29 to which test might be beneficial in their own particular case. Participation in genomics  
30  
31 conferences would contribute to improving healthcare professionals' genomics education.  
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35 To this end, there are a plethora of genomics conferences that are organized in  
36  
37 various countries worldwide. However, registration and tuition fees to attend these  
38  
39 conferences, that are mostly organized in the United States and Western Europe, are  
40  
41 prohibitively expensive for participants originating from developing countries and low-  
42  
43 resource environments, such as South East Asia, the Middle East, South and Central  
44  
45 Europe, Africa and Latin America. There has thus been an urgent need to establish a series  
46  
47 of Conferences in Genomic Medicine and Pharmacogenomics, where high scientific  
48  
49 quality coupled with affordable registration fees would attract participants from the  
50  
51 developing world.  
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55 Ideally, if high profile academics and researchers were invited as plenary and  
56  
57 keynote speakers to genomics conferences organized in these regions, this would in turn  
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3 attract corporate and charitable entities as sponsors of these scientific events, which would  
4  
5 reciprocally reduce the overall registration fees, thereby making these meetings more  
6  
7 affordable for participants from developing countries. Moreover, organizing such  
8  
9 conferences in different venues and with different themes related to Genomic Medicine,  
10  
11 would reduce the logistical burden and make it easier and more cost-effective for  
12  
13 participants from developing countries to attend.  
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16  
17 The above advances and considerations gave rise to the concept of the Golden  
18  
19 Helix<sup>®</sup> Conferences, as high level scientific summits focusing on themes pertaining to the  
20  
21 fields of genomics, pharmacogenomics and personalized medicine. In brief, the Golden  
22  
23 Helix<sup>®</sup> Conferences aimed to advance genomics worldwide under three interlinked themes  
24  
25 of interest to precision medicine without borders:  
26

- 27  
28 • **The Golden Helix Symposia** (<http://symposia.goldenhelix.org>) range in length  
29  
30 from 2 to 4 days, with an average attendance of 450 participants (ranging from  
31  
32 250 to 900 participants). Conferences are usually held in an environment outside  
33  
34 the mainstream settings that is conducive to multidisciplinary thinking and  
35  
36 collaboration.  
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- 38  
39 • **The Golden Helix Pharmacogenomics Days**  
40  
41 (<http://pharmacogenomicsdays.goldenhelix.org>) are international educational  
42  
43 event series organized in major cities with tertiary academic healthcare facilities.  
44  
45 The aim of this event is to provide timely updates on the field of  
46  
47 pharmacogenomics to local biomedical scientists and healthcare providers.  
48  
49 Contrary to the Golden Helix Symposia, the Golden Helix Pharmacogenomics  
50  
51 Days have a more educational ethos, span between a half-day to a full day in  
52  
53 length, and address on average 150 participants. Registration is free-of-charge,  
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3 attracting mostly local scholars but also participants from neighboring countries  
4  
5 and regions.  
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- 7 • **The Golden Helix Summer Schools** (<http://summerschools.goldenhelix.org>) are  
8  
9 a new forum in the Golden Helix<sup>®</sup> Conference series. Established conceptually in  
10  
11 2013, and jointly organized under the umbrella of the Golden Helix Foundation  
12  
13 and the Genomic Medicine Alliance, the Golden Helix Summer Schools are 5-  
14  
15 day long international educational activities, usually organized in the summer  
16  
17 period to allow attendance by scholars in training and others, that aim to provide  
18  
19 a unique academic program, catalyzing collaborations and opening up future  
20  
21 training opportunities for participants.  
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27 Since November 2008, when the 1<sup>st</sup> Golden Helix Symposium<sup>®</sup> was organized in  
28  
29 Athens, Greece, there have been 32 Golden Helix Conferences that have been organized in  
30  
31 27 major cities in 18 different countries in Europe, the Americas, the Middle East, Africa  
32  
33 and South East Asia, attracting more than 6000 participants from more than 100 countries  
34  
35 from all five continents, from students to senior academics and researchers; several  
36  
37 participants have registered to attend recurrent events, an indication of the impact of these  
38  
39 gatherings. The concept of the Golden Helix<sup>®</sup> Conferences represents a paradigm of a  
40  
41 well-designed and coordinated effort to improve the genomics education of healthcare  
42  
43 professionals, specifically addressing the needs of participants from developing countries.  
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47 Furthermore, to enable smoother integration of genomics into medicine, there is a  
48  
49 need to raise genomics awareness of patients and the general public. To this end, Genome  
50  
51 British Columbia coordinates such a dedicated initiative, known as Geneskool  
52  
53 (<https://www.genomebc.ca/education/outreach-programs>). This program focuses on  
54  
55 providing basic genomic education and awareness to children from 9<sup>th</sup> to 12<sup>th</sup> grade,  
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3 including classrooms and full day campus workshops, traveling suitcase exhibits and  
4  
5 summer science programs for teens. Similar initiatives were also developed in Mexico, in  
6  
7 an effort to engage the young Mexican public on issues of genomic medicine, where  
8  
9 INMEGEN (<http://www.inmegen.gob.mx>) has developed a comic book series on genomic  
10  
11 medicine.  
12

