Genomic Medicine:
the reconceptualization of health and disease

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These are times of change and reconceptualization in medical science, education, politics and economics. Healthcare expenditure is becoming a major political and economic problem in the developed world, especially in the USA and the EU. In some European countries, the cost of healthcare is causing a global bankruptcy in the public sector. Pharmaceutical expenditure represents about 10-20% of total healthcare costs. Spending on pharmaceuticals throughout the OECD countries has increased by over 35% since 2000. The health expenditure share of the GDP in OECD countries remains about 6-9%. OECD pharmaceutical spending was over $650 PPP in 2010, with significant differences among countries. These international differences in drug expenditure, in part, also reflect similar differences in applied health technology, the furtherance of science and scientific production, together broadening the inequalities among countries and enhancing the economic disequilibrium aggravated by the global crisis in which the engines of the world economy are now immersed. This circumstance will undoubtedly affect the implementation and/or maintenance of national healthcare programs, the cost of drugs, new investments in drug development and budgetary decisions in medical science.

The heroic task of the pioneering leaders of the Human Genome has crystallized into the conceptual revolution which substantiates the foundations of a modern, innovative genomic medicine. Genomic medicine is not fulfilling the naïve expectations created 20 years ago; however, the future of genomic medicine will be brilliant and indispensable for the progress of medical praxis in the short- and medium-terms. Health priorities have changed in Western countries. A clear shift from acute diseases (e.g. infections) to chronic diseases (e.g. degenerative disorders) has been observed over the past 50 years in developed countries. In the USA, death rates for the leading causes of death are heart disease (200.2 per 100,000), cancer (180.7 per 100,000), and stroke (43.6 per 100,000). The aging of the population is modifying the medical epidemiology of many developed and developing economies. Dementia is becoming a major problem of health, and concomitant pathologies are highly common among patients with dementia. In countries with low and middle income, dementia makes the largest contribution to disability with a prevalence of 25.1%, followed by stroke (11.4%), limb impairment (10.5%), arthritis (9.9%), depression (8.3%), eyesight problems (6.8%) and gastrointestinal impairments (6.5%). Approximately 20% of patients with Alzheimer's disease are hypertensive, 25% are diabetic, 50% are hypercholesterolemic, and 23% are hypertriglyceridemic. Over 25% of the patients exhibit some degree of liver dysfunction, 5-10% show anemic conditions, and 30-50% have some cerebrovascular dysfunction. Significant differences are currently seen between females and males, indicating the effect of gender on the phenotypic expression of the disease. Elderly patients may take 6-12 different drugs per day, with the consequent risk for adverse drug reactions and side-effects associated with drug interactions.

The major challenges of genomic medicine are concentrated around 4 main areas: (i) pathogenesis, (ii) diagnosis, (iii) treatment and (iv) prevention. The pathogenic mechanisms underlying human diseases are largely unknown; our understanding of major complex disorders is deficient because the pathogenesis of these diseases is poorly defined in more than 80% of the cases. We lack predictive markers of disease (many years before the onset of the disease); and medical diagnosis is based on clinical symptoms (phenotypes) devoid of accurate biomarkers (except for infectious diseases and a few other medical conditions). In many cases, diagnosis is late and inaccurate. In global terms, pharmacological

treatment is effective in only 20-30% of the cases. It is expected that genomic medicine will help us to develop predictive markers for an early diagnosis, assuming that in over 70-80% of complex disorders the clinical phenotype is the result of a defective genomic background in conjunction with environmental factors and epigenetic phenomena. Without predictive biomarkers, prevention is a difficult task, if not impossible. Since treatment and the search for health conditions is the final goal of any medical process, it is reasonable to predict that one of the first priorities of genomic medicine might be the implementation of programs for a personalized treatment. Among genomic factors, nutrigenomics and pharmacogenomics may account for more than 80% of efficacy-safety outcomes in current therapeutics.

