The current paradigm of modern healthcare is a reactive response to patient symptoms, subsequent diagnosis and corresponding treatment of the specific disease(s). This approach is predicated on methodologies first espoused by the Cnidean School of Medicine ~2500 years ago. More recently a rapid improvement in OMIC analyses, bioinformatics and knowledge management tools, as well as the emergence of big data analytics, and systems biology has led to a better understanding of the profound, dynamic complexity and variability of individuals and human populations in their daily activities. These developments in conjunction with escalating healthcare costs and relatively poor disease treatment efficacies have fermented a rethink in how we carry out such medical practices. This has led to the emergence of “P-Medicine”. The initial wave was in the form of Personalized Medicine, which encompasses elements of preventive, predictive, and pharmacotherapeutic medicine and focuses on methodologies and data output tailored to a person’s unique molecular, biochemical, physiological and pathobiological profile. Personalized Medicine is still in a fledgling and evolutionary phase and there has been much debate over its current status and future prospects. A confounding factor has been the sudden development of Precision Medicine which has also joined the P-Medicine “revolution” and currently has captured the imagination of policymakers responsible for modern medical practice. There is some confusion over the terms Personalized versus Precision Medicine. Here we attempt to define the key components of P-Medicine and provide working definitions, as well as a practical relationship tree. The development and growth of P-Medicine and its impact on the healthcare system as well as the individual patient will be fueled by the informed and knowledgeable consumer as well as the thoughtful clinician armed with the right tools and technologies and approach to deal with the complexity of disease diagnosis, onset, progression, treatment, prognosis and outcome.

Introduction

Current medical practice in the developed world appears to be in a crisis of identity. There is a perceived lack of delivered value on the part of most stakeholders including the patients, i.e. the consumer. Many of these patient complaints involve diagnostic and prognostic accuracy, poor treatment efficacies of a disease condition, and timely access to patient care. This general dissatisfaction is apparent irrespective of the specific healthcare system. The patient could be participating in a single payer, socialized medicine system like the National Health Service (NHS) of the UK, or a market driven, predominantly privatized model, such as the US healthcare system. How did we get to such a critical, and some might argue dysfunctional point in the evolution of medical practice?
If we look to the past for insight, then the clouds of history are constantly swirling and possibly confusing. Our understanding of individual and collective contributions to a particular subject can be shrouded in uncertainty. Nonetheless it is illuminating to consider the influence of early pioneers such as Alcmaeon, Hippocrates, Huang Di, and Shen-Nong, and their contribution to modern medicine as practiced in both the “East” and “West”. For example Alcmaeon (lived 5th Century BC) wrote the very first book in Greek medical literature entitled “Concerning Nature”. He was a practitioner of the Cnidean School of Medicine. This school of medical thought relied solely on a subjective reporting of symptoms by the patient. Cnidean practitioners also considered the body as a collection of isolated parts or organs, and disease manifestation and treatment were considered as localized events of the body. As this approach evolved it relied on the comparison of a patient’s individual symptoms and treatment regime to a population of patients with the same disease. This became the paradigm for current modern medical practice in the diagnosis and treatment of individual diseases. In contrast, Hippocrates (born circa 460 BC), who is regarded as the “Father” of modern medicine, believed that disease was a product of environmental forces, diet and lifestyle habits, and that treatment should focus on patient care (prevention) and prognosis (prediction). He argued that the human body functioned as one unified organism and should be treated as a coherent entity. In the diagnosis of disease he believed that both subjective reporting by patients as well as objective assessment of disease symptoms must be considered. He helped found the Coan school of medicine and should more accurately be described as the “Father” of Personalized Medicine, with an emphasis on the prevention, prediction, diagnosis and treatment of disease at it pertains to the individual patient system.

Finally, the Yellow Emperor’s Inner Canon is a multi-volume treatise written over 2000 years ago. It is based on the original work and practices of the legendary “Yellow Emperor” Huang Di and Shen-Nong, an expert herbalist, both of whom lived around 2000 BC. This work was the written foundation on which Traditional Chinese Medicine (TCM) is now practiced, and is somewhat similar to the Coan School in that it is predicated on the diagnosis and treatment of individual patients without the necessity of comparison to a controlled population data set. All of this is captured and summarized in part in Figure 1.

The current modus operandi of modern medicine is based on the determination of an individual’s symptoms, along with an associated diagnosis and subsequent response to a specific treatment as compared to a statistically similar and relevant patient population dataset or database. There is also a focus on a specific disease indication as it pertains to compartmentalized tissue and organs involving a highly specialized, silo-orientated clinician. The current healthcare system tends to be reactive, providing treatment post-onset of the disease, with limited attempts at prevention and prediction. All this reliance on the comparative analysis of an individual compared to a defined population tends to neglect and disregard human individuality, complexity and variability. It also fails to recognize the systems level interconnectedness of human molecular biology, biochemistry, metabolism and physiology in the form of systems biology. The irony is that all these issues/failings were enunciated by Hippocrates approximately 2500 years ago in his critique of the Cnidean School methodology and addressed by the development of the Coan School of medicine.