13  
14 At the same time, the seamless incorporation of genomic medicine into clinical  
15  
16 practice is hindered by insufficient genomics education, which is not uniformly provided in  
17  
18 the various academic institutions worldwide (Mai et al., 2014, Mitropoulou et al., 2014,  
19  
20 Pisanu et al., 2014). By analyzing a large number of post-graduate and undergraduate  
21  
22 curricula in 98 Universities in 11 South Eastern European countries, Pisanu and coworkers  
23  
24 have shown that there are major discrepancies in the provision of pharmacogenomics  
25  
26 education, compared to the situation in North Western Europe (Pisanu et al., 2014). Such  
27  
28 studies might provide the basis to harmonize pharmacogenomics education in South East  
29  
30 European countries with those of North West European countries with a view to bringing  
31  
32 about a smoother integration of pharmacogenomics into mainstream medical practice.  
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### 38 **Genomic Medicine and Public Health**

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40 Integration of genomics research findings into medicine is a multistep approach  
41  
42 that depends upon several disciplines mostly related to public health. Such disciplines  
43  
44 include addressing the ethical, social and legal issues pertaining to genomic medicine,  
45  
46 assessing the educational needs of healthcare professionals, both at the undergraduate and  
47  
48 postgraduate levels, as far as genomic medicine is concerned, and precisely mapping the  
49  
50 environment of the stakeholders and decision makers that are involved in genomic  
51  
52 medicine. In this latter case, there are several key players and stakeholders, whose  
53  
54 genomics awareness and views vary significantly; hence, performing a systematic mapping  
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3 of these views and different genomics awareness levels should impact positively on our  
4  
5 better understanding of the policy environment as well as the role of the relevant key  
6  
7 stakeholders in the field.  
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9  
10 Previously, Mitropoulou and coworkers have assessed the level of support (or  
11  
12 opposition) to pharmacogenomics and genomic medicine in Greece (Mitropoulou et al.,  
13  
14 2014). These authors have shown that the majority of the stakeholders, namely academic  
15  
16 and research institutions, biomedical scientists, physicians, geneticists, biotechnology and  
17  
18 pharmaceutical companies, to name a few, have a positive attitude to genomic medicine. It  
19  
20 is however noteworthy that the Ministry of Health and the Public Health insurance funds  
21  
22 are more skeptical as far as implementation of genomic medicine is concerned, most likely  
23  
24 due to the large initial investment and reimbursement requirements.  
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27  
28 A similar project is currently under way in the UAE. In particular, the main aims of  
29  
30 this project are to: (a) investigate the state of genomics education in the UAE, by assessing  
31  
32 the pharmacogenomics educational environment in undergraduate and post-graduate  
33  
34 University and college curricula, (b) assess the level of genomics education of  
35  
36 undergraduate students, residents and specialized physicians, (c) assess the level of  
37  
38 awareness of healthcare professionals and the general public as far as genomic medicine is  
39  
40 concerned, and (d) survey the currently available provisions for implementing genomic  
41  
42 medicine and pharmacogenomics. To this end, there is a productive partnership between  
43  
44 the Zayed Bin Sultan Center for Health Sciences (United Arab Emirates University) and  
45  
46 the Golden Helix Foundation (see above). This is the first time that such a project will have  
47  
48 been implemented in the UAE and the GCC countries in general, allowing the canvassing  
49  
50 of the genomic medicine environment in the UAE and ultimately extending this project  
51  
52 into neighboring GCC countries with the aim of harmonizing genomics education and the  
53  
54 provision of genomic medicine in the UAE and the GCC countries in general.  
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3 Similarly, a Public Health Genomics project is planned, in parallel to the 100  
4 Pharmacogene Resequencing Project in South East Asia (see above), and in partnership  
5 with the Golden Helix Foundation, so that the benefits of the pharmacogenomic analysis in  
6 these populations can be maximized. As with the related project already running in the  
7 UAE, this parallel project will include: (a) mapping the pharmacogenomics educational  
8 environment in the participating countries in South East Asia, and (b) raising  
9 pharmacogenomics awareness among healthcare professionals by organizing scientific  
10 conferences and other educational activities, similar to those described above.  
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21 Regrettably, in Africa, the proportion of medical professionals with a thorough  
22 understanding of human and medical genomics is still relatively low. An attempt in sub-  
23 Saharan Africa to triangulate the views of multiple stakeholders related to prenatal  
24 diagnosis of SCD revealed several discrepancies that usefully inform future policy actions  
25 (Wonkam and Hurst, 2014). In fact, scientists originating from Africa are participating in  
26 studies focusing on the genomics of monogenic diseases (Mercier et al., 2013, Mtatiro et  
27 al., 2014, Wonkam et al., 2014, Wonkam, 2015) and multifactorial conditions (Tekola  
28 Ayele et al., 2012), with findings that are expected to assist the effective practice of  
29 genomic medicine, that is well established in South Africa (Beighton et al., 2012), in some  
30 Northern African countries (Chaabouni-Bouhamed, 2008, El-Beshlawy et al., 2012) and  
31 recently initiated in Central Africa (Wonkam et al., 2011).  
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45 In addition, the knowledge of the nature of pathogenic variants of various  
46 monogenic conditions among people of African Ancestry needs to be accelerated, for the  
47 purpose of molecular diagnosis in clinical setting, taking advantage of the power of next  
48 generation sequencing technologies. For example, recent data have shown that *GJB2* and  
49 *GJB6* pathogenic variants that account for nearly 50% of causes on Non-Syndromic  
50 Hearing Impairment in populations of European and Asian descent, are virtually  
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3 nonexistent among Africans (Wonkam, 2015). In a small group of 10 families, the use of  
4 targeted panel sequencing, including 116 hearing impairment genes, have identified mostly  
5 novel pathogenic variants in 7/10 families in Cameroon, indicating the opportunity for  
6 novel variants and gene discovery in Africa (Lebeko et al., 2016).  
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### 13 14 **Economics in Genomic Medicine**

