Pharmacogenetics: from bench to bedside

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The realization of personalized medicine in drug selection and dosing is among clinicians a common and long lasting demand to improve the generally adopted "one size fits all" approach. This advance is particularly required in case of drugs with narrow therapeutic index, drug resistance or hypersensitivity among treated subjects and/or drugs characterized by large inter-individual variations in therapeutic dose.

Environmental and patient-specific factors concur to the outcome of a pharmacological intervention, both in terms of efficacy and safety. The deep knowledge of the involved parameters and their relative relevance in determining the drug response is the precondition to develop a personalized pharmacological strategy. Pharmacogenetics (PGX) deals with the portion of patients-specific factors whose variability is genetically determined and its major beneficial role in patients care has been forecast since many years ago.

In 2003 the completion of the Human Genome Project marked a fundamental scientific achievement that has unveiled new scientific scenarios with potentially revolutionary translations to many areas among which genomic medicine and pharmacogenetics in particular.

The increased scientific interest in PGX studies has been further boosted, in last years, by the advances in genomic analysis achieved with microarray and second generation sequencing technologies allowing genome wide association studies (GWAS) and whole genome sequencing. Actually, thanks also to these new analytical platforms, we are facing a tremendous increase in PGX scientific production, particularly in basic research; several new association between gene variants and specific drugs treatments are presented each month. Related PGX clinical studies have led the US Food and Drug Administration (FDA) to approve labels modification to more than 30 drugs by including pharmacogenetics informations (http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm last accessed April 13 2011).

Moreover many commercially available platforms and pharmacogenetics tests have been approved in recent years by regulating agencies like FDA and are of easy implementation in laboratories with adequate expertise in genetic analysis.

Notwithstanding this, the number of PGX test implemented in routine clinical practice is still limited. This situation contrasts with the growing expectation of the scientific community for pharmacogenetics to impact significantly human health.

Many challenges still prevent the translation of PGX knowledge to clinical practice. This translation depends on the fulfillment of a series of consecutive steps bridging basic research, clinical research and finally clinical practice. In particular clinical research should unambiguously asses the clinical utility of PGX tests, selecting those clinically relevant, providing scientific evidence both of their cost effectiveness and of their usefulness in patient care. Major challenges in this process are related to the definition of the minimum threshold of evidence to be achieved before acceptance of a PGX tests and to the way of generation of this evidences, with particular regard to the study design adopted in clinical trials. Randomized controlled trials, although very powerful in evidence based medicine, suffer from limitations of high cost and long time requirements. Robust observational studies combined with adequate clinical trials might speed up, in some cases, the generation of high quality PGX evidences.

Challenges in the widespread of clinically validated PGX test in healthcare practice are related also to difficulties in the translation of genetic results into practical prescribing recommendations particularly when personalized drug dose adjustments are required. The development of consensus guidelines by the scientific community will facilitate the overcoming of this obstacle as well as the improvement of widespread acceptance of PGX testing among clinicians and general practitioners.

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