Whilst there have been significant improvements in patient care over the past century, the current approach has led to ever-increasing healthcare costs and has had limited impact on the prevention, prediction, accurate

![Figure 1. Historical development of modern medical practice. A simple taxonomic tree of Personalized and Precision Medicine.](image-url)
diagnosis, and effective treatment of both acute and chronic diseases. This lack of progress in concert with a growing awareness of the complexity and variability of individual patients as well as our limited understanding of causal mechanisms of onset, progression and treatment of most 21st century diseases has led to a growing demand for paradigm change. The clamor for change has led to the emergent growth of “P-Medicine”. The P-Medicine list of endeavors includes Personalized, Precision, Preventive, Predictive, Pharmacotherapeutic and Patient Participatory Medicine. Current conventional medicine seeks to treat disease post-onset based on the population comparison model described above. In contrast P-Medicine attempts in part, to identify molecular profiles pre-onset of the disease and prior to expression of specific clinical pathologies somewhat reminiscent, of the Coan philosophy of medicine espoused by Hippocrates. In this treatise we discuss the emerging evolution of P-Medicine and the current debate about the working definitions of Personalized versus Precision Medicine.

CONSEQUENCES OF HUMAN DYNAMIC COMPLEXITY AND VARIABILITY

The annals of history indicate that our understanding and appreciation of human complexity and variability at the cellular, individual and population level has constantly been constrained by lack of adequate technologies. In addition our comprehension of the dynamic nature of human metabolism and physiology as a function of time, ranging from minutes to years, is also still extremely limited. Furthermore, diagnosis, prognosis and treatment decisions have been driven by a reductionist approach, which has led to the development of relatively simple physiological models, as well as a rudimentary and incomplete understanding of complex biological processes and systems analysis in patients. This has all contributed to our inability to make unambiguous and decisive decisions about optimal healthcare for individual patients. In the early 1990’s there was a recognition that significant technical difficulties existed in terms of obtaining meaningful analytical measurements on complex biological systems (e.g. organisms, organs, tissue, cells, organelles, or biomolecular pathways/networks) which resulted in limited data and information output. Thus a series of initiatives was started in the 1990’s forging the “Decade of Measurements” which begat numerous high throughput analytical tools and technologies as well as bioinformatic and knowledge assembly/management tools. The consequence of this “Omic Revolution” has been the development of platforms that now routinely produce copious and substantial, genetic, genomic, transcriptomic, proteomic, functional proteomic and metabolomic datasets. As these datasets have been acquired and analyzed our previous perspective on biological processes (e.g. homeostasis), appears to have been simplistic. For instance, even at the cellular level, well defined biochemical pathways appear to be interconnected, modulated, regulated with significant redundancy built into them. Proteins do not normally function as single entities, but act via stoichiometrically-defined complexes that can contain 10-100’s of proteins. The formation and disassembly of such complexes are under remarkable, control and modulation elements. It would appear that in the health and life sciences, and thus healthcare, ‘as we have learned more, we appear to understand less!’

One other consequence of the “Decade of Measurements” was the emergence of applied Systems Biology. As healthcare researchers and clinicians struggled with the avalanche of data, a rethinking of how to process and utilize the resulting information content occurred. In part this was also a concerted attempt to produce new knowledge and understanding about complex biological processes and systems, and by extrapolation dissect human complexity and variability. This nascent field, also referred to as pathway, network, or integrative biology has attracted considerable attention and effort, and appears to be an approach which has afforded significant new insight into the complexities of human health, and disease. This has led to a radical rethinking about how we go about gathering healthcare data and its conversion into information, and ultimately the production of new understanding and knowledge that can translate into better diagnosis, prognosis, treatment and outcome for patients.

It is salutory to consider the dynamic complexity and variability of an individual human being as well as a population. For example at the cellular level an individual human cell (Figure 2a) is made up of ~100 trillion water molecules, ~20 billion proteins, ~850 billion fat molecules, ~5 trillion sugars and amino acids, ~1.5 trillion inorganic moieties, ~50 million RNA molecules and 2 meters of DNA within 23 pairs of chromosomes. We estimate that based on the energy requirements of individual cells in the form of adenosine triphosphate (ATP) turnover, there are ~ 860 billion chemical reactions/interactions performed per day in a single cell! Each cell has additional fine structure in the form of organelles, which are responsible for specialized processing steps in cellular function. They include:

- Nucleus- contains chromosomal DNA
- Rough & Smooth Endoplasmic
- Reticulum and Ribosomes- polypeptide production
- Mitochondria- energy production in the form of ATP
- Golgi Apparatus- sorts and packages macromolecules
- Lysosomes and Peroxisomes- intracellular catabolism
- Secretory Vesicles- transport system in/out of the cell
- Microfilaments & Microtubules- structural elements
- Centrosomes- cell division
- Cilia & Flagella- cell movement

This is summarized and captured in Figure 2a.
Figure 2. Representation of the nature of human complexity at the:
- Cellular Level
- Individual Human Level
At the individual level a single human being (see Figure 2b) consists of $\approx 37.2$ trillion cells, made up of 210 different cell types and 78 organs/organ systems. In addition, each one of us hosts $\approx 100$-300 trillion microbes, composed of $\approx 10,000$ different species that constitute 1-3% of our body weight and contain an estimated 8 million protein-coding genes. These microorganisms play an intimate and interwoven role in the health and pathobiology of the human host. The molecular machinery of the human body comprises $\approx 19,000$ coding genes, $\approx 20,000$ gene-coded proteins and 250,000-1 million splice variants and post-translationally modified proteins, over 100 million antibodies and $\approx 40,000$ metabolites. The combined length of DNA in an individual is calculated at approximately $2 \times 10^{13}$ meters, which is the equivalent of 70 round trips between the earth and the sun. We estimate also that the total number of chemical reactions/interactions occurring in a single individual is $\approx 3.2 \times 10^{25}$ per day! This exceedingly large number is actually greater than the number of grains of sand estimated to be present on the entire planet, which has been calculated at $7.5 \times 10^{18}$ grains. Even when considering a single organ, such as the brain, the complexity is still stupefying. The human brain consists of $\approx 86$ billion neurons accompanied by, at minimum, an equal number of glial cells. The wiring of the brain consists of $\approx 86$-100 trillion synaptic connections.

A further layer of complexity is that an individual human is obviously not a closed system. On a daily basis each one of us has both inputs and outputs. For example we consume on average $\approx 1.27$ Kg/day of food, and drink (if you are following current healthy living advice) $6$-8 Liters/day of fluid. It is also thought-provoking to consider that more than 25,000 bioactive food and beverage components have been identified. At any one time in the consumption of a normal meal an individual may consume several thousand individual bioactive chemicals. In addition we plaster onto our bodies $\approx 100$-500 cosmetic ingredients on a daily basis. In terms of output, we lose 6 Liters of fluid/day via urination, which contains $\approx 3000$ active chemical constituents. We also remove on average $\approx 350$-500 grams of solid waste products through defecation on a daily basis, and up to 6 Liters of sweat depending on physical exertion. All of this activity is mediated by a transport system consisting of $\approx 100,000$ Kilometers of arteries, veins, and capillaries moving approximately 5 Liters of blood and lymph fluid throughout the body. It is interesting to put all this into context and consider that a modern miracle of technology, the beloved Boeing 747 airplane has only 6 Million parts, and a mere 285 Kilometers of wiring of tubing. Is it reasonable to wonder aloud why we struggle with accurate prognosis, diagnosis, and treatment or indeed as to why we actually function at all?

We have previously discussed that it is possible to quantify human complexity, but in the case of human variability we are confounded by the range and subtlety of these differences (Figure 3). Such traits can be transitory or permanent, and influenced in complex ways by both genetic and/or environmental factors. Sources of human variability include gene mutation (germ-line and somatic), allelic differences, genetic drift, social and cultural influences, and nutrition. Common human variations include obvious visible differences such as gender, age, and physical appearance. These differences are determined through poorly understood molecular processes. Such processes are modulated by a wide variety of molecular entities and processes that include but not restricted to single nucleotide polymorphisms (SNP’s), alternative gene splicing, and protein isoforms (e.g. cytochrome P-450 super family) and epigenetic phenomena. Our basic understanding of these processes have led to the creation of simple semantic descriptors which define such differences and include concepts such as gender, age differentiation (child versus adult) and race.
WHY CHANGE? - CURRENT HEALTHCARE

Our inability to unravel the complexity of disease onset, progression and ensuing treatment has led to escalating healthcare costs. Unfortunately this has not led to a concomitant improvement in outcomes and improved healthcare delivery. This juxtaposition is occurring on a global scale and does not appear to be ameliorated by any specific healthcare delivery system. For example the healthcare systems of the USA, Switzerland, Japan and the UK are representative of a range from the predominantly private-sector driven USA, to the archetypal socialized medicine system of the NHS in the UK. These are briefly considered and described below:

However, such coarse descriptions do not provide adequate insight into the significant and subtle differences that separate us at the molecular level, given that ALL humans are 99.9% genetically the same at the DNA level.4,5