To achieve substantial goals, genomic medicine has to rely on structural genomics, transcriptomics, functional genomics, proteomics, epigenetics, and metabolomics, together with bioinformatics and high-tech diagnostic tools. Structural genomics would define the cartographic disposition and polymorphic variation of genes associated with human disease. Over 12,000 of the 35,000 genes which integrate the human genome might be assigned to specific traits, either Mendelian or susceptibility traits. Functional genomics would show the influence of genes on disease pathogenesis and phenotype expression. Transcriptomics and proteomics would help to elucidate the role of abnormal gene expression in the pathogenesis of a particular disease. Epigenetics refers to phenotypic changes with no apparent alterations in structural DNA. Classical epigenetic mechanisms, including DNA methylation, histone modifications, and regulation by microRNAs (miRNAs), are among the major regulatory elements that control metabolic pathways. Epigenetic modifications are reversible and can potentially be targeted by pharmacological and dietary interventions. The metabolome is the repertoire of biochemicals present in cells, tissues, and body fluids, whose dysfunctional interactions may lead to disease pathogenesis. Mitochondrial DNA abnormalities and aberrant interactions between mtDNA and nuclear DNA products are also subtle fields to be investigated in genomic medicine with repercussions in human disease.

Our understanding of the pathophysiology of complex disorders (cardiovascular disorders, cancer, or CNS disorders, representing 60-80% of the major causes of death) has advanced dramatically over the last 30 years, especially in terms of their molecular pathogenesis and genetics. The drug treatment of complex disorders has also made remarkable strides, with the introduction of many new drugs. Improvement in terms of clinical outcome, however, has fallen short of expectations, with up to one third of the patients continuing to experience clinical relapse or unacceptable medication-related side-effects in spite of efforts to identify optimal treatment regimens with one or more drugs. Potential reasons to explain this historical setback might be that: (i) the molecular pathology of most complex disorders is still poorly understood; (ii) drug targets are inappropriate, not fitting into the real etiology of the disease; (iii) most treatments are symptomatic, but not anti-pathogenic; (iv) the genetic component of most complex disorders is poorly defined; and (v) the understanding of genome-drug interactions is very limited.

The optimization of therapeutics requires the establishment of new postulates regarding (i) novel strategies for drug development (a reduction in the time to reach the market, identification of optimal targets, pharmacogenetic-oriented methodologies), (ii) the cost of medicines, (ii) the assessment of protocols for multifactorial treatment in chronic disorders, (iii) the implementation of novel therapeutics addressing causative factors, and (iv) the setting-up of pharmacogenomic strategies for drug development and drugs in current use.

The pharmacogenomic outcome depends upon many different determinant factors including (i) genomic profile, (ii) disease phenotype, (iii) concomitant pathology, (iv) genotype-phenotype correlations, (v) nutritional conditions, (vi) age and gender, (vii) pharmacological profile of the drugs, (viii) drug-drug interactions, (ix) gene expression profile, (x) epigenetic modifications, (xi) transcriptomic cascade, (xii) proteomic profile and (xiii) metabolomic networking. The dissection and further integration of all these factors is of paramount importance for the assessment of the pharmacogenomic outcome in terms of safety and efficacy.

Significant advances have expedited the introduction of pharmacogenomic approaches in drug development and also in clinical practice to optimize therapeutics; however, pharmacogenomics is still in a very primitive stage. Personalized therapeutics requires a better understanding of the effects of drugs on gene expression in pathogenic cascades, and the influence that different genes and their products exert on the fate of drugs before, during and after impacting with pathogenic targets. At least 5 different categories of genes are potentially involved in the pharmacogenomic process: (i) genes associated with disease pathogenesis, (ii) genes associated with the mechanism of action of a particular drug (e.g. synthesizing enzymes, catabolizing enzymes, receptor genes), (iii) genes associated with phase I (CYPs) and phase II reactions (UGTs, GSTs, SULTs, NATs), (iv) genes associated with transporters (ABCs, SLCs, OATs), and (v) pleiotropic genes involved in multifaceted cascades and/or genes associated with concomitant pathologies. Over 100 genes may be involved in the therapeutic outcome associated with the efficacy and safety of a specific drug.