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17 Genome-guided drug treatment modalities are expected to reduce national healthcare  
18 expenditure (Snyder et al., 2014). To date, the scientific discipline of economic evaluation  
19 in genomic medicine, pharmacogenomics and public health genomics is still poorly  
20 developed. However, there are several studies that have demonstrated that genotype-guided  
21 therapy can not only be cost-effective but may also help to improve the quality of life of  
22 the patients. The most remarkable example related to resource-limited countries comes  
23 from the Thai population, where it has been previously shown that HLA-B\*15:02-guided  
24 carbamazepine treatment is cost-effective compared to conventional treatment and can  
25 reduce the incidence of Stevens-Johnson syndrome/Toxic Epidermal Necrolysis  
26 (SJS/TEN), a severe carbamazepine-induced adverse drug reaction (Grosse, 2008,  
27 Rattanavipapong et al., 2013). Similar results were also obtained for the Singaporean  
28 population (Dong et al., 2012).  
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45 A few studies have aimed to assess the cost-effectiveness of genome-guided  
46 interventions in cardiology. In particular, Mitropoulou and coworkers attempted  
47 prospectively to evaluate the cost-effectiveness of warfarin treatment in Croatian elderly  
48 ischemic stroke patients with atrial fibrillation (Mitropoulou et al., 2015). These authors  
49 have shown that pharmacogenomics-guided warfarin treatment represented a cost-effective  
50 therapeutic option for the management of these patients, with an estimated incremental  
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3 cost-effectiveness ratio of the pharmacogenomics-guided versus the control groups of  
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5 €31,225/QALY (Quality-Adjusted Life Year). Additionally, a retrospective economic  
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7 analysis of genome-guided clopidogrel treatment in Serbia indicated that  
8  
9 pharmacogenomics-guided clopidogrel treatment may represent a cost-saving approach for  
10  
11 the management of myocardial infarction patients undergoing primary percutaneous  
12  
13 coronary intervention (Mitropoulou et al., 2016). Such analyses would also be facilitated  
14  
15 by the development of standardized methodologies for the economic evaluation of  
16  
17 genome-guided interventions (Fragoulakis et al., 2016, Fragoulakis et al., 2017), which, in  
18  
19 addition to the already existing economic evaluation models in genomic medicine, will be  
20  
21 of the utmost importance as innovative tools for performing cost-effectiveness analyses in  
22  
23 such a rapidly evolving discipline.  
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28 Lastly, the issue of pricing and reimbursement in genomic medicine is a  
29  
30 cornerstone for the incorporation of genomics into clinical medicine, given the lack of  
31  
32 harmonization between pricing and reimbursement policies between European countries,  
33  
34 contrary to the situation pertaining in the United States (Logue, 2003). In Europe, very few  
35  
36 countries (e.g. the Netherlands, the United Kingdom, Switzerland) reimburse genetic  
37  
38 testing services, while other countries clearly lag behind. As such, the general strategy  
39  
40 towards pricing and reimbursement for genomic medicine should first be outlined,  
41  
42 providing an overview of the rationale and basic principles guiding the governance of  
43  
44 genomic testing services, clarifying their objectives, and allocating and defining  
45  
46 responsibilities among and between stakeholders, focusing on different EU countries'  
47  
48 healthcare systems.  
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51  
52 Particular attention should be paid to issues pertaining to pricing and  
53  
54 reimbursement policies, the availability of essential genomic tests which differ between  
55  
56 various countries owing to differences in disease prevalence and public health relevance,  
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3 the prescribing and use of genomic testing services according to existing or new  
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5 guidelines, budgetary and fiscal control, the balance between price and access to  
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7 innovative testing, monitoring and evaluation for cost-effectiveness and safety, and the  
8  
9 development of research capacity (Vozikis et al., 2016). Subsequently, it is hoped that a  
10  
11 more technical analysis will lead to the introduction of a robust policy in relation to pricing  
12  
13 and reimbursement in genomic medicine, thereby contributing to an effective and  
14  
15 sustainable health-care system with benefits to the economy at large.  
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### 20 21 **Building regional and global genomic medicine research networks**