Finally an even poorer understood process is the temporal effects on complexity and variability. Paradoxically, it is the most obvious manifestation of change in terms of a function of age. We can all recognize the phenotypical differences between an infant versus a young girl versus an elderly women as highlighted in Figure 4. Also it is “well known” that we lose bone density, shrink and our metabolism slows down. However, our understanding of the changes of individuals or populations at the molecular and cellular levels is still in its infancy. The tools we have developed lend themselves to unraveling all of this dynamic complexity and variability, but how is the current healthcare system coping with these issues?
**USA Healthcare System** - This is a patchwork system that is dominated by the private sector. However, there are government administered programs that are extensive, but are typically administered via third party private insurance companies. The major programs include Medicaid (low income and limited resource individuals and families eligible), Medicare (senior citizens 65 and older eligible) and the Veterans Health Administration (serving military personnel and veterans are all eligible). In 2010 the US Congress passed the Patient Protection and Affordable Care Act (known in the USA as “Obamacare”), which was/is an attempt to provide adequate healthcare coverage to 48 million uninsured Americans. In 2014 healthcare costs constituted 16.4% of GDP, by far the most money spent on healthcare at the national level by any individual country. The spending can be further broken down into 8.5% of GDP by the private sector, and 7.9% by government supported programs, as noted in Table 1.

**Japanese Healthcare System** - The Japanese have attempted to create a universal healthcare system in which patients pay ~30% of costs and the remaining ~70% is covered by government subsidies. In addition there is a concerted attempt to provide an equal access for all policy, and the government attempts to achieve such a goal by administering price controls. At present this approach is under a systematic review by the current government of Prime Minister Shinzo Abe. Japan spent 10.2% of its GDP on healthcare in 2014 in which only 1.7% was from the private sector and 8.5% was spent by government (Table 1).

**UK Healthcare System** - The UK NHS was the prototypical system for universal healthcare under the control of a government socialized medicine program. The NHS was founded in 1948 under the stewardship of Aneurin Bevan. The current system consists of four separate, publicly funded initiatives, namely NHS England, NHS Scotland, NHS Wales and Health and Social Care – Northern Ireland all under the umbrella of the UK NHS system. The UK spent 8.5% of GDP on healthcare services in 2014 made up of a 1.5% contribution from the private sector and 7.3% from government (Table 1).

**Swiss Healthcare System** - The Swiss system is a universal healthcare system. Health insurance is compulsory for all residents of Switzerland (residency constitutes living there more than three months). It is a mixed system consisting of a combination of public, subsidized private and completely private organizations. Healthcare spending in Switzerland in 2014 was 11.1% of GDP, and consisted of 3.7% private sector and 7.3% government spending (Table 1).

Efforts to offer universal healthcare are a paramount driving force in most developed and developing countries. Even the USA, the paragon of private enterprise has continued to strive towards such a goal with the passage of the Affordable Care Act. However such efforts come at a substantial cost. The OECD estimates that healthcare costs have increased more than 4.3% annually in member countries in the past decade (1995-2010), of which only ~0.5% can be attributed to “purely demographic” developments. In the case of the four representative healthcare systems, over the past ~45 yrs (1970-2013) the percentage of GDP spent on healthcare has increased in the USA by 164.5%, Switzerland 126.5%, Japan 131.8% and the UK by 112.5% (see numbers contained in reference 29). It is noteworthy that the USA continues to spend by far the largest % GDP on healthcare based on current figures available for 2013, at 16.4%, compared to Switzerland (11.1%), Japan (10.2%) and the United Kingdom (8.5%) and this is summarized in Table 1.
There appears to be no correlation between the amount of money spent on healthcare or the particular healthcare delivery system compared to the effectiveness of disease treatment and longevity, and this is summarized in Table 1. As can be seen the USA has the shortest lifespan expectancy (as determined from birth) for both females (81.2 years) and for males (75.4 years). In the UK, which spends approximately 1/3 less than the USA in terms of %GDP on healthcare, females and males can currently expect to live 1.7 years and 0.8 years longer, respectively, compared to their American counterparts. The data is even more compelling when viewed over a 50 year period. The life expectancy of females and males (averaged values for both sexes) has increased 12.6% in the USA (70.7yrs to 81.1yrs; 1963-2013), compared to 14.7% in the UK (70.7yrs to 81.1yrs), 16.3% in Switzerland (71.3yrs to 82.9yrs) and a dramatic 19.4% in Japan (69.8yrs to 83.4yrs).

Table 1.
Analysis of percent GDP spent on healthcare compared to life expectancy and individuals afflicted with Diabetes and Malignant Neoplasms. All data from OECD 2015 Report.29,30.

