

Personalized and Predictive Medicine in Turkey: A Symposium Report of the Istanbul Working Group on Personalized Medicine, Istanbul, Turkey, September 10-12, 2009

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Abstract: Pharmacogenetics has its roots in the 1950s with pioneering studies of monogenic variations in drug metabolism and pharmacokinetics. With the availability of high-throughput genomics technologies and the completion of the Human Genome Project in 2003, we are now in the postgenomics era. This transition is increasingly marked with study of polygenic and multifactorial traits such as common complex human diseases as well as pharmacodynamic differences among populations. Changes that emerge from postgenomics medicine are not, however, limited to seismic shifts in scale and scope of pharmacogenetics research. Importantly, many low- and middle-income countries (LMICs) of the South, Asia-Pacific, Eastern Mediterranean and the Middle-East are becoming notable contributors with rapid globalization of science and increasing access to genomics technologies. This brings about, in parallel, an acute demand for regional capacity building in LMICs so that the future evaluation and implementation of postgenomics technologies in personalized medicine take place in an integrated, sustainable and equitable manner. With this overarching vision, we herein report the founding of the Istanbul Working Group in Personalized Medicine (IWG-PM, represented by the authors of this report) that was inaugurated as a component of the 2nd Symposium on Personalized and Predictive Medicine held in Istanbul, sponsored by the Yeditepe University, and the Turkish Scientific and Technological Research Council (TUBİTAK) (10-12 September, 2009). While highlighting the applications of personalized medicine in oncology, psychiatry, nutrition, infectious diseases, occupational health, genetic testing and systems biology, the symposium also raised challenging questions in the context of LMICs. How can we best evaluate the promises, intended and unintended impacts of personalized medicine and enabling technologies in the context of Turkey, and the LMICs more generally? IWG-PM is a small but significant and necessary step to initiate regional capacity building in Turkey. We trust that the IWG-PM initiative may also provide a constructive example to further develop capacity in other LMICs in the Eastern Mediterranean region.

Keywords: Lower and middle income countries, LMICs, personalized medicine, pharmacogenomics-guided pharmacovigilance, regional capacity building.

1. INTRODUCTION

The era of postgenomics medicine arrived with the completion of the Human Genome Project in 2003, exactly 50 years after the discovery of DNA by Watson and Crick. An important conceptual shift in this period is a greater emphasis on "prediction/prevention" of future health outcomes (e.g., disease susceptibility, response to health interventions)

with use of individual genetic/genomics information. A corollary is that preventive and customized interventions and diagnostic tests may now be conceptualized (and in some cases implemented) during the presymptomatic phase of a disease or before pharmacotherapy is initiated. The concept of prevention represents the next step in the development of the "predictive medicine" as conceived by Jean Dausset, one of the three winners of the Nobel Prize in Physiology/Medicine in 1980. Dausset has suggested the term "predictive medicine" as a prerequisite step for preventive medicine [1]. Subsequently in 1993, Jacques Ruffie offered a more comprehensive definition for the term, and laid the philosophical basis for this new field in a book entitled

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"Naissance de la Médecine Prédictive" (Birth of Predictive Medicine) [2]. Today, the term "predictive medicine" is replaced by one that is more precise: "personalized medicine" enabled by the introduction and availability of high throughput genomics technologies

In the present postgenomics era, we are witnessing the increasing applications of genomics technologies in multiple sectors of health. The genomics science has now left the laboratory space and rapidly diffusing to many segments of the global society not only in North America and Western Europe but also in many other global regions and countries [3-7]. Importantly, a number of low- and middle-income countries (LMICs) are firmly engaged in large-scale genotyping projects to discern the genetic diversity among their populations and apply such knowledge to discovery of health interventions in the form of novel pharmaceuticals, vaccines and companion diagnostics to customize their targeted optimal use [3-7]. It is anticipated that both discovery and development of medicines and their postmarketing pharmacovigilance can substantially benefit from the availability of mechanistic biomarkers of drug treatment outcomes.

