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Application of Genomic Technologies in Clinical Pharmacology Research

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ABSTRACT

Technology is the basis of scientific progress and is an essential component for continued competitiveness in industry. The development of a new drug candidate is a long and expensive process, in which a molecule undergoes several stages of research (both pre-clinical and clinical) before being approved for commercialization. Scientific progress has revolutionized the pharmaceutical industry and reshaped the processes by which new drugs are discovered, investigated, and developed. Currently, the influence of genomic variations in drug metabolism must be better understood to predict an individual´s response to a given treatment. Employing genomics tools, an individual's genetic profile may be obtained and used as the basis for prescription of the best treatment option, thus personalizing medicine. In this review, we discuss how current mainstream genomic technologies used in clinical pharmacology research can accelerate the identification of populations that can benefit the most while reducing adverse events. (REV INVES CLIN. 2015;67:212-8)

Key words: Pharmacogenetic. Personalized medicine. Diagnostic genomic device.

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BETTER TECHNOLOGY TO DEAL WITH MORE REGULATION

Technology is fundamental in scientific progress and has far-reaching implications in industrial competitiveness. The pharmaceutical industry uses many technologies in the development of new drugs and therapies[1]. However, the generation of novel pharmacological alternatives still requires a lengthy and costly process due to the extensive drug development cycle, which requires many different stages of research. These stages are divided into pre-clinical and clinical phases, which verify if a compound meets the requirements of efficacy, safety, and therapeutic preference required for commercialization.

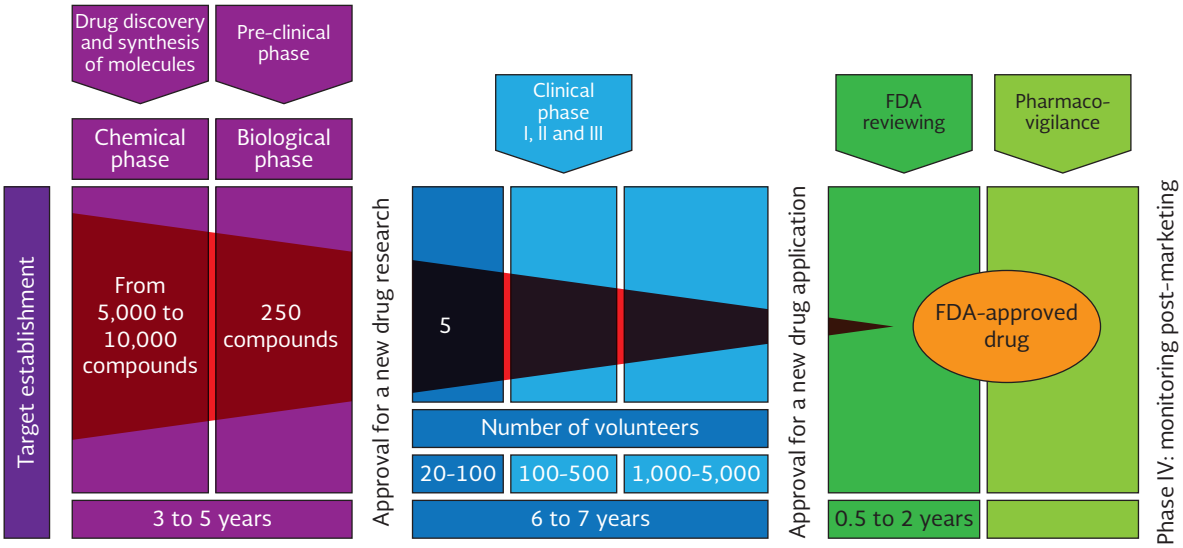
Towards the end of the 1960s, drug development became regulated to ensure safe application of newly introduced drugs and to protect volunteers participating in clinical research. These regulations had a strong impact on the pharmaceutical industry, as they increased research and administrative expenses and extended approval periods, leading to reduced industry profits[2,3]. The research and development (R&D) of new products became the most important competitive factor. Near the end of the 1970s, new companies emerged that integrated the innovations of biotechnology and bioinformatics, and offered alternatives for accelerated development of new drugs, especially those of a biological nature. The large pharmaceutical companies were slow to decide whether or not to venture into these new areas, since such a commitment would mean a large capital investment in new technology and human resources for R&D. By the 1980s, pharmaceutical companies had committed to enter this new segment; however, for the investment in R&D to be profitable, the exploitation of the full patent lifetime, 20 years in the United States, was essential.