<table>
<thead>
<tr>
<th>Country</th>
<th>%GDP</th>
<th>%Govt</th>
<th>%PS</th>
<th>Life Expectancy</th>
<th>Diabetes</th>
<th>Neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>16.4</td>
<td>7.9</td>
<td>8.5</td>
<td>81.2 females</td>
<td>78.2 males</td>
<td>9.6</td>
</tr>
<tr>
<td>Switzerland</td>
<td>11.1</td>
<td>7.3</td>
<td>3.7</td>
<td>85.0 females</td>
<td>80.7 males</td>
<td>6.0</td>
</tr>
<tr>
<td>UK</td>
<td>8.5</td>
<td>7.3</td>
<td>1.5</td>
<td>82.9 females</td>
<td>79.2 males</td>
<td>5.4</td>
</tr>
<tr>
<td>Japan</td>
<td>10.2</td>
<td>8.5</td>
<td>1.7</td>
<td>86.6 females</td>
<td>80.2 males</td>
<td>3.0</td>
</tr>
</tbody>
</table>

There is obviously an encouraging trend of enhanced life expectancy as evidenced in the four OECD countries discussed here. However, when you consider individual disease states and the impact of modern medical practice and treatment efficacy there is clear evidence of the limitation of current healthcare systems. Inspection of Table 1 reveals that the USA fares poorly in the prevention and treatment of disease. This is exemplified by the fact that 9.6% of the population suffers from diabetes (includes both Type I and Type II) and 318/100,000 patients have malignant neoplasm (data for 2013). These incident rates are considerably higher than Switzerland and the UK, with Japan being noteworthy for its relatively low numbers. However, what is considerably more disconcerting is to review the mortality rates of these two disease indications over a 50 yr period (1963-2012). In the case of malignant neoplasms all four healthcare systems have experienced a significant increase in the mortality rates of patients. After correcting for population growth Japan has seen an increase in malignant neoplasm mortalities of 240.9% over the past ~50 yrs. Similarly the USA has experienced an increase in malignant neoplasm mortality rates of 35.6% compared with the UK 16.5% and Switzerland 13.5% (base data obtained from reference 29). A comparable trend is observed for the most part, in the analysis of mortality rates for diabetes. In the past ~50 yrs Japan has seen increase in diabetic mortality rates of 240.9% (corrected for population growth), and likewise the USA has seen an increase of 47.0% and the UK an increase of 19.4%. The one outlier is Switzerland which has actually seen a decrease in mortality rates from diabetes when corrected for population growth of ~8% (original data from reference 29).

Every metric of modern healthcare systems indicates that current approaches to diagnosis, prognosis, treatment and outcome of disease are having limited impact. Indeed as discussed above dramatic increases in spending on healthcare have failed to reduce mortality rates of major diseases. These are powerful factors that have contributed significantly to the questioning of current medical practice and the desire for elucidating the problems and implementing new solutions to the treatment of patients. Thus was born the fledgling roots of the P-Medicine revolution.

P-MEDICINE DEFINITIONS AND RELATIONSHIPS
As with any new and emerging field of endeavor, clear definitions are often a work in progress as terminology evolves and/or disappears. In the case of Personalized and Precision Medicine it is complicated by the fact that they are often used interchangeably as umbrella terms to cover a number of other sub-specialties. Hence, the terms Personalized and/or Precision Medicine and how they are practiced have broad interpretations.

Personalized Medicine
Historically, Personalized Medicine was the initial root formation for the evolution of P-Medicine to emerge in the early 2oo0’s. This was engagingly noted by Francis Collins who wrote that “[Today] we are witnessing a revolution in the understanding of the human genome and the subsequent creation of a map
of human genetic variation. And, like most historic movements, this revolution has been given a name: personalized medicine\textsuperscript{3}. The Personalized Medicine Coalition, founded in 2004 to represent the interests of the then fledgling Personalized Medicine community, defined Personalized Medicine 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\textsuperscript{4}. Today they have modified their definition to “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 those tests with an individual’s medical history, circumstances and values, health care providers can develop targeted treatment and prevention plans\textsuperscript{5}”. In either definition it is clear that the Coan School of influence has been substantive in the shaping of Personalized Medicine and its evolution as indicated in Figure 1 and discussed above.

In those early halcyon days of thoughtfulness we and others suggested that Personalized Medicine was a descriptor that encompassed Predictive Medicine, Preventative Medicine, Pharmacotherapeutics, Pharmacogenetics, and Pharmacogenomics\textsuperscript{6-33}. The beginnings of P-Medicine started to emerge as well as some ontologies. In regards to the other main components of the P-Medicine family, Predictive medicine was defined as “the detection of changes in a patients’ disease state prior to the manifestation of deterioration or improvement of the current status\textsuperscript{34}”. Predictive medicine is a discipline that attempts to predict statistically what disease a person may get thereby allowing one to take steps to prevent disease onset or progression predictive medicine (like preventative medicine) is distinguished from other aspects of personalized medicine primarily with respect to time. Predictive medicine attempts to halt onset and early progression of disease before more invasive procedures are required; other areas of personalized medicine (see below) attempt to tailor therapy to a patient’s unique biochemical profile after disease is discovered and is at a later stage of progression. For example, a patient may have a genetic profile that indicates he is likely to develop coronary heart disease. His/Her physician may then prescribe a statin in order to delay or even completely eliminate the onset of disease.

