

## Prakriti-Based Medicine to Personalized Precision Medicine: A Historical Journey

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### Opinion

Personalized Medicine is not new and was even practiced thousands of years ago. Charaka Samhita, who practiced Ayurveda, a natural health care that originated in India more than 5000 years ago once said "Every individual is different from another and hence should be considered as a different entity. As many variations are there in the universe, all are seen in human beings". Charaka's tridosha theory formed the Prakriti-based medicine [1]. The seeds of Personalized and Precision Medicine were hence sown by Charaka Samhita. The concepts of prakriti-based medicine were carried over to the Cnidian School of Medicine at the time of birth of Hippocrates (approximately 2500 years ago), which considered the body to be merely a collection of isolated parts and saw disease manifesting in a particular organ or body part as affecting that body part alone and not that the whole body was involved. Alcamaeon (5th century BC), a practitioner of the Cnidian School, wrote the first book in Greek medical literature entitled "Concerning Nature". Hippocrates, considered as the "father" of modern medicine, disagreed with this Cnidian School of thought.

Centuries later, Charaka's sentiments were echoed by Hippocrates (500 B.C.) who combined an assessment of the four humors-blood, phlegm, yellow bile and black bile, to determine the best course of treatment for each patient. Hippocrates said, "The body of man has in itself blood, phlegm, yellow bile, and black bile; these make up the nature of the body, and through these he feels pain or enjoys health. Hippocrates who founded the Coan School of Medicine, believed that the disease was a result of environment, diet and habits and that the treatment should involve patient care and prognosis. Now, he enjoys the most perfect health when these elements are duly proportioned to one another in respect to the compounding, power and bulk, and when they are perfectly mingled. Pain is felt when one of these elements is in defect or excess, or is isolated in the body without being compounded with all the others". Hippocrates then went on to say, "It is far more important to know what person has the disease than what disease the person has". A sapling of Personalized/Precision Medicine sprouted. In earlier 1950s, scientists working on DNA, used the term "gene", as the smallest unit of genetic information, but they had no idea how a "gene" looked like structurally and chemically and how it was copied generation after generation. Oswald Avery in 1944 showed that DNA was the "transforming principle", the carrier

of hereditary information in pneumococcal bacteria. Watson and Crick in 1953 discovered the double helix, the twisted-ladder structure of deoxyribonucleic acid (DNA), a landmark discovery in modern molecular biology that led to deeper insights into the genetic code and protein synthesis. Advances in recombinant DNA technology, genetic engineering, rapid gene sequencing and monoclonal antibodies revolutionized modern Medicine and provided fertile grounds for the concepts of personalized and precision medicine to grow.

The discovery in 1953 of the double helix, the twisted-ladder structure of deoxyribonucleic acid (DNA), by James Watson and Francis Crick marked a milestone in the history of science and gave rise to modern molecular biology, which is largely concerned with understanding how genes control the chemical processes within cells. In short order, their discovery yielded ground-breaking insights into the genetic code and protein synthesis. During the 1970s and 1980s, it helped to produce new and powerful scientific techniques, specifically recombinant DNA research, genetic engineering, rapid gene sequencing, and monoclonal antibodies, techniques on which today's multi-billion-dollar biotechnology industry is founded. Major current advances in science, namely genetic fingerprinting and modern forensics, the mapping of the human genome, and the promise, yet unfulfilled, of gene therapy, all have their origins in Watson and Crick's inspired work. The double helix has not only reshaped biology, it has become a cultural icon, represented in sculpture, visual art, jewelry, and toys.