There are currently two major international bodies dedicated to the regulation of new drug approvals: the Food and Drug Administration (FDA) in the USA and the European Medicines Agency (EMA) in the European Economic Community[2-4]. In order to comply with the growing regulatory requirements of these agencies, the pharmaceutical industry has integrated molecular biology, biotechnology, bioinformatics, and genomic science into its R&D efforts[1,4-6].

TRADITIONAL RESEARCH AND PRODUCTION OF NEW DRUGS

Combinatorial chemistry has gradually displaced plants[7,8] as the raw material for generating active substances for drugs[5,6]. Typically, only one out of 5,000 to 10,000 candidate compounds is approved. The pharmaceutical industry invests about 10- to 15-year preclinical and clinical R&D efforts and approximately 800 million to 1 billion dollars in this process (Fig. 1)[9].

Figure 1. Traditional development phases of a drug. In the pre-clinical phase, the therapeutic objective is established. The biological phase consists of evaluating *in vitro* toxicity and cytotoxicity. The clinical phase is evaluated in clinical trials in humans in distinct stages (phase I, II, and III). Phase IV is better known as pharmacovigilance, and is evaluated after a drug is marketed.



NEW-GENERATION DRUGS

With the emergence of recombinant DNA technology in the late 1970s, gene expression in recombinant hosts allowed for the innovative production of proteins. The impact of this capability in medical research has been tremendous as illustrated by the success of the first modern biotechnology company: Genentech, Inc. Genentech produced the first FDA-approved, genetically engineered human protein produced by recombinant bacteria. Humulin® is a human recombinant insulin that was marketed in 1982 by Lilly to treat diabetes mellitus[10]. In 1989, Amgen announced that it had cloned and expressed the gene for erythropoietin (Epogen®), which is used in the treatment of anemia associated with chronic renal failure, among other diseases. As of the 1990s, a biotech approach has been successfully applied to develop a growing variety of products, therapeutic biomolecules, vaccines, new foods, enzymes, and other products. The strategy for drug discovery using biotechnology focuses on the identification of specific proteins and their encoding genes, and their role in pathogenesis and treatment of disease. This field greatly profited from the information generated by the human genome project[11]. This worldwide project contributed tools that allow predicting an individual´s response to a certain pharmacologic treatment[12]. The new horizon of pharmacogenetics focuses on identifying existing genomic variations in different populations and uses this information to design personalized drug therapies based on ethnic-specific variations, and within these, those of an individual[13,14]. Regardless of their nature, drugs emerging from pharmacogenetic research are subjected to the same stages of pre-clinical and clinical research for approval prior to commercialization.

GENETICS AND THERAPEUTICS

Pharmacogenetics is defined as the study of gene variations that influence the absorption, distribution, metabolism, and excretion (ADME) process that drugs undergo in the human body, which can be decisive in an individual's response to drug therapy[15]. This process can be divided into two main parts: exposure and response to the medication. Exposure focuses primarily on dosing, drug plasma levels, and overall pharmacokinetics, according to drug concentration curves in the serum and target organs. On the other hand, pharmacodynamics focuses mainly on systemic drug effects, and monitors the impact of administered drugs on various physiological and pathological processes, which includes the assessment of therapeutic efficacy and adverse drug reactions (ADR)[16]. Genetic variation not only influences the susceptibility to a disease[17,18], its progression and recurrence, but also affects treatment, as it is responsible for the heterogeneity of the drug response among individuals of the same age, height, and weight treated with the same drug scheme[19,20]. Thus, understanding the genetic variation of an individual and correlating it with the ADME process and ADRs, is decisive for choosing the drug that is most likely to offer therapeutic success with a minimum of adverse or toxic reactions[21].