The American Board of Preventive Medicine defined Preventative Medicine as “...that specialty of medical practice which focuses on the health of individuals and defined populations in order to protect, promote, and maintain health and well-being and prevent disease, disability, and premature death\textsuperscript{35}”. The term preventative medicine, as envisioned by Hippocrates, is a proactive medical practice that attempts to prevent disease onset and mitigates the need for medical intervention. Often Preventative Medicine involves changes in lifestyle including diet, level of physical activity, the use of supplements (vitamins and minerals), as well as the avoidance of environmental factors associated with the onset of disease. Preventative Medicine utilizes general holistic principles for healthy living. Indeed, for individuals as well as society to fully benefit from personalized medicine they must take advantage of preventative medicine. Currently it is an underutilized tool to combat disease in the developed world.

We have defined Pharmacotherapeutics as the identification of a select therapeutic agent best suited for the treatment of a specific patient possessing a well elucidated and defined molecular profile at the genomic, proteomic and metabolomic level\textsuperscript{35}. In a related manner The National Center for Biotechnology Information defined Pharmacogenomics as “a science that examines the inherited variations in genes that dictate drug response and explores the ways these variations can be used to predict whether a patient will have a response to a drug, a bad response to a drug, or no response at all\textsuperscript{36}”. Finally, the Royal Society of Medicine has defined the term “Pharmacogenetics” as an “emerging science that seeks to determine how people’s genetic make-up affects their response to medicines\textsuperscript{37}”. Essentially, Pharmacogenetics is a relatively mature field that seeks to determine the genetic role in drug response differences between individuals\textsuperscript{4}.

Hood continued to develop Personalized Medicine and masterfully interwove systems biology and big data analytics into a practical model of implementation\textsuperscript{38}. In addition he introduced the concept of P\textsuperscript{4} Medicine and its application to health, wellness and disease management. P\textsuperscript{4} Medicine was defined of “predictive, preventive personalized and participatory medicine and is the clinical application of the tools and strategies of Systems Medicine to quantify wellness and demystify disease for the well-being of the individual\textsuperscript{39}”. In that thoughtful process he introduced a new member of the P-Medicine family, namely the Participatory Patient. He argued that in the current healthcare systems the major stakeholders consist of the payers, hospitals/clinics, clinicians, pharmaceutical companies and Government regulatory and policy-setting bodies. Hood noted that in the new “Systems Medicine” (P-Medicine) approach individual patients/consumers, patient networks and patient advocacy groups would be the dominant force for change to current medical practice. He wrote that “...today’s educated consumers are beginning to demand that science-based healthcare addresses their needs for assistance in managing their own [individual] health\textsuperscript{39}.

Other independent developers of Personalized Medicine, as well as Hood, continued to stress the importance of the individual. The belief was that “actionable understanding of disease and wellness as a continuum of network states unique in time and space to each individual human being” is possible\textsuperscript{32}. The thought
process being developed suggested that the accumulation of network analysis should provide the clinician with enough information that a specific and unique care-delivery treatment could be then designed for each individual. As a continuum of that focus on the individual, it has been recently suggested that it was now time for clinical trial protocols consisting of a single patient (N-of-1 trials)38. Schork argues compellingly for adoption of such an approach but rightly notes that regulatory agencies, clinicians and research scientists would be opposed to such a model since it lacks the population-based protocols current clinical trials and medical practice require.

The prevailing theme of specific-tailored treatments for individuals was subsequently clouded by a flurry of disparate definitions of Personalized Medicine39. They included:

“...a medical model that proposes the customization of healthcare, with decisions and practices being tailored to the individual patient by use of genetic or other information.40...

“...the tailoring of medical treatment to the specific characteristics of each patient. [It] does not literally mean the creation of drugs or medical devices that are unique to a patient. Rather, it involves the ability to classify individuals into subpopulations that are uniquely or disproportionately susceptible to a particular disease or responsive to a specific treatment41.

“...a form of medicine that uses information about a person’s genes, proteins, and environment to prevent, diagnose, and treat disease42..." 

Redekop does an excellent analysis of the Personalized Medicine field as well as the plethora of competing definitions. However, he concludes that the most appropriate definition for Personalized Medicine is "the use of the combined knowledge (genetic or otherwise) about a person to predict disease susceptibility, disease prognosis, or treatment response and thereby improve that person’s health"... Thus he reinforced the idea of specific analyses for treatment of the individual.