The vast majority (78%) of the 200 most prescribed drugs in the USA are metabolized via enzymes of the cytochrome P450 family (CYPs), with major contributions from CYP3A4/5 (37% of drugs) followed by CYP2C9 (17%), CYP2D6 (15%), CYP2C19 (10%), CYP1A2 (9%), CYP2C8 (6%), and CYP2B6 (4%). The genes encoding CYP2D6, CYP2C19, CYP2C9, and CYP3A4/5 isoenzymes are highly polymorphic, with great allelic variation in different ethnic groups. These genes are very promiscuous, influencing the metabolism of different drugs. Very few drugs use an exclusive metabolic pathway for their degradation and subsequent elimination. About 10,600 genes (of the 5 categories previously referred) may participate in the metabolism of 1,392 drugs approved by the FDA, EMEA, and Koseisho. CYP3A4/5 participates in the metabolism of 525 drugs (37.71%), CYP2D6 in 315 (22.63%), CYP2C9 in 287 (20.62%), CYP2C19 in 244 (17.53%), and ABCB1 in 272 (19.54%). Of 7,742 chemicals studied, 982 drugs have been related to CYP2D6 metabolism, of which 205 drugs have been characterized as major substrates, 166 as minor substrates, 75 as strong inhibitors, 183 as moderate inhibitors, 117 as weak inhibitors, and 18 drugs as inducers; 691 drugs have been related to CYP2C9 metabolism (177 major substrates, 134 minor substrates, 102 strong inhibitors, 181 moderate inhibitors, 92 weak inhibitors, and 41 inducers); 576 drugs have been related to CYP2C19 metabolism (151 major substrates, 130 minor substrates, 64 strong inhibitors, 127 moderate inhibitors, 72 weak inhibitors, and 23 inducers); and 1,937 drugs have been related to CYP3A4/5 metabolism (897 major substrates, 136 minor substrates, 141 strong inhibitors, 437 moderate inhibitors, 118 weak inhibitors, and 241 inducers). ABCB1 is a very important transporter, with 1,214 related drugs (897 major substrates, 136 minor substrates, 141 strong inhibitors, 437 moderate inhibitors, 118 weak inhibitors, and 241 inducers).

Multidrug resistance is a major obstacle to successful cancer treatment. An important mechanism by which oncogenic cells may become resistant to chemotherapy is the epigenetically regulated expression of transporter proteins that transport a wide variety of substrates across the cell membrane.

Clinicians currently have no way of predicting who will respond appropriately to a given drug, and the paradigm of trial-and-error is especially distressing for patients with chronic disorders and/or severe acute illness. Pharmacogenetic association studies may provide insight into which genetic polymorphisms might be clinically relevant for personalizing pharmacotherapeutic regimens. In the Western population, only 25% of its members are extensive metabolizers (EM) for the trigenic cluster integrated by CYPs 2D6+2C19+2C9, the most relevant genes (and enzyme products) involved in drug metabolism, together with CYP3A4/5. The other 75% of the population is potentially at risk for developing adverse drug events due to defective variants encoding deficient enzymes which give rise to intermediate (IM), poor (PM) or ultra-rapid metabolizers (UM). This population cluster of defective metabolizers requires dose adjustment to avoid side-effects and, in the case of PMs, the administration of another drug with alternative metabolic pathways should be the norm in order to avoid toxicity.

Ethnic differences must be taken into consideration when developing new drugs or when prescribing

drugs which were tested in different ethnic groups. Although global clinical trials can enable the development of new agents efficiently, whether the results of clinical trials performed in one population can be fully extrapolated to another population remains highly questionable due to clear ethnic differences associated with genotype-related drug metabolism. Therefore, pharmacogenomic differences associated with individual responses to drugs should be carefully considered when conducting clinical trials or when prescribing drugs for chronic disorders.