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Researchers working on DNA in the early 1950s used the term "gene" to mean the smallest unit of genetic information, but they did not know what a gene actually looked like structurally and chemically, or how it was copied, with very few errors, generation after generation. In 1944, Oswald Avery had shown that DNA was the "transforming principle," the carrier of hereditary information, in pneumococcal bacteria. Nevertheless, many scientists continued to believe that DNA had a structure too uniform and simple to store genetic information for making complex living organisms. The genetic material, they reasoned, must consist of proteins, much more diverse and intricate molecules known to perform a multitude of biological functions in the cell. In 2003 advances in the gene sequencing technology led to the completion of human genome project (HGP). Since the completion of HGP a decade earlier, significant advances in genome technology have led to drastic decrease in sequencing costs from \$ 3 to 5 thousand down to just \$1000. Advances in genomic technology translated into major biological insights and medical advances in addition to the development of more than 100 drugs whose labels now include pharmacogenomic information [2]. Given that an estimated 5.3% of all hospital admissions are associated with adverse drug reactions [3], many such reactions may be attributed to variations in genes that code for these metabolizing enzymes such as the Cytochrome P450 system [4,5]. Predated on this genomic understanding of the drug metabolizing Cytochrome P450 system, right drug may be administered to the right person at the right dosage at the right time. Hence personalized medicine has already begun to drastically reduce the healthcare expenditure. With the advent of Personalized Medicine, improved understanding of posology have provided improved patient management in a wide ranging conditions such as depression and anxiety, coronary and peripheral artery disease, inflammatory bowel disease and cancer. Thus, by embracing preventative strategies, avoiding drug-drug interactions and adverse drug effects, reducing trial and error prescriptions, increasing patients' compliance to treatment, personalized medicine may hope to improve quality of life and help control healthcare expenditure.

Given the variability of patients and our current limited understanding of the onset, progression and treatment of different disease processes, there is an imminent need of a paradigm change. The emergence of "P-Medicine" and its concept of including Personalized Medicine, Precision Medicine, Preventive Medicine, Predictive Medicine, Pharmacotherapeutic and Patient Participatory Medicine will create that paradigm change in patient management [6]. Personalized Medicine is defined as "...the management of a patient's disease or disease

predisposition, by using molecular analysis to achieve the optimal medical outcomes for that individual-thereby improving the quality of life and health, and potentially reducing overall healthcare costs" [7]. The definition has now been modified to reflect "Personalized Medicine is an evolving field in which physicians use diagnostic tests to determine which medical treatments will work best for each patient. By combining the data from these tests with an individual's medical history, circumstances and values, healthcare providers can develop targeted treatment and prevention plans" [8]. Perhaps the most appropriate definition of personalized medicine is "the use of combined knowledge (genetic or otherwise) about a person to predict disease susceptibility, disease prognosis, or treatment response and thereby improve that person's health" [9]. The concept of Precision Medicine began to put the technological breakthroughs in genomics to facilitate accurate diagnosis and effective treatment. The term "Precision Medicine", first coined by Clayton Christensen in his book the Innovators Prescription [10], gained wide acceptance following a report entitled "Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a new Taxonomy of Disease" was published by the United States National Research Council (NRC) in 2011 [11]. The Institute of Precision Medicine definition stated "Precision medicine is targeted, individualized care that is tailored to each patient based on his or her specific genetic profile and medical history. Unlike in traditional one-size-fits all medicine, practitioners of precision medicine use genomic sequencing tools to interrogate a patient's entire genome to locate the specific genetic alterations that have given rise to and are driving his or her tumor" [12]. The recognition of Precision Medicine perhaps reached its climax when on January 2015, USA President Barack Obama launched a new Precision Medicine initiative and committed a \$215 Million into it said "...what if matching a cancer cure to our genetic code was just as easy... the promise of Precision Medicine delivers the right treatments, at the right time, every time, to the right person" [13,14]. Thus, we have entered an era of Personalized Precision Medicine and hope that the current day maladies afflicting mankind may be accurately diagnosed and effectively treated. Personalized and Precision medicine are expected to shape the future of cancer therapies. Understanding the roles played by stem cells in cancer, scientists are now able to find normal stem cells, including a stem cell that seems to build the entire vertebrate skeleton [15].

From Charaka's Prakriti-based medicine to Obama's Precision Medicine Initiative, it has indeed been a tumultuous historical journey. Only time will tell the true impact of Precision Medicine Initiative on the healthcare of an individual.

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