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Review

Genomic translational research: Paving the way to individualized cardiac functional analyses and personalized cardiology

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ABSTRACT

For most of Medicine's past, the best that physicians could do to cope with disease prevention and treatment was based on the expected response of an average patient. Currently, however, a more personalized/*precise* approach to cardiology and medicine in general is becoming possible, as the cost of sequencing a human genome has declined substantially. As a result, we are witnessing an era of precipitous advances in biomedicine and bourgeoning understanding of the genetic basis of cardiovascular and other diseases, reminiscent of the resurgence of innovations in physico-mathematical sciences and biology-anatomy-cardiology in the Renaissance, a parallel time of radical change and reformation of medical knowledge, education and practice. Now on the horizon is an individualized, diverse patient-centered, approach to medical practice that encompasses the development of new, gene-based diagnostics and preventive medicine tactics, and offers the broadest range of personalized therapies based on pharmacogenetics. Over time, translation of genomic and high-tech approaches unquestionably will transform clinical practice in cardiology and medicine as a whole, with the adoption of new personalized medicine approaches and procedures. Clearly, future prospects far outweigh present accomplishments, which are best viewed as a promising start. It is now essential for pluridisciplinary health care providers to examine the drivers and barriers to the clinical adoption of this emerging revolutionary paradigm, in order to expedite the realization of its potential. So, we are not there yet, but we are definitely on our way.

It is more important to know what sort of person [*individuality*] has a disease, than to know what sort of disease a person has — *Hippocrates (460–370 BCE), and Sir William Osler (1849–1919)*

Diathesis (Gk., signifying a constitutional predisposition toward a particular state or condition and especially one that is abnormal or diseased) **... is nothing else but a chemical individuality ... the factors which confer to us predispositions to and immunities from the various mishaps which are spoken of as diseases, are inherent in our very chemical structures** — *Sir Archibald Garrod (1857–1936)*

1. Hippocratic origins of personalized medicine

Every patient is unique or distinctive, and the evolving field of personalized medicine (PMed) aims to ensure the delivery of the proper treatment to the right patient at the right time. It was Hippocrates (born c. 460 BC, island of Cos, Greece; died c. 375, Larissa, Greece), the Father of modern Medicine [1] (see Fig. 1), who first underscored the patient as the most important determinant of therapeutic efficacy. He had somehow recognized the central principle of PMed: human beings are innately (genetically) different from one another, and this individuality affects both their predisposition/susceptibility to disease and their response to therapeutics [2]. Accordingly, optimal clinical practice must entail a personalized or individualized approach to diagnosis and treatment. The ramifications of such a personalized approach and resultant ideas also extend into academic realms traditionally reserved for the social sciences, philosophy, ethics and religion, as well as jurisprudence, the discipline of what is just and unjust.

Hippocrates advanced a rational, targeted therapeutic strategy. Treatment should be etiological (*cause*-oriented) rather than phenomenological (symptom-oriented) [Places in Man; v. VIII, 1995]. Therefore, it is necessary to inquire into and treat the *etiology* or cause [Nature of Man; v. IV, 1931] of why manifest symptoms come about [Ancient medicine; v. I, 1923] [3]. It is essential to first understand disease pathophysiology, which in turn requires the knowledge of human biology [Nature of Man; v. IV, 1931] [3].

Hippocrates was the first to highlight that there are critical natural nonuniformities and a great difference in the constitution of individuals: each person exhibits one's *idiosyncrasia* (idiosyncrasy) [On Joints; v. III, 1928] [3]. Idiosyncrasy predisposes to or protects from particular diseases [The Sacred Disease (*Epilepsy*); v. II, 1923] [3]. The individuality that Hippocrates first identified is today understood at long last as an individuality at the level of the genome/epigenome, which encode the information that governs the human body's composition, traits, disease predisposition, response to treatment, and prognosis.

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Fig. 1. Marble statue of Hippocrates, ancient Greek physician considered as the Father of Western Medicine, in the city of Larissa in Thessaly, on the mainland of Greece. He envisioned the need for a Personalized Medicine.

2. Genomic structures weave a thread through modern medicine: gene therapy

Developments and breakthroughs in the basic sciences and biotechnology have in our day revolutionized medical research, including cardiovascular investigations, bringing about diversified advances many of which could not have been forecasted even 1–2 decades ago. Progress in computational methods, biomedical engineering, multimodal and multiscale imaging, molecular and cellular biology and genetic engineering, genomic sciences, proteomic technologies, and epigenetics are among the many advances that have speeded up the pace of biomedical research. Today we are aware that biology creates its structures—proteins, hormones, cells, tissues, organs and the like—by putting genes into intricately regulated action.

In our own species there are roughly 21,000 protein encoding genes (estimates continue to fluctuate), and genome-wide variation from one person to another can be up to 0.5% (99.5% agreement). Interestingly, cats have 90% of homologous genes with humans [4] and 50% of *Drosophila melanogaster* ("fruit fly") protein sequences have mammalian homologs [5], while about 75% of known human disease genes have a recognizable match in the genome of *D. melanogaster* [6]. Evidently, all organisms have a common ancestor and therefore share many components of their genomes. Individual genes function collectively as the parts of a programing language for the formation of an enormous variety of products of diverse form and function. Organisms cast themselves in many distinctive shapes and amazingly disparate species by using much the same set of genes "programed"—in conjunction with "environmental/epigenetic factors—to become activated in precise progressions and operational integrative patterns, in health and disease.

2.1. The restructuring of genetics and its convergence with medicine

Genetics nowadays has established itself not only just as a specialty of medicine but also as a thread throughout all of health care [7] and is now embarking on the most ambitious and inventive phase of its existence. By 1965, when I was being taught different aspects of molecular biology—a melding of biochemistry and genetics—by the Medicine Nobel Laureates Severo Ochoa and Baruch Benacerraf at NYU School of Medicine, molecular biology had laid bare the basic secrets of genetics residing on the DNA double helix consisting of antiparallel helical strands, with complementary bases. Without the ability to manipulate genes, however, the understanding was more theoretical than operational.

In the 1970s, this situation was transformed by the recombinant DNA technology, which led to transgenic organisms and gene therapies. A variety of enzymes were discovered, made by bacteria, which allowed DNA manipulation as needed. Bacteria make *restriction enzymes*, which cleave DNA at specific sequences and function as defense against invading viruses, and *ligases*, which join DNA fragments. With these and other tools—which today are available commercially—it became possible to cut and paste DNA fragments from one genome to another as desired and using a variety of recombinant DNA technologies introduce them, through a vector, into cells to supplant variant defective human gene(s) directly and thereby enable endogenous production of desirable compound(s). Such nanoscale therapeutic interventions can result in as impressive outcomes as conventional interventional cardiology procedures [8].

Generally, gene transfer entails adding a functional gene (a transgene) into a recipient's body, correcting a dysfunctional gene to wheedle tissue production of desirable compounds endogenously, or altering the expression of a naturally occurring gene; accordingly, gene transfer and gene therapy are not synonymous. Today, DNA fragment cloning procedures altering gene expression also allow investigators to reproduce unlimited quantities of specific DNA molecules and, along with the polymerase chain reaction (PCR) that allows one to directly amplify a specific DNA sequence and the invention of DNA sequencing—the process of determining the order of bases in a segment of DNA—have led to mapping and detailed understanding of many individual genes and coordinated, integrative gene networks.

In consequence, in our time, it is acknowledged that virtually all human ailments/disorders excluding random trauma, have some genetic

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