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23 Synergizing efforts among researchers with common research interests from  
24  
25 various parts of the world could significantly expedite efforts to bring genomic medicine,  
26  
27 as with every other discipline, closer to fruition (Manolio et al., 2015).  
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29  
30 The Genomic Medicine Alliance (GMA; <http://www.genomicmedicinealliance.org>)  
31  
32 was established in mid-2013 with the primary goal of developing a global network  
33  
34 focusing on the translation of genomic knowledge into clinical use, with a special focus on  
35  
36 the participation of developing countries and of resource-limited settings. The GMA has  
37  
38 several unique features as a research network, in which it differs from existing consortia  
39  
40 and initiatives in this field (Cooper et al., 2014). First, membership is free of charge, which  
41  
42 is important to attract members from developing countries. Second, it has a flat governance  
43  
44 structure, comprising the Scientific Advisory and the Steering Committees. Third, this  
45  
46 network has a stated goal and commitment to bring together genomics research institutions  
47  
48 from developing countries with those from developed countries (Cooper et al., 2014).  
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52 The GMA aims to: (a) Encourage and catalyze multidisciplinary collaborative  
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54 research between partner institutions and/or scientists, with at least one partner affiliated  
55  
56 with an institute in a developing country, (b) Liaise between research organizations,  
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3 clinical entities and regulatory agencies on topics related to genomic medicine, (c)  
4  
5 Facilitate the introduction of pharmacogenomics and advanced 'omics technologies and  
6  
7 analyses into mainstream clinical practice, (d) Propose international guidelines and draw  
8  
9 up recommendations for activities pertaining to genomic medicine, in close collaboration  
10  
11 with other scientific academic entities, agencies and regulatory bodies, and (e) Develop  
12  
13 independently and coordinate, in close collaboration with partner institutions, educational  
14  
15 activities in the sphere of genomic medicine (Cooper et al., 2014). GMA research activities  
16  
17 span seven different Working Groups, namely Genome Informatics, Pharmacogenomics,  
18  
19 Cancer Genomics, Rare Diseases, Public Health Genomics, Genethics and Economic  
20  
21 Evaluation in Genomic Medicine. Each of the Working Groups' activities are coordinated  
22  
23 by the corresponding Working Group and Activity leaders.  
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27  
28 Consistent with one of the stated goals of the GMA, namely the fruitful  
29  
30 engagement between research groups from both developing and developed countries to  
31  
32 study families with rare diseases or unique clinical features (especially countries with a  
33  
34 higher incidence of consanguinity and/or well-defined founder populations), the GMA  
35  
36 actively participates in the DRIFT (Discovery Research Investigating Founder Population  
37  
38 Traits) Consortium. In early 2016, a call for research collaboration was made by the  
39  
40 Regeneron Genetics Center (RGC) and the GMA, aimed specifically at developing  
41  
42 countries. DRIFT aims to understand the genetic architecture of founder populations  
43  
44 throughout the world with direct impact on human health and disease. The DRIFT  
45  
46 Consortium aims to catalogue population-specific allelic architecture, with a view to  
47  
48 understanding the biological and functional consequences of specific genomic variants  
49  
50 identified, and to sharing best-practice approaches to relieve disease burden in these  
51  
52 populations. Ever since its establishment, the expansion of the GMA membership base has  
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54 progressed at a very rapid pace, currently comprising over 1,300 members from >70  