PHARMACOGENETICS

Genetic differences among different populations, and even among individuals within a population, vary from single nucleotide polymorphisms (most abundant) and short sequence tandem repeats, to changes in the number of copies of a gene (copy number variations), and insertions and deletions of genetic material (indels)[22-24]. The genes most screened for genetic diversity in relation with new drug development are: (i) those relevant to the drug´s pharmacokinetics (ADME); (ii) those that code for the intended and unintended targets of the drug (drug effect)[21]; and (iii) those considered prognostic markers, i.e., genes that predict the incidence or progression of disease (e.g., the likelihood of cancer or metastasis attributable to gene mutations in the oncogene *K-ras* in the case of colorectal cancer)[25]. At present, genetic variability is more frequently associated with pharmacokinetic than with pharmacodynamic differences. The relationship between genetic profiles and pharmacokinetic parameters that differ between individuals is easy to measure, since it is reflected in the drug concentrations and levels of metabolites in biological body fluids, depending on time post-exposure. Some of these parameters are: area under the curve (AUC), maximum concentration (C_{max}), time to C_{max} (T_{max}), clearance, volume of distribution, and activity half-life.

On the other hand, the impact of genetic factors that affect pharmacodynamics is more complicated to assess because the clinical effects have greater variation between individuals, and they are more prone to

inaccuracies in measurements. Furthermore, they are influenced by several factors, including target affinity for the substrate, pH and other conditions in local environments, and overall health and activity of organ systems. In conclusion, genetic factors influence both pharmacokinetics and pharmacodynamics, and as a consequence, the response to any given therapeutic regimen. Thus, the early determination of genetic variation in volunteers or patients in experimental drug treatments (clinical protocols) is important for defining what is clinically relevant[21].

ACCOMPANYING PHARMACOGENETIC TESTING

The inclusion of pharmacogenetic research in drug development promotes understanding of the etiology of inter-individual variations in efficacy and safety of experimental drugs. Pharmacogenetics requires the collection and analysis of biological samples to generate data. In the development of new drugs, these data can be used to: (i) identify the reasons for the pharmacokinetic and pharmacodynamic differences (variability in clinical response); (ii) prioritize research design and use of drug-drug interaction; (iii) design clinical trials to evaluate the effects on identified subgroups (different types of metabolism); and (iv) reveal the molecular basis of differences and lack of efficacy or the clustering of adverse events.

Furthermore, pharmacogenetic tests allow to predict individual drug responses: (i) therapeutic success; (ii) increased risk of adverse drug reactions; (iii) lack of treatment benefit; and (iv) the need for a genotype-specific drug dose or drug interval. Additionally, the inclusion of pharmacogenetic studies in phase III clinical research allows: (i) the identification and selection of populations that require a minimum, standard, or maximum dose; (ii) the definition of a range of doses for further testing; and 3) the identification of high-risk groups, i.e., those more likely to experience adverse reactions (Fig. 2).

The identification of the various pharmacogenetic groups in the study population would allow an individualized treatment approach (e.g., in cancer patients or those suffering from chronic disorders) to predict the response to treatment through predictive biomarkers and the genomic profile, making the R&D of new drugs more dynamic[21].

THE VALUE OF PHARMACOGENETICS

The most current pharmacogenetic information is obtained from post-marketing studies. Incorporation of pharmacogenetic studies into clinical trials would increase the safety and efficacy of drug candidates, and may even increase the number of approved drugs.

The value of pharmacogenetics is illustrated by the growing number of drugs that include a differential prescription based on pharmacogenetic profiles. The FDA collates a list of drugs, including their labeling details, which have data related to pharmacogenetic testing to consult before prescription. This list includes not only drugs that may have adverse effects based on their dose-response relationship, but also those that may present an excessive response, i.e., drugs associated with specific high-risk genotypes (Table 1)[21,26-32].

There are databases that contain information about drugs, their metabolizing enzymes, and the effect of a certain genotype, for example, http://bioinformatics.charite.de/supercyp[33] and http://medicine.iupui.edu/Clinpharm/DDIs. These freely accessible databases are helpful tools for physicians to personalize drug treatment according to the genotype/phenotype profile of a patient, including the selection of alternative treatments in order to improve drug response or to diminish/prevent an adverse reaction. The FDA has a list of pharmacogenetic biomarkers and drug labels. It is important to consult its content before prescribing drugs to a patient[34].