Notwithstanding these real promises that may come to fruition in the postgenomics era, technologies, alone, do not invariably translate into tangible public health or socioeconomic benefits unless sound and integrated science, regulatory and innovation frameworks are developed in parallel, along with the capacity to independently design and interpret appropriately targeted investments in postgenomics medicine [4, 8, 9]. Socio-ethical and policy issues surrounding postgenomics medicine are also varied and dynamic which collectively reflect the complexities of the underlying science and technologies [9]. Even with the resources of developed countries of the North, these issues are difficult to resolve. There is therefore reason for concern that developing countries and LMICs may be left behind, further augmenting the already existing genomics gap relative to developed countries. Moreover, when new technologies become available in LMICs, there is potential risk that they can be applied in a piecemeal fashion without adequate regulatory oversight and local capacity to evaluate the benefits and limitations while taking into account the unique needs and priorities of their population health.

2. EXECUTIVE HIGHLIGHTS AND SUMMARY OF THE SYMPOSIUM

Against this background of the growing confluence of postgenomics medicine with pharmacogenomics and personalized medicine applications in LMICs, we herein report the founding of the Istanbul Working Group in Personalized Medicine (IWG-PM, represented by the authors of this report). The IWG-PM was conceived and inaugurated as a component of the 2nd Symposium on Personalized and Predictive Medicine held in Istanbul (10-12 September, 2009). The primary aim of the IWG-PM is to serve as a "seminal nucleus" and launching platform to initiate and develop capacity and expertise in pharmacogenomics and personalized medicine in Turkey. We submit that Istanbul, by virtue of its

strategic geographical location situated between the developed countries and the LMICs and as a "postmodern transition zone" bridging the east and the west, as well as its growing population and technological expertise in diagnostic medicine is well poised to serve this overarching aim. The IWG-PM is represented by the authors of this report and includes membership to establish liaisons with other regions of the country (e.g., the Aegean Province, and others to be enlisted in the near future) and the European countries. The symposium was sponsored by the Yeditepe University and the Scientific and Technological Research Council of Turkey (TUBITAK). This scientific event was attended by approximately 300 undergraduate and graduate students in biomedicine, Yeditepe University medical faculty, the regional industry, government and academic representatives who shared an interest in personalized medicine, genomics and pharmacovigilance. While highlighting the applications of personalized medicine in oncology, psychiatry, nutrition, infectious diseases, occupational health, genetic testing and systems biology, the symposium also raised challenging questions in the context of LMICs. How can we best evaluate the promises, intended and unintended impacts of personalized medicine and enabling technologies in the context of Turkey, and the LMICs more generally? Are there lower hanging fruits in personalized medicine research that can be effectively translated to tangible applications and products to benefit population health in Turkey and LMICs?

The symposium opened with an introductory lecture by **Inci Ozden** (Yeditepe University, İstanbul) who pointed out the significance of predictive and personalized medicine and pharmacogenomics in public health. The symposium chair **Candan Hizel** (C2H-Vichy Genomics, France and Yeditepe University, İstanbul) provided an in-depth sketch of the context and framework for the symposium. Together with the local academic chair of the symposium **Ece Genç** (Yeditepe University, İstanbul), Hizel emphasized the need for regional capacity building in personalized medicine in Turkey at this critical transition point to postgenomics medicine. In his lecture, Hizel explained the importance of interaction between human genome and the environment in study of multifactorial common complex diseases (e.g., in oncology), drug efficacy and safety, as opposed to previous dichotomy of "nature versus nurture" in late 1990s. The significance of focusing pharmacogenomics research on the narrow therapeutic window anticancer drugs was further emphasized as a measure to prioritize limited research funds in the context of LMICs. This was considered important in light of the growing epidemic of noncommunicable diseases in LMICs, in addition to traditional and long-standing concerns such as infectious diseases. To these ends, specific examples were provided regarding the uridine diphosphate-glucuronyltransferase 1A1 polymorphism (*UGT1A1**28 allelic variation) and irinotecan toxicity such as neutropenia and severe diarrhea in metastatic colorectal cancer. He also spoke on the impact of *CYP2D6* polymorphism on poor outcome during tamoxifen adjuvant therapy because of the reduced active metabolite endoxifen plasma concentration in women who

are CYP2D6 poor metabolizers. The importance of balanced and objective interpretation of pharmacogenetic test results was emphasized further.

Ece Genç (Yeditepe University, İstanbul) delivered a speech on drug metabolism and targeted pharmacotherapy. She emphasized the significance of absorption, distribution, biotransformation and elimination (pharmacokinetics) for rational and customized development of drugs in different global regions and human populations. In her concluding remarks, she commented on the inducibility and inhibition of CYP450 enzymes by various xenobiotics and the attendant role of human genetic variation for these complex phenotypes.