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3 countries worldwide, from academia as well as from corporate and regulatory sectors,  
4  
5 including developing countries in the Middle East, Asia and Latin America.  
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7 The Human Variome Project (HVP; <http://www.humanvariomeproject.org>) is an  
8  
9 international non-governmental organization that is working to ensure that all information  
10  
11 on genetic variation and its effect on human health can be collected, curated, interpreted  
12  
13 and shared freely and openly (Kaput et al., 2009). The Human Variome Project provides a  
14  
15 central coordinating function for national and international efforts to integrate the  
16  
17 collection, curation, interpretation and sharing of information on variation in the human  
18  
19 genome into routine clinical practice and research. HVP members number over 1,100  
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21 individual researchers, healthcare professionals, policy makers and organizations coming  
22  
23 from 81 countries that collaborate to develop and maintain the necessary standards,  
24  
25 systems and infrastructure to support global-scale genomic knowledge sharing.  
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29 The HVP aims to: (a) Collaboratively develop technical standards and harmonized  
30  
31 common approaches so that data from different sources can be easily shared in an  
32  
33 interoperable manner that is sensitive to the ethical, legal and social requirements of both  
34  
35 the data sources and consumers; (b) Coordinate an international platform to facilitate  
36  
37 discussion of genomics in global health with the aim to fostering necessary professional  
38  
39 interaction and debate in the area of genomics, global health, service delivery and safety;  
40  
41 (c) Link world leading professionals and institutions with genomics professionals,  
42  
43 researchers, and academics in all parts of the world, facilitating knowledge exchange and  
44  
45 interactive debate, and (d) Establish a global evidence base for knowledge sharing in  
46  
47 medical genetics and genomics and bringing relevant issues to the attention of Ministries  
48  
49 of Health, Science and Technology and Education.  
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53 At the same time, the SEAPharm Consortium (<http://www.pharmagct.org>) is a  
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55 regional pharmacogenomics network in South East Asia, consisting of leading researchers  
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3 from Japan, Korea, Taiwan, Malaysia, Indonesian and Thailand that share knowledge and  
4  
5 experience in pharmacogenomics research. The network organizes its annual meeting each  
6  
7 year and envisages the achievement of sustainable pharmacogenomics research, so that  
8  
9 South East Asian countries can liaise and work together in conducting clinical studies for  
10  
11 various drugs, which can be effective and safe for the 560 million South East Asians.  
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14 There are also other important international efforts, such as the Global Alliance for  
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16 Genomics and Health (GA4GH; <http://www.ga4gh.org>), the Human Genome Organization  
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18 (HuGO; <http://www.hugo-international.org>) and the Global Genomic Medicine  
19  
20 Collaborative (G2MC; <http://www.g2mc.org>). These organizations have various activities  
21  
22 related to genomic and precision medicine, such as genomic data sharing (GA4GH),  
23  
24 implementation of genomic medicine (G2MC), with activities that are also relevant to  
25  
26 resource-limited countries. The activities of these organizations have been outlined  
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28 elsewhere and as such lie outside the scope of this article.  
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## 34 Discussion