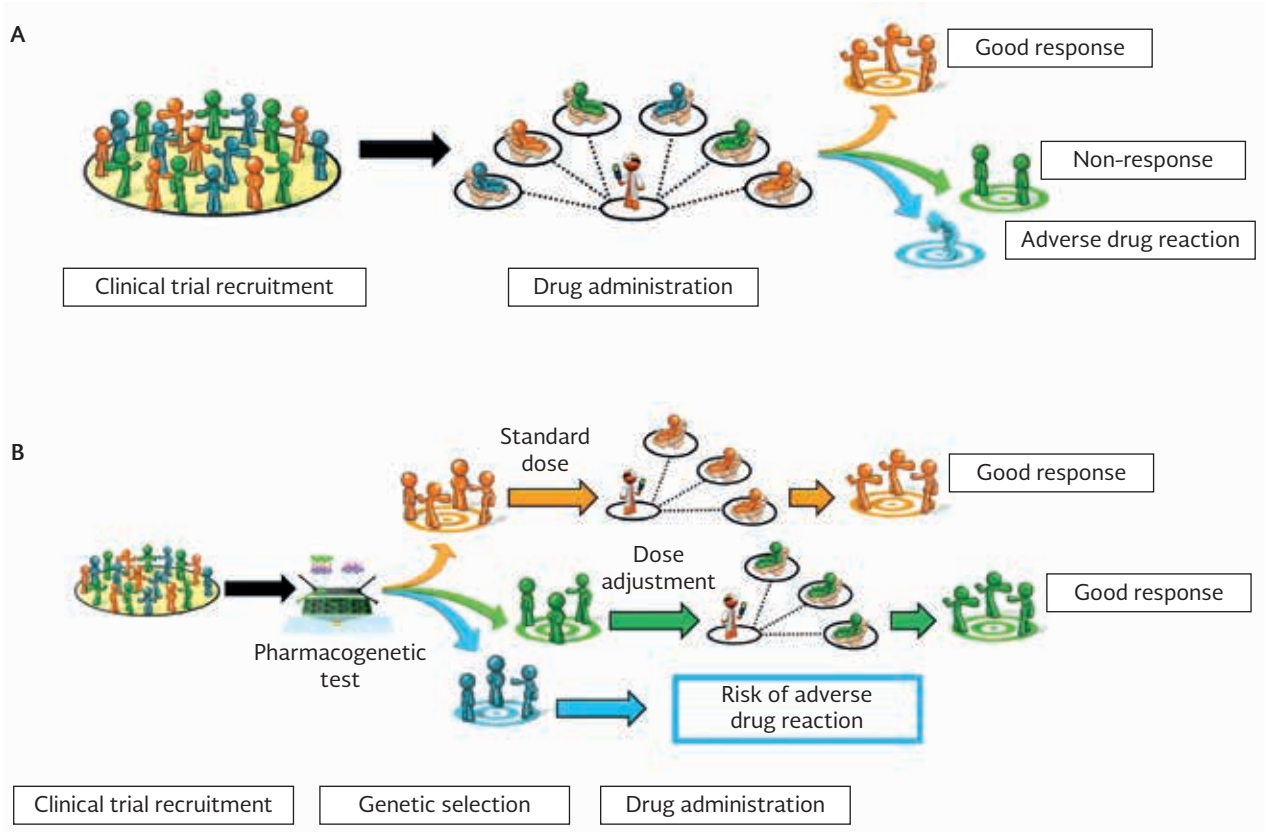
DIAGNOSTIC DEVICES FOR PHARMACOGENETICS

Personalized medication based on pharmacokinetics requires the genomic profiling of an individual. Currently, the most common next-generation pharmacogenetic tools are genomic microarrays or DNA chips. Our group has pioneered their use with Mexican patients, demonstrating their value for the medical community and public interest.

WHAT IS A DNA CHIP?

The DNA microarrays or DNA chips are, in general, a collection of thousands of DNA fragments attached

Figure 2. The value of clinical pharmacogenetics. **A:** a traditional clinical trial recruits volunteers from the general population and administers a drug to all volunteers. However, variation in drug metabolism causes variation in drug response. **B:** pharmacogenetic testing classifies the participants in good and bad responders previous to personalized drug administration, diminishing adverse reactions and high variability in drug response. Human figures were taken from CanStockPhoto and modified before compilation.



to a glass surface that detect, by complementary hybridization, mutations, genetic polymorphisms, and copy number variations of certain regions of the genome, as well as relevant variations of gene expression. This innovative genomic technology reveals particularities of the genome of each individual in order to diagnose disease, predict hereditary risks, evaluate prognosis, and determine the metabolic capacities that condition the person´s response to treatments. Typical classification related to the latter are: a poor metabolizer (ineffectiveness for metabolizing drugs and pro-drugs causing inefficacy and adverse effects); a normal metabolizer (efficacy for metabolizing pro-drugs, which reduces the probability of presenting toxic effects); or an exaggerated metabolizer (accelerated metabolism of drugs and pro-drugs, avoiding an adequate drug concentration with no pharmacological response)[14,35].