Semra Sardaş (Marmara University, Istanbul), as Chair of the Pharmacovigilance Scientific Advisory Board of Turkish Ministry of Health, provided an in-depth and intersectoral account on the confluence of pharmacovigilance and pharmacogenomics. She presented the new term “pharmacogenovigilance” to express the marked role of genetic factors in identification, monitoring and remedy of “medication incidents” in the course of pharmacotherapy, particularly in the postmarketing phase of pharmaceutical use. She provided examples on the role of human genetic variation in drug metabolizing enzyme genes as a susceptibility factor to adverse drug reactions and lack of drug efficacy. It became evident that active and high level participation and support at the regional and national government level would be timely and necessary to establish a model leadership in public health and health diplomacy in this important intersection of post-genomics medicine and pharmacovigilance. She explained the pharmacovigilance systems in an international context, and introduced the Pharmacovigilance Center of Turkey (TUFAM) founded in 2003 [10]. She underscored that there is sadly underreporting of adverse drug reactions by healthcare professionals in Turkey.

Esra Sağlam (Maltepe University, Istanbul), presented the concepts pertinent for “Individualized Treatment in Psychiatry.” She described that although pharmacotherapy has been an important component of the treatment of depressive disorders, it is often associated with inadequate response and/or severe antidepressant drug related side effects. She additionally provided clinically relevant examples of pharmacogenomics variation in schizophrenia focusing on drugs such as clozapine, risperidone, quetiapine and haloperidol.

Dominique Bernard-Gallon (Département d'Oncogénétique du Centre Jean Perrin, France) spoke on the importance of nutrition and breast cancer by providing examples on the effect of phytoestrogens such as genistein and daidzein on changes in mRNA expression after knockdown of BRCA1 or BRCA2 with siRNA in tumor breast cell lines subsequent to treatment with these nutrients. Results obtained by pangenomic microarrays, and confirmed with Taqman Low Density Array (TLDA), indicated that phytoestrogens might exhibit chemopreventive properties in breast cancer by modulating expression of molecular pathways involved in car-

cinogenesis such as cell communication, apoptosis, xenobiotic metabolism and angiogenesis.

Tamir Kocagöz (Acibadem University, İstanbul) lectured on the important contribution of advances in genomics and proteomics biotechnologies for diagnosis, prevention and treatment of infectious diseases endemic in Turkey, and provided detailed background information to investigate the immune response of the host against infectious agents. He emphasized the importance of multidrug-resistant tuberculosis as an important illness affecting the populations in LMICs including Turkey. He also observed that inappropriate anti-tuberculosis treatment, particularly at the beginning of the disease, is a major cause of drug resistance. Hence, efforts for early diagnosis of individuals at risk for treatment resistance would be an important aid to optimize therapy for tuberculosis.

Christine Maugard (Université de Montreal, Montreal, Hôpitaux Universitaires de Strasbourg), in her lecture entitled “Genetics of Breast Cancer”, summarized the characterization of *BRCA1* and *BRCA2* mutations in the French-Canadian population of Quebec. She emphasized that some of the findings offer the promise of pharmacogenomics applications in high-risk families. She noted that there is an urgent need to improve the early detection tools in women who are carriers of *BRCA1/2* mutations.

Selma Dejgaard (McGill University, Canada) presented on the visualization technologies in cell biology with a view to applications in personalized medicine. She described recent research on identification of the Rab and Arf-family GTPase coordinating membrane trafficking pathways in the endoplasmic reticulum/Golgi system by confocal microscopy. She proposed that similar microscopy-based approaches could be applied for screening and diagnostic purposes and for diagnostic assays as a complement to molecular genomics approaches.

Vural Ozdemir (University of Montreal, Canada) presented a public health based analysis of the omics technology applications (e.g., pharmacogenomics, nutrigenomics and ecogenomics) and the need for establishing a credible evidence base for the growing armamentarium of genomics tests that are often provided direct-to-consumer. In addition, he also noted that the regulatory frameworks from the genetics age are no longer sufficient to understand the nuances of genomics medicine, and for efficient transition of genomics discoveries to genomics products that are equitably available in the clinic.