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39 The implementation of genomic medicine does not always progress at a uniform  
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41 pace in all parts of the world. There are countries, like the United States and countries in  
42  
43 Northern Europe, where genomic medicine is being implemented at a more rapid pace,  
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45 depending on different factors, such as the sufficient genetic literacy of healthcare  
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47 professionals, state-of-the-art infrastructure and established reimbursement rules for  
48  
49 genetic testing and legislation governing the use of genetic tests. Nevertheless, there are  
50  
51 several examples of the successful implementation of genomic medicine applications in  
52  
53 countries that do not fall into the previous category and can be considered as developing or  
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55 low-resourced countries from South East Asia, the Middle East and Latin America. In  
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3 these countries, the genomic medicine applications are mostly confined to those genetic  
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5 conditions that are prevalent in the region and hence may constitute a significant health  
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7 and/or economic burden for these countries.  
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9 Carriers of the *HLA-B\*1502* allele receiving carbamazepine treatment may develop  
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11 Stevens-Johnson syndrome/Toxic Epidermal Necrolysis (SJS/TEN) (Chung et al., 2004,  
12  
13 Borchers et al., 2008) and the same is true for carriers of the *HLA-B\*5801* allele who may  
14  
15 develop severe cutaneous adverse reactions (Hung et al., 2005), when treated with  
16  
17 allopurinol. In Taiwan, the value of pharmacogenomics in tailor-made therapeutics has  
18  
19 been acknowledged and, following a large prospective clinical study that confirmed the  
20  
21 benefit of *HLA-B\*1502* genotyping to identify subjects at genetic risk for the  
22  
23 abovementioned conditions (Chen et al., 2011), the Taiwanese government began to  
24  
25 reimburse the genotyping costs as of 2010.  
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29 In South East Asia and in Thailand in particular (Ramathibodi Hospital; Bangkok),  
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31 a pharmacogenomics card was adopted to summarize patients' HLA gene variant  
32  
33 information to predict the risk of developing SJS/TEN. Such pharmacogenomics cards  
34  
35 have also been used in other settings and clinical studies, such as the PREPARE study of  
36  
37 the Ubiquitous Pharmacogenomics (U-PGx) Consortium ([www.upgx.eu](http://www.upgx.eu)) and could be  
38  
39 readily applied in the context of tailor-made therapeutics.  
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43 In the UAE, following pharmacogenomics research into the role of variants in the  
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45 *G6PD* gene and their association with drug-induced hemolytic anemia (Bayoumi et al.,  
46  
47 1996) and the prevalence of *NAT2*, *CYP2D6*, *CYP2C9* and *VKORC1* pharmacogenomic  
48  
49 variant allele frequencies in the Emirati population (Woolhouse et al., 1997, Qumsieh et  
50  
51 al., 2011, Fortina et al., 2014, Al-Gazali et al., 2016), Dubai Hospital was prompted to  
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53 integrate pharmacogenomics information for chemotherapeutic agents, while the UAE  
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55 Health Authority policy of reporting adverse drug reactions in the UAE currently requires  
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3 expert pharmacogenomics recommendation within the first 24 hours related to each  
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5 adverse drug reaction reported (<http://www.haad.ae>). Similarly, raising pharmacogenomics  
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7 awareness among healthcare professionals is currently gathering momentum in other  
8  
9 Middle Eastern countries, such as Oman (Pathare et al., 2012), Saudi Arabia (Abu-Elmagd  
10  
11 et al., 2015), Lebanon (Ossaily and Zgheib, 2014) and Qatar (Elewa et al., 2015).  
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14 In Latin America, the National Institute of Genomic Medicine (INMEGEN;  
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16 <http://www.inmegen.gob.mx>) was built in Mexico as a capacity building effort to establish  
17  
18 infrastructure for research and educational activities for Genomic Medicine, not only for  
19  
20 Latin America but also for the wider Latin American region. In Africa, the burden of  
21  
22 HIV/AIDS, tuberculosis and malaria is disproportionately high compared to other  
23  
24 countries/regions, and genomic data have been used to show that several genetic variants  
25  
26 can provide increased resistance or susceptibility to HIV infections (Sirugo et al., 2008),  
27  
28 while the variability observed in the patterns of genomic variations in the CYP genes  
29  
30 among African populations has also been used to rationalize drug use (Dandara et al.,  
31  
32 2014). The above constitute some of the most successful examples of the implementation  
33  
34 of genomic medicine in resource-limited countries, while other examples have been also  
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36 reported with significant impact on the provision of medical services in developing  
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38 countries (Mitropoulos et al., 2015; Lopez-Correa and Patrinos, unpublished).  
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## 45 **Conclusions and Outlook**