The first validated DNA chip was PHARMAchip from the Basque firm Progenika Biopharma, S. A.[36]. This chip identifies 85 of the most relevant and best characterized pharmacogenetic polymorphisms in the international scientific literature, with a sensitivity and specificity of over 99.9%, spanning the cytochrome P450 gene family and 25 genes involved in phase II drug metabolism enzymes, transporters, and receptors. This device also provides output that predicts the drug metabolism phenotype of the patient for each of the genotypes revealed, thus allowing recommendations on the type and dose of drugs needed to achieve a therapeutic effect for a given patient. Rather than the molecular genetic analysis of a single mutation, this new genomics approach facilitates a high-throughput screening of many sequence variations in all relevant genes associated with drug metabolism and disease susceptibility[37,38].

Table 1. High-risk genotypes for selected drugs

Drug	Application	Genes/Alleles	Effect	Ref.
Warfarin	Thromboembolism	*CYP2C9, VKORC1*	Adverse reaction	21, 26, 27
Clopidrogel	Atherothrombosis	*CYP2C19*	Adverse reaction	28
Abacavir	AIDS	*HLA-B*5701*	Hypersensitivity	29
Tamoxifen	Anti-neoplastic (breast cancer)	*CYP2D6, CYP3A5*	Alter efficacy	30, 31
Capecitabine	Anti-neoplastic (breast cancer)	*DPD*	Toxicity	32
6-mercaptopurine	ALL	*TPMT*	Toxicity and therapeutic efficacy	27

ALL: acute lymphoblastic leukemia.

OPPORTUNITIES FOR GENOMICS IN CLINICAL PHARMACOLOGY

Clinical pharmacology studies represent a window of opportunity to integrate pharmacogenetics and evaluate inter-individual genetic variability and its impact on subsequent clinical studies. So far, there are few studies that select subjects based on their genomic profile or on a precise genotype to stratify specific treatment groups and to maximize response. Clinical pharmacology studies may be enriched by including the analysis of pharmacogenetic aspects such as:

– The pharmacokinetics and pharmacodynamics in healthy subjects. The drug in question is metabolized by an enzyme encoded by a polymorphic gene whose most frequent genotype must be present in ≥ 1% of the individuals of a population to determine the degree of variability and maximum differences in systemic exposure between genotypes.

– The pharmacokinetics and pharmacodynamics in patients. Considering the previous requirement, to select patients based on genotype to identify potential responders and eliminate patients likely to experience a toxic effect.

– Dose-response studies. Where biomarkers or clinically relevant signs are monitored for therapeutic efficacy and safety in order to determine appropriate doses as well as to establish the dose range at which adverse effects occur[21,39,40].

In pharmacogenetic studies involving clinical analysis of pharmacokinetics and pharmacodynamics, special attention is paid to the effects of sex, age, weight, and ethnicity. However, in addition to these demographic characteristics of the study population, there are safety considerations which must be taken into account, such as: the use of healthy volunteers in evaluations where the drug does not jeopardize the health of the subject studied (as occurs in the case of cytotoxic chemotherapeutics) and, in contrast, the use of patients for whom the experimental drug may be an opportunity to explore the pharmacodynamics or specific clinical endpoints which cannot be measured in healthy volunteers[21,39].

The personalization of treatments will not only be crucial for optimizing cost, duration, and success rate of clinical trials, but also gathering the most informative data with the least volunteers for data submission to regulatory agencies[41].

CONCLUSION

Pharmacogenetics may be used to optimize the R&D of biosimilar drugs since it allows the selection of genetically appropriate subjects for each test. This strategy not only reduces the number of subjects needed for different clinical stages, but also reduces the risk of experiencing adverse effects of a given drug candidate under evaluation.

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