Nezih Hekim (Pakize Tarzi Laboratories, İstanbul), in his talk on systems biology and personalized medicine, highlighted the need and importance of systems biology for describing quantitatively the interactions among the individual components of the cell and the whole organism. The ultimate aim of such an approach is to develop computational models of these complex systems so that the response of a biological system to any kind of environmental or physiological perturbation can be comprehensively described and predicted as an

essential prerequisite foundation for personalized medicine and prediction of host responses to drugs and other health interventions such as nutrition. It was deemed that conceptual and technical advances in systems biology are important for developing countries to effectively apply complex quantitative approaches and algorithms to personalize drug treatment in the future.

Aysen Fenercioğlu (Yeditepe University, İstanbul), in her talk on “Significance of Pharmacogenetics in Drug Efficacy Studies”, gave a thorough summary of the history of human genetic variation and responses to xenobiotic exposures, pointing out early examples of hemolytic anemia produced after consumption of fava beans, the phenylthiourea nontasting phenotype and the genetic control of drug acetylation. Interestingly, she also explained the clinical significance of measuring 14-hydroxy clarithromycin concentrations and how the ratio of 14-hydroxy clarithromycin to clarithromycin could be used as an interpretation of genetic variation in drug bioequivalence studies.

Ahmet Demirkazık (Ankara University, Ankara) delivered a lecture on approaches to cancer therapeutics in the postgenomic era. He pointed out that although recent breakthroughs in diagnostic technologies identified several novel genomic markers that predict inter-individual variability in anticancer drug response, pharmacogenomics will only be incorporated into routine clinical practice when it is used in a cost-effective way. He emphasized the importance of pharmacogenomics testing especially in determining the toxicity of chemotherapeutics, such as 5-fluorouracil, irinotecan, thiopurine and in determining the therapeutic response to treatment with specific drugs such as imatinib, rituximab, and gefitinib.

Hilmi Sabuncu (Yeditepe University, İstanbul) gave an in-depth analysis of the genetics/genomics risk factors in occupational health and occupational exposures to xenobiotics. He also stressed the need for comprehensive data and databases on occupational diseases in Turkey. In order to improve occupational hazards impacted by human genomic variation, Dr. Sabuncu suggested that genetic testing may play a role in the near future in Turkey.

3. CONCLUSIONS AND FUTURE OUTLOOK

The symposium was an important starting point for establishing a pharmacogenomics and personalized medicine knowledgebase in İstanbul and Turkey, as genomics technologies continue to rapidly diffuse to various known and remote regions of the world. Without regional scientific, technical, regulatory and socio-ethical expertise, postgenomics medicine may stall in its progress and the existing genomics gaps can be markedly widened around the globe. We trust that the IWG-PM initiative may also provide a constructive example to further develop capacity in other LMICs in the Eastern Mediterranean region. The IWG-PM will strengthen the translational bridges between medical research in pharmacogenomics and its applications in clinical practice by providing physicians, academics, biotechnology

and pharmaceutical industry, government policy makers and other stakeholders with an important regional resource. To this end, we wish to emphasize, as noted in the introduction, genomics should be viewed through a lens of population and public health to move beyond a simplistic focus on biotechnology. Hence, expertise in both genomics technologies as well as regional capacity to design rational pharmacogenomics studies and interpretation of genomics tests will be crucial. Equally important is to devise strategies to effectively integrate social and biological (including genomics) determinants of health considering the unique health and socioeconomic priorities and the limited resources of developing countries and the LMICs. Even though presently in its infancy, the IWG-PM is a small but significant and crucial step to initiate regional capacity building in Turkey and integrate local and international expertise in personalized medicine.

ACKNOWLEDGMENTS

The 2nd İstanbul Symposium on Personalized and Predictive Medicine was supported by grants-in-aid from the Yeditepe University and the Scientific and Technological Research Council of Turkey (TÜBİTAK). The authors thank Yeditepe University Board of Trustees, Professors Ayca Vitrinel (Dean, School of Medicine, Yeditepe University) and Ahmet Serpil (President, Yeditepe University) for feedback and enthusiastic support for the development of the Symposium and the IWG-PM. The views expressed herein reflect the personal views of the authors only and do not necessarily represent the position of the affiliated institutions or the symposium sponsors.

DUALITY/CONFLICT OF INTERESTS

None declared/applicable.

ABBREVIATIONS

IWG-PM	= İstanbul Working Group in Personalized Medicine
LMIC	= Low- and middle-income country
TUFAM	= Pharmacovigilance Center of Turkey

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Received: September 28, 2009

Revised: October 12, 2009

Accepted: October 14, 2009