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50 The implementation of genomic medicine in resource-limited environments can be  
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52 a difficult and lengthy process, which could deprive less privileged populations of the  
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54 benefits that genome-guided interventions have to offer. Given the scarcity or even lack of  
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56 resources in developing countries, the implementation of genomic medicine can only be  
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3 realized in these environments under certain conditions. First of all, generation of primary  
4 data in under-equipped research institutions may be a challenging task. As such, and as far  
5 as advancement of genomics research is concerned, strategic partnerships should be  
6 established with research entities from developed countries, which are likely to create  
7 benefits for all parties involved. Not only will developing countries benefit from the  
8 various training opportunities that will be created in addition to knowledge transfer, but  
9 developed countries may benefit too, through participation in multicenter projects to study  
10 cases and individuals with unique clinical features and/or rare diseases (Cooper et al.,  
11 2014, Manolio et al., 2015).  
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23 On the implementation front, it would be highly beneficial for developing countries  
24 to prioritize their efforts towards implementing actionable genomic medicine interventions,  
25 including but not limited to pharmacogenomic tests, genetic testing for the highly prevalent  
26 inherited conditions, which differ dramatically around the world. Therefore, country-,  
27 population- and region-specific data and research are needed. At the same time, it seems  
28 reasonable for decision makers and policymakers to invest an equal amount of effort into  
29 expanding the public health aspects of genomic medicine interventions, such as (a)  
30 mapping the stakeholders' environment and their opinions and stance related to genomics,  
31 (b) enacting new legislation and measures to set out a legal framework for the provision of  
32 genetic services, so that quality is ensured and the general public and the patients are  
33 safeguarded, and (c) adopting guidelines for the reimbursement of genetic tests, based on  
34 related cost-effectiveness analyses.  
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49 Lastly, if for some countries, the acquisition of expensive genomic technology and  
50 equipment may seem unrealistic, investment in continuous genomics education of  
51 healthcare professionals and biomedical scientists would be far easier and with a short- to  
52 medium-term return on such investment. Continuous genetics education can be provided to  
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3 both graduate professionals that should be encouraged to attend, from which  
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5 certificates/diplomas will be obtained and also to undergraduate students, by harmonizing  
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7 the university curriculum with those of other developed countries, which could be used as  
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9 paradigm for this purpose. In all of the above, synergies should be sought not only with  
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11 renowned academics and institutions from developed countries but also with entities from  
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13 other developing countries that have successfully implemented genomic medicine  
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15 interventions.  
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19 Human genomics promises to transform medical practice around the world. Much  
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21 attention has been focused on developed countries where most research leading to  
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23 Genomic and Precision Medicine is performed. However, resource-poor developing  
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25 countries also have the potential to adopt genomic medicine. Therefore, we strongly  
26  
27 believe that the examples described in this article could be readily replicated by other  
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29 countries with a view to expediting their transition to the genomic medicine era, by  
30  
31 harmonizing their strategies and policies with those of various other national healthcare  
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33 systems that already enjoy the tangible benefits of genomics. Clearly, the inclusion of other  
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35 omics into Precision Medicine will further contribute to these developments.  
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39 Ultimately, broadening our thinking beyond the linear model of innovation, to  
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41 encompass such models as the Fast-Second Winner model of knowledge-based innovation,  
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43 should help enable the vision and practice of genomics without borders in both developed  
44  
45 and resource-limited settings.  
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10