**Precision Medicine**

The emphasis on a potential treatment of an individual without a perceived reference to a control population appears to have caused some considerable discomfort and concern. Whilst Hippocrates and the Coan School may have revered in ancient Greece, their approach to medical practice today still does not appear to be gaining traction! Thus the question became, in the minds of many, how was it possible to incorporate the exciting technological advances articulated so well by Hood that would facilitate more accurate diagnosis and effective treatment for the patient? Precision Medicine was born and joined the P-Medicine family!

The term "Precision Medicine" was first coined by Clayton Christensen in his book the Innovator’s Prescription43 published in 2009. However, the term did not gain wide acceptance and usage until a report entitled “Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease” was published by the US National Research Council (NRC) in 201144. The report laid out a series of recommendations for disease ontology predicated on molecular information content in the form of causal genetic variants or genomic information rather than a symptom-based classification system. This prompted a firestorm of activity, and the initial focus of Precision Medicine was on genetic and genomic underpinnings of disease. For example, an early definition was provided by the Institute for Precision Medicine that 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 tumor45. This type of approach garnered significant attention, but it was difficult to discern the fundamental differences practised by the Precision Medicine versus Personalized Medicine communities.

On January 15th 2015, US President Obama announced that the USA was launching a new Precision Medicine initiative. He stated that “...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”46,47. In addition he committed a $215 Million investment into Precision Medicine from his 2016 budget. Francis Collins (now Director of the National Institutes of Health) weighed in again almost ten years after his Personalized Medicine pronouncement48. He stated “advances in data science....cost to sequence an individual’s entire genome makes 2015 a perfect time to launch the Precision Medicine imitative48. Not to be outdone, the US Congress has placed an undue and heavy emphasis and reliance on genomics and Precision Medicine in the “21st Century Cures Bill” making its way through the House of Representatives (passed on July 10th 2015) and the Senate49.

More recently the scope of Precision Medicine has expanded to address much more than a genetic/genomic driven approach. A recent article suggested that Precision Medicine relies heavily on “...the ability to study biological phenomena at the OMICS level49. Even President Obama’s Precision Medicine initiative broadened the scope, and they no...now state “Precision Medicine is an emerging approach to promoting health and treating disease that takes into account individual differences in people’s genes, environments, and lifestyles, making it possible to design highly effective, targeted treatments for cancer and other diseases” (see reference 49). This is eerily reminiscent of the early, heady days of Personalized Medicine but without the very public support of politicians and policy-makers. All this begs the question what is the difference between Personalized and Precision Medicine!
CLARITY OR CONFUSION - PERSONALIZED VERSUS PRECISION MEDICINE

After the publication of the NRC report in 2011, there was a movement led by Stephen Galli (Chair of Pathology, Stanford University and NRC Committee member) to morph the name of Personalized Medicine into Precision Medicine. The argument was made that much of Personalized Medicine has been predicated on single, anecdotal stories involving lone individuals. In addition the anti-Coan School argument that the “N-of-1” model makes for a weak foundation on which to make a diagnosis, treatment and prognosis recommendation to a patient by a clinician appeared to gain credence. Another common complaint manifested was that the term Personalized Medicine implies the prospect of creating a unique treatment for each individual patient. Whilst the actual practitioners’ of Personalized Medicine have not suggested any such thing, the premise took hold and fueled the disappointment and disillusionment with Personalized Medicine.

The NRC Council Report in 2011 attempted to define and differentiate Precision Medicine from Personalized Medicine. They stated that “Precision Medicine is the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease, in the biology and/or prognosis of those diseases they may develop, or in their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not. Although the term “personalized medicine” is also used to convey this meaning, that term is sometimes misinterpreted as implying that unique treatments can be designed for each individual. For this reason, the Committee thinks that the term “precision medicine” is preferable to “personalized medicine” to convey the meaning intended in this report. It should be noted that the word “precision” in Precision Medicine is used colloquially to include both accurate and precise scientific measurement. However, based on the NRC definition, it is clear that the Precision Medicine approach utilizes individuals and well-defined (sub-)population-based cohorts that have a common knowledge network of disease (or health) taxonomy. In addition it requires an integrated molecular and clinical profile of both the individual as well as the subpopulation-based cohort. Zhang has described Precision Medicine, predicated on the individual patient/subpopulation model as “one-step-up” from the individual patient focus of Personalized Medicine. Implicit in his statement is that Personalized Medicine is based on the single individual “N-of-1” model whereas Precision Medicine uses a “1-in-N” model predicated on widely used biostatistical data analysis and “big data” analytical tools. Precision Medicine can best be described as an amalgam of Personalized Medicine and modern conventional medicine and is captured in Figure 1 (above) which depicts the taxonomic tree relationship of Precision and Personalized Medicine.

