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Genomic Personalized Medicine: a dream or a reality?

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The huge biotechnology development permitted in the last years an enormous increase of knowledge regarding the genetics field and its possible applications. This great progress in the knowledge of the human genome sequence and of its inter-individual variability has consequently permitted an important impact of the genomics on the clinical practice and in particular in the field of prevention in its different aspects.

The inter-individual variability is an evident phenomenon: everyone shows different phenotypic features, as well as each person has a different susceptibility to various multifactorial diseases, or is more or less resistant to infectious agents. In the same way each individual responds very differently to the same drug, both in terms of efficacy and toxicity, as well as every person may need different doses of the same drug to have a therapeutic effect.

While a part of this inter-individual variability is due to "environmental factors", an important contribution is due to genetic factors.

In the years 2000-2003 was completed the "Human Genome Project",[1-3] the great international collaborative effort that allowed to determine for the first time the entire nucleotide sequence of the human genome. Since then, several studies on the inter-individual genome variability[4-7] have shown that each individual shows around 99.9% of genetic identity compared to any other subject while about 0.01% presents inter-individual variability, due to the presence of different types of "genetic variants or polymorphism".

Moreover, with the fast development of technologies in the last 10 years, the new analyses at increasingly larger scale, (i.e. GWA – Genome Wide Association Study) and the recent new approach of "Next Generation Sequencing – NGS"[8] have allowed to identify more genes and variants. In particular, this NGS approach has permitted a great progress in the identification of mutations that causes monogenic disorders, or "familiar" cancer. Anyway, the last decade has also seen the identification of common variants contributing to complex diseases susceptibility and to the different individual response to drugs, making the concept of "Personalized or Genomic Medicine" more real and close to prevention and clinical practice.

Besides diagnostic genetic testing (used to identify mutations in monogenic disorders or chromosomal abnormalities), in the last ten years there was a great development of the so called predictive or susceptibility testing to complex diseases and of Pharmacogenomics testing.

The initial perspective in the use of predictive tests was to analyze genotypes/haplotypes/genomic profiles involved in susceptibility to some complex diseases in order to act a more specific and personalized prevention. However, it should be highlighted that predictive tests apply to complex diseases and identify situations of genetic susceptibility to these diseases, the occurrence of which, however, also depends by many environmental factors. They can help to identify a statistically increased genomic risk to develop the disease but do not give any certainty about the occurrence of the disease in the lifetime. The utility of these tests is much debated. The evaluation of the clinical utility of carrying out these tests, as well as the correct interpretation and communication of the result to the patients, should be carried out by qualified personnel (through genetic counseling).[9]

The genetic inter-individual variability is also involved in the individual variability in response to drug treatments, that is one of the most significant issues in prevention and clinical practice. In fact it is possible to observe very different response to a drug, both in terms of efficacy and toxicity. Today it is estimated that about 30% of patients derive no benefit from a given drug. In addition, adverse reactions to drugs are a major cause of hospitalization and in some cases can even be lethal. It is obvious that the response to a drug is multi-factorial and therefore this variability is due to a complex mix of genetic and environmental factors (such as the presence of concomitant diseases, interactions with other drugs) interacting with each other. Genetic factors plays an important role at various levels: drug transport, absorption, metabolism and excretion (pharmacokinetics) as well as the interaction with the target of the drug and the relationship between concentration and effect (pharmacodynamics). Individual differences in these processes may be due to polymorphisms present in the genes coding for enzymes, receptors and proteins involved in these different steps of pharmacokinetics and pharmacodynamics. This field of research is called pharmacogenetics. This discipline, originally addressed to the study of single genes (or a limited number of them), has undergone an evolution in recent years due to the sequencing of the human genome and the development of the latest technologies, making it a broader discipline that considers many genes simultaneously as well their expression, the Pharmacogenomics.

Pharmacogenetics/Pharmacogenomics aims are to study the genetic inter-individual variability involved in the response to a drug, identify "responders" and "non-responders", identify people who have a high risk to experience toxicity of a drug and help the development of new "personalized" drugs. The aim is to avoid both the lack of efficacy as well as the toxicity, allowing the doctors to better treat patient with more "tailored" therapies, and also save time, reaching the optimal therapy and the optimal

dosage more quickly. Besides better prevention and public health effect, this approach could also result in a consistent reduction of public health costs.

Pharmacogenomics is certainly one of the most promising areas of genomic personalized medicine.

It is impossible in this context to illustrate all the clinical applications in different fields[10-20] (oncology, cardiovascular diseases, infectious diseases and many others). Anyway, it is important to know that in recent years many of these Pharmacogenomics tests entered into clinical practice and some of them have been made mandatory (or recommended) by International Regulatory Agencies for the administration of the drug itself since it was demonstrated their decisive clinical utility to predict efficacy and toxicity. Genomic studies have also entered in many clinical trials.[21-23]

Moreover, the recent huge technological development of Whole Genome Sequencing (that is allowing to analyze quickly and with relatively low cost the whole genome) is making it feasible the prospective of a large-scale decoding of the genomic profiles that make us more or less susceptible to certain diseases or that make us more or less responsive and sensitive to drugs.

Concluding, it is possible to say that the idea of a "Genomic Medicine" or "Preventive Personalized Medicine" can be considered no more a dream but a real perspective.

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