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19  
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21  
22 Medicine Alliance.  
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### 25 26 27 28 **Alphabetical list of abbreviations**

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32 CFSI: Centers for Fast-Second Innovation

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34 GWAS: Genome Wide Association Studies

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37 SCD: Sickle Cell Disease  
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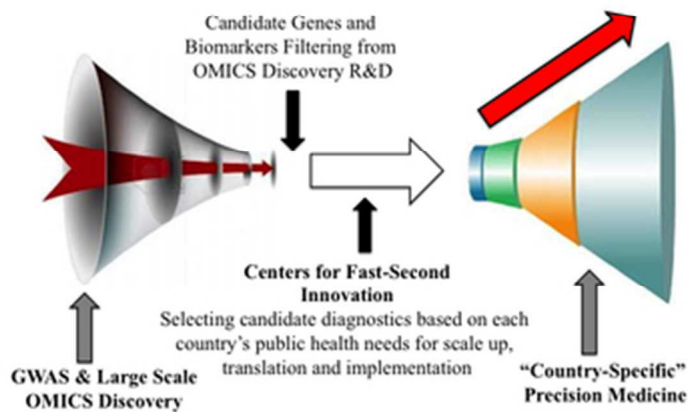
## 18 **Figure Legend**

### 19 **Figure 1.**

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23  
24 Outline of the Fast-Second Winner model, as an *à la carte* innovation model to tailor  
25 global genomic and personalized medicine development in a country-specific manner.  
26  
27 Please note that this model is not only based on wet-lab scientific aspects but also, and  
28 most importantly, applies to other public health-related process of implementing genomics  
29 in clinical practices that involve many different aspects (cost effectiveness analysis,  
30 education, local health priorities, etc.  
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**Fast-Second Winner Strategy for Genomics and Precision Medicine without Borders**



Outline of the Fast-Second Winner model, as an à la carte innovation model to tailor global genomic and personalized medicine development in a country-specific manner.

15x11mm (600 x 600 DPI)



**Table 1.** Features of the two large population pharmacogenomics projects, conducted in developing countries. <sup>a</sup>: Refers to 3 South African sub-populations, <sup>b</sup>: Sample collection is expected to begin in fall 2017.

<b>Study</b>	<b>No. of populations</b>	<b>No. of samples</b>	<b>Reference</b>
<b>Population</b>			
<b>Euro-PGx project</b>			
<b>European</b>	18	1105	<b>Mizzi et al., 2016</b>
Saudi Arabian	1	499	
South African	3 <sup>a</sup>	106	
<b>100 Pharmacogene Resequencing Project <sup>b</sup></b>			
<b>Southeast Asian</b>	8	800	<b>Ongoing</b>
European	3	300	
Latin American	3	300	
Middle Eastern	2	200	