To achieve a mature discipline of pharmacogenomics it would be convenient to accelerate the following processes: (i) educating physicians and the public on the use of genetic/genomic screening in the daily clinical practice; (ii) the standardization of genetic testing for major categories of drugs; (iii) the validation of pharmacogenomic procedures according to drug category and pathology; (iv) the regulation of ethical, social, and economic issues; and (v) the incorporation of pharmacogenomic procedures to both drugs in development and drugs on the market, in order to optimize therapeutics.

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Can we sustain an ageing population?

With people living longer, and health systems under strain, Adjacent Government looks at the worldwide impact of an aging population...

The World Health Organization (WHO) predicts that between now and 2050, the number of people over the age of 60 worldwide is likely to rise, from 11% in 2000 to 22%. The proportion of over 60s is expected to increase from 605 million to 2 billion over the same period. The biggest concern with these figures is the detrimental impact an aging population can have on our health systems.[1]

In November 2014, Dr John Beard, Director of the Department of Ageing and Life Course at WHO warned that, "Deep and fundamental reforms of health and social care systems will be required." [2]

As people reach age 75 and over, the risk of chronic diseases can increase. It is estimated that around 25-30% of people aged 85 or older will have some degree of cognitive decline, such as dementia. If we continue to see a rise in the number of people that can no longer look after themselves, it will have a huge bearing not only on social care services, but also the economy.

For the first time in history, it is predicted that by 2020 the number of people aged 60 or over will outnumber the number of children aged under 5. Worldwide expectancy will continue to rise with 80% of these older people believed to be living in low-income and middle-income countries, says The World Health Organization (WHO). The long-term challenges of illness and reduced wellbeing will not only affect the patient, but also their family. With forecasts predicted to accelerate, latest estimates indicate that the number of people with dementia is anticipated to rise further, from 44 million in 2014, to 135 million in 2050.

Dr Ties Boerma, Director of the Department of Health Statistics and Informatics at WHO said, "We must be careful that these reforms do not reinforce the inequalities that drive much of the poor health and functional limitation we see in older age.

"While some interventions will be universally applicable, it will be important that countries monitor

the health and functioning of their ageing populations to understand health trends and design programmes that meet the specific needs identified."

Dr Boerma added: "Cross-national surveys such as the WHO study on Global Ageing and Adult Health (SAGE), the Gallup World Poll, and other longitudinal cohorts' studies of ageing in Brazil, China, India and South Korea, are beginning to redress the balance and provide the evidence for policy, but much more remains to be done."

WHO believes that strategies are needed to help prevent and better manage chronic conditions that blight ageing populations. "Collectively, we need to look beyond the costs commonly associated with ageing to think about the benefits that an older, healthier, happier and more productive older population can bring to society as a whole," added Dr Chatterji, also from the Department of Health Statistics and Information Systems at WHO.

Francesca Colombo, Head of the Health Division at the OECD told Adjacent Government [3] that she believes an ageing population is "an opportunity," and that we need "to take ageing as something to celebrate."

She believes that encouraging healthier lifestyles early in life can help to prevent the development of chronic diseases, and other disabilities. However she explained it is vital services do not become over stretched to help deal with the ageing population.

She said: "Health systems must adapt to changing patterns of morbidity and disease burden. Health systems across the OECD are still too much hospital focused and struggle to innovate approached to care for an ageing population.

"The way health systems have developed is more orientated towards the treatment of disease and dealing with acute episodes of care, rather than focussing on preventing ill health, managing chronic care needs and encouraging continuity of care."

She added that GPs and primary care providers should play a more central role, working alongside community health and social care services.

WHO have launched a draft 'Global Strategy and Action Plan on Ageing and Health' [4] The Strategy aims to define the goals, strategies and actions that WHO will pursue, and to clearly lay these out for public health action. With the Strategy WHO aim to provide a comprehensive framework for action on ageing and health, identify gaps and suggest future priorities.