It is approximately 15 years since the advent of Personalized Medicine. In that time there appears to have been an emerging consensus that Personalized Medicine failed to deliver on its over-hyped promises. In that same period we have transitioned from a “N-of-1” model to a “1-in-N” model! At face analysis this does not appear to be significant progress, particularly in regards to patient disease diagnosis and treatment. However, this modest change and the rapid emergence of Precision Medicine have clearly captured the attention of the clinical community, policy makers and politicians. Currently political and clinical momentum is with Precision Medicine. Perhaps this is not surprising, since the “1-in-N” model is more closely aligned with conventional modern medicine which is predicated on the population model of conventional modern medicine.

The current surging trend of Precision Medicine is real and incorporates the “1-in-N” model in concert with integrated molecular and clinical data. Ten years ago we suggested that Personalized Medicine was an umbrella descriptor for a number of P-Medicine sub-specialties. The premise holds true today for Precision Medicine. We suggest that Precision Medicine is an umbrella term that includes Predictive, Preventive, Pharmacotherapeutic, Participatory Patient, Pharmacogenomic and Pharmacogenetic Medicine. This is captured and summarized in Figure 5. In all cases however these sub-specialties are also built on the “1-in-N” model accompanied by integrated molecular and clinical data.

A parallel thread that is interwoven with Precision Medicine is the development of Big Data Analytics. In this latter regard OMIC, mobile device, and electronic medical record (EMR) data will all be mined, analyzed and utilized in unprecedented ways in the future. In particular Portable (mobile) devices will be used by patients/consumers in innovative ways to monitor, maintain and diagnose health/disease states. Thus we suggest the addition of Portable Medicine to the family tree (Figure 5). Finally, there has been widespread discussion and debate about the privacy rights of patients in regards to their data and EMR’s, therefore we propose the addition of Protective Medicine under the auspices of Participatory Patient Medicine to the P-Medicine tree (Figure 5).
CONCLUSIONS

We started this paper with the statement “Current medical practice... appears to be in a crisis of identity”. Clearly the value proposition of current medical practice in the developed world leaves much to be desired. Irrespective of the healthcare system, a patient is more likely to die today of diabetes or a malignant neoplasm than 50 years ago. Is this not a searing indictment of the way we practice medicine and translate basic clinical research into actionable effect on the diagnosis and treatment of disease in patients? Part of the reason for such poor healthcare metrics is due to the staggering and poorly understood dynamic complexity and variability of individual human beings as well as populations. The “Decade of Measurements”, advent of systems biology and initiatives in bioinformatics, knowledge assembly and Big Data Analytics has at least provided us with the tools necessary to measure, analyze and understand this complexity and variability. Precision Medicine in the form of Personalized and Precision Medicine is our first attempt at realistically applying these technologies in an appropriate, meaningful and efficient manner. The goal is clearly to improve patient diagnosis, treatment and outcomes. However it is disconcerting to realize that it took ~15 years to change from a “N-of-1” model to a “1-on-N” model! In the process it has left many patients, clinicians and researchers confused and concerned that their respective contributions and needs are being ignored. It certainly raises the spectra of whether P-Medicine is simply a glacial evolutionary process, or a revolutionary process. The conundrum we all face is that “only time will tell” yet Governments keep spending and patients keep dying.

There is a weary skepticism and growing concern that P-Medicine is simply part of another hype cycle consisting of unbridled promises and claims and negligible execution and delivery. In almost every other industry hype is exposed, results in the swift demise of the company/industry sector and replaced by something that can deliver on what the customer (patient) needs and wants. In the case of healthcare, there is no alternative industry replacement, only more efficient ways to carry out allotted tasks. In that regard can P-Medicine deliver on its current promises, emanating from such lofty heights as the Office of the President of the USA? People like Gary An clearly say NO- at least not as currently designed, envisioned and stated. He argues that “...the “omics”-centric/Big Data approach to Personalized/Precision medicine is likely to fail due to the ... reasons, which, in our opinion are hard, scientific constraints”. He argues that the use of dynamic computational and mathematical modeling directed at translating cellular and molecular mechanisms to generate clinical conditions, ... provides a path towards Personalized/Precision Medicine that actually is consistent with the scientific method.”

He is not alone in his concerns, and has compelling suggestions that need to be considered. The more compelling question at the moment is, will it take another 15 years to effect simple change which only results in a name change and semantic arguments?

The global healthcare system is filled with bright, passionate and enthusiastic people at the basic/clinical research, clinical and policy levels, who have never lost sight of the needs of the patient. If only the system could learn from the Physics community. After all the latter is only dealing with the origins of the Universe, matter and space composition, and whether or not God exists!

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