

## **THERAGNOSTICS - A SILENT REVOLUTION**

Medicine has evolved over time based on two distinct components: new concepts on how to integrate and interpret the various data available and the continuous technological evolutions that provided more precise data concerning patient's status. While this second part is constantly viewed and publicized in the media as driving effectiveness of health care this is in fact not entirely the case and major changes in the modalities to view the disease concept have driven major changes.

Medicine started as an art of healing based on philosophical consideration about health status and the possible modalities to reverse disease status to health. Hippocratic medicine has introduced the direct and systematic observation of clinical signs and the theory of the equilibrium of humors and marked a rupture with the previous concepts of the divine nature of disease. Hippocrates had a deterministic view of the health and disease status and that both could be influenced by concrete actions of man. The following 2,000 years were marked by a better understanding of basic principles of anatomy and physiology in parallel of the development of the techniques of macroscopically and microscopically examinations but without major developments in terms of therapeutic options. The next step in our understanding of illness was the development of the anatomoclinical method proposed by Giovanni Morgagni and developed by Xavier Bichat, René Laennec and Jean-Martin Charcot. For them every disease and clinical sign had an anatomic-pathological correspondent

and therefore it was sufficient to carefully know these correlations in order to properly diagnose a disease. This approach led to the identification of most of the major nosologic groups known today. In parallel, the introduction of Claude Bernard principles of scientific experimentation resulted in major understanding of the disease process and massive advancement in terms of available efficient therapeutic interventions. However this approach resulted in an archetypal understanding of disease and each patient was fitted in a global model of the pathological process without clear possibilities to explain differences in presentation, evolution and response to treatment between patients. Progressively, the understanding of individual variability due to a better understanding of human genetics and its interactions with environmental variables based on the advances in molecular biology and epidemiology set the foundation for *personalized medicine*, the next evolutive step in medical science.

Until then a relatively homogenous group of patients as defined by various clinical, biochemical and pathological features will receive the "standard" best treatment available and afterwards interventions were adapted based on response to treatment and toxic effects of therapy. This result in three groups of patients: those who benefit from therapy and improve / cure patients who do not benefit from therapy and patients with toxic effects from therapy with some possibilities of overlap between these groups. Using this approach the critical issue was to correctly name the disease process without

any possibility to predict in advance how our patient will respond, this being usually inferred from a post hoc analysis. Eventually, treatment strategy was modulated based on heuristics resulting from previous experience of the clinician.

Advances in the understanding of genetic background of disease and patients enable us now to predict to some extent which disease will respond to a particular treatment and which patients will have toxic effects from therapy. Thus major progresses were possible concerning treatment: we now expect to be able to predict the effects of therapy both in terms of efficacy and toxicity thus maximizing benefit of therapy.

Still, such an approach is not without difficulties. First we need to have a good understanding of the disease process at the molecular level. This represents an important effort which should be done for every disease process we know or that is newly identified. The actual experimental approach is not sufficient for this since we need to cover most if not all disease subtypes. For this to be successful, we first need to obtain biological samples at every level (biopsies, blood and other bodily fluids) store them in large biobanks and to have access to a complete clinical and therapeutic profile of individual patients. The

development of robust statistical methods for analysis of these “*Big Data*” collections is also a challenge since classical statistical analyses are not applicable.

Second we need to completely change our way to develop drugs. Instead of testing “*blindly*” a large number of drug in preclinical or animal models and then in clinical trials we need to create (in parallel to drug development) a companion diagnostic test that is sufficiently predictive for drug efficacy. This necessity is not only imposed by the need to maximize drug benefit but mainly for diminishing toxicity and to limit the cost of treatment. Indeed the costs of drug development are rising fast and consequently innovative drugs have very high prices despite of a limited increase of the production costs. Thus it is no more possible to administer drugs to all patients and then evaluate their efficacy because such an approach is not sustainable from the payer’s perspective.

This whole new domain called *theragnostics* is rapidly imposing itself as the standard approach to disease and today most developments of drugs follow this path. Despite being promising we still need global analyses both from clinical trials and from day to day practice that prove that such an approach will both improve treatment success and keep costs at a tolerable level.

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