Strategic objectives for the next 5 years are:

- Fostering healthy ageing in every country;
- Aligning health systems to the needs of the older populations;
- Developing long terms care systems;
- Creating age-friendly environments;
- Improving measuring, monitoring and understanding.

The draft Strategy is currently open for consultation, and an updated version is to be presented to the WHO Executive Board in January 2016.

[1] http://www.who.int/ageing/about/facts/en/

[2] http://www.who.int/mediacentre/news/releases/2014/lancet-ageing-series/en/

[3] http://www.adjacentgovernment.co.uk/lg-edition-007/adapting-ageing-population-2/20387/

[4] http://www.who.int/ageing/global-strategy/GSAP-ageing-health-draft.pdf?ua=1

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World Guide for Drug Use and Pharmacogenomics

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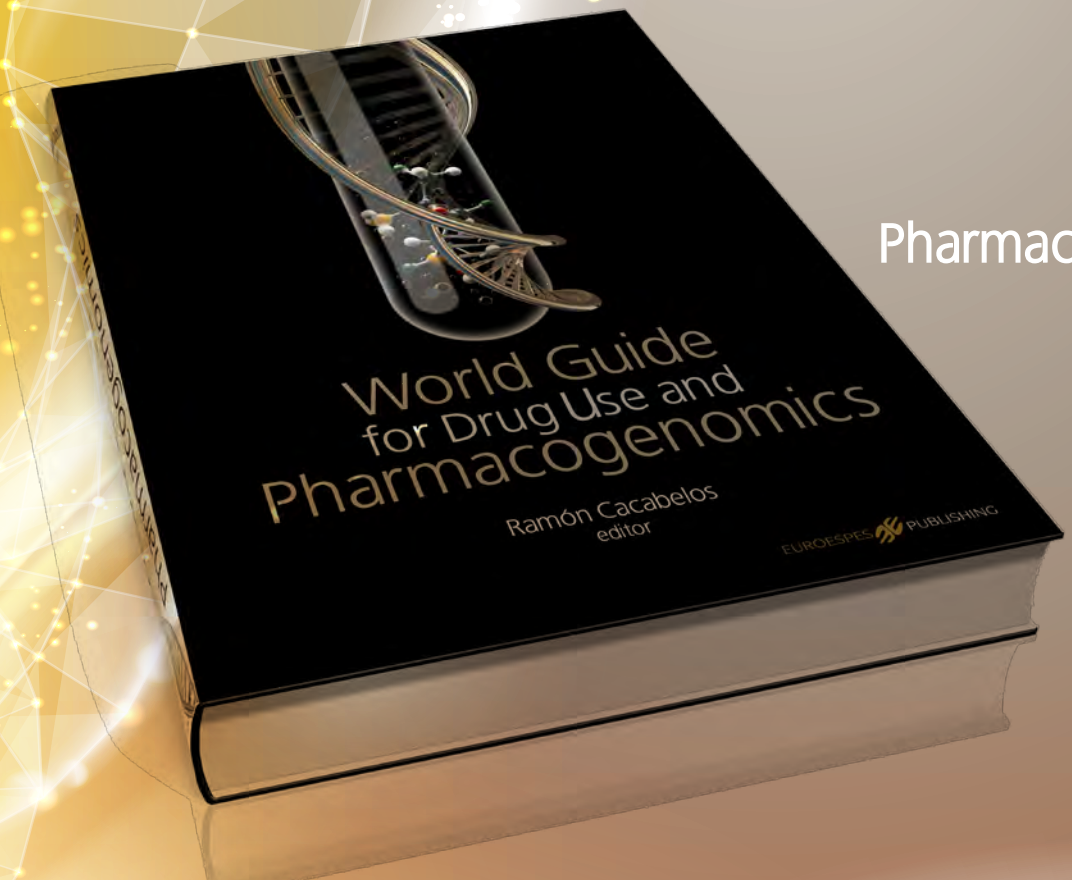

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