Journal of Genomic Medicine and Pharmacogenomics

JGMP, 1(1) www.scitcentral.com

Original Editorial: Open Access



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Received July 29, 2016; Accepted July 30, 2016; Published July 31, 2016

Personalized medicine could be the teleological consummation of the medical aphorism "there are no diseases, but only sick persons" (attributed to Claude Bernard (1813-1878) or Samuel Hahnemann (1755-1843)), preached in the faculties of medicine and ignored in medical centers. The actual implementation of personalized medicine would provide the coordinates of the Holy Grail of a medical practice of excellence; but this feasible reality stumbles over the force of habit, bogged down in restorative medicine instead of predictive medicine, aimed at identifying the risks so as to avoid their consequences. This paradigm shift represents the first fundamental step, a change in mindset and procedures, necessary in order to embark on the path of a true personalized medicine (without medical marketing ornamentation).

The practice of medicine, in all its modalities, has never been as near this possibility as now, thanks to the huge advances of Genomic Medicine, based on the knowledge derived from the research of the Human Genome and the attractive field of epigenomics. The three great contributions of genomic medicine to the medical practice focus on pathogenesis, diagnosis and treatment, the key goals of any good medicine since the time of Hippocrates (400 BCE).

Structural and functional genomics, transcriptomics, proteomics and metabolomics are today the essence of the etiopathogenic knowledge. Currently, only 10% of the primary causes responsible for human pathology appear to be known. If we do not know the pathogenetic mechanisms underlying the clinical manifestation of a particular disease, we can hardly diagnose it reliably and much less deal with it efficiently. About 80% of common complex diseases of the adult (cardiovascular disorders, cancer, pathologies of the central nervous system), which contribute to over 75% of morbidity and mortality worldwide, are associated with multiple genomic defects that make a person more or less vulnerable. A golden rule of human genomics in complex disorders establishes that the larger the number of genetic defects distributed across the human genome, the greater the

chance of developing a disease, the faster its clinical course, and the poorer the therapeutic response to conventional treatments; in contrast, the lesser the number of vulnerable genetic loci, less risk, later onset, slower course and more favorable therapeutic response to treatment. This challenging postulate should stimulate health authorities and the medical community to invest in predictive measures in order to be preventive rather than restorative when dealing with human health.

Predictive diagnosis by means of biomarkers of high reliability is the basis on which any preventive approach can be founded. Without predictive ability there is no possible prevention. At present, over 90% of human diseases lack reliable biomarkers for an early diagnosis. Therefore, this is an urgent need for molecular diagnosis to become a mature discipline in genomic medicine.

In general, pharmaceutical treatment accounts for 15-25% of direct costs in most diseases. From a therapeutic point of view, the vast majority of drugs we prescribe is only effective in 20-30% of cases, with the consequent waste of health expenses in useless and/or toxic drugs. In this regard, the implementation of Pharmacogenomics to customize treatment is an unavoidable challenge for the pharmaceutical industry, the Regulatory Agencies, and the medical community.

The genes responsible for the effectiveness, resistance or toxicity of any medication are framed into several categories:

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Citation: Cacabelos R. (2016) Genomic Medicine: A Conceptual Revolution in Medical Practice? J Genomic Med Pharmacogenomics, 1(1).

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(i) pathogenic genes (associated with disease pathogenesis); (ii) mechanistic genes (associated with the mechanism of action of the drug), (iii) metabolic genes (encoding the enzymes responsible for the metabolism of a drug; phase I and phase II enzymes), (iv) transporter genes (encoding transporter proteins for the influx/efflux of xenobiotics, with special importance in cancer and in the penetration of drugs into the brain through the blood-brain barrier), and (v) pleiotropic genes (which act in different metabolic pathways with multifunctional activity). All these genes are under the control of the epigenetic machinery (DNA methylation, histone modifications, chromatin changes, microRNA regulation) which regulates their normal or abnormal expression, thus contributing to drug efficacy and safety. In practice, most complex disorders exhibit epigenetic anomalies which are particularly relevant in different types of cancer.

About 80% of the Caucasian population are deficient metabolizers for haplotypes integrating polymorphic variants of the *CYP2D6*, *CYP2C9*, *CYP2C19* and *CYP3A4/5* genes, responsible for the metabolism of over 60-70% of common drugs of current use in the world. This indicates that when we prescribe a drug by trial-and-error, neglecting the pharmacogenetic profile of the patient, the possibility of being wrong (causing toxicity or ineffectiveness) is greater than 60% in the majority of the diseases treated with conventional drugs.

This reality, which scares some and motivates others, is what genomic medicine is uncovering for the medical practice to experience a qualitative leap in terms of efficacy and safety. As novelty scares off weak people and provokes defensive reactions in those with conflict of interest, some theoretical thinkers hide behind the fallacy that the implementation of genomic medicine would be unacceptable due to unpredicted costs. The truth is located in the opposite pole of this erroneous concept. The extra cost of the pharmaceutical expenditure due to inefficiency or toxicity is estimated to be over 40% of the cost of the initial inappropriate medication. The implementation of pharmacogenetic procedures to customize drug treatment, in the mid-term would cause a reduction in the net pharmaceutical expenditure of close to 20-30% in chronic patients with expensive long-term treatments.

The use of molecular diagnostic biomarkers will be replacing many unspecific techniques in current use and questionable value, without having to result in an increase in the differential cost of more than 5% per decade, for in the next decade technology costs will decrease by 35% or more (as happened with mobile phones or telecommunications, in general).

The pharmaceutical industry will have to get used to developing new custom drugs whose clinical trials will include each patient pharmacogenetic profile. This will save lives in experimental trials. It will also preclude the condemnation of some valuable drugs, potentially safe in a minority of patients with a defined genotype-related pathology, which can be lethal when administered to other genomically defective patients. Pharmacogenomics will help the pharmaceutical industry to cultivate the loyalty of patients; and physicians will know with a high degree of certainty which medication must be prescribed to a particular patient and the medication whose prescription should be avoided in other patients with a defective pharmacogenetic profile. And all this is capable of happening without additional costs, unnecessary repetitive tests or routine procedures of doubtful prognostic value, since the pharmacogenetic profile is screened once and lasts forever.

This vision of the future of medical practice does not imply a conceptual revolution. It is just a marvelous opportunity for those who wish to incorporate the novel tools that genomic medicine can provide for optimizing our medical resources to the benefit of our patients. It is also very likely that many expectations related to the potential impact of genomic medicine in human health will turn into frustration and disenchantment due to an excess of unfounded scientific optimism. When this happen it will be necessary to look back and see if the project was destined to fail or if the conductors were not skillful enough to manage its potential for a successful destination. As pointed out by William Osler (1849-1919), 'Medicine is a science of uncertainty and an art of probability'; and genomics, methodologically, is a probabilistic approach to health and disease.

I hope that the Journal of Genomic Medicine and Pharmacogenomics will become an open-minded intellectual vehicle for turning genomic science into an efficient and updated tool for optimizing Personalized Medicine.