Personalised Medicine

PERSONALISED MEDICINE
technological innovation and patient empowerment or exuberant hyperbole?

By Adam W. Culbertson, Dr Stephen J. Valentine and Dr Stephen Naylor

The current paradigm of modern healthcare focuses on patient symptoms, subsequent diagnosis and corresponding treatment of the specific disease(s). Escalating healthcare costs and a trial and error approach to diagnosing and treating disease have fermented a rethink in how we carry out such practices. This has led in part to the advent and development of personalised medicine, which encompasses elements of preventive, predictive and pharmacogenomics/pharmacotherapeutic medicine and focuses on methodologies and data output tailored to a person's unique molecular, biochemical, physiological and pathobiological profile. Personalised medicine is still in a fledgling and evolutionary phase and there has been much debate over its current status and future prospects. However, there are already examples of personalised medicine that have been utilised for the benefit of the patient. In addition there are numerous efforts to develop new and innovative tools, technologies and services to satisfy the growing demand from both patients and physicians. Here we describe the concept of personalised medicine, its current state of practice and impact on the pharmaceutical sector, as well as suggestions to future direction. In part the development and growth of personalised medicine will be fuelled by the informed and knowledgeable consumer as well as the thoughtful physician struggling with the complexity of disease diagnosis, onset, progression and treatment.

Hippocrates (born circa 460BC) was a visionary! While known as the Father of Modern Medicine, he might better be described as the Father of Personalised Medicine. He argued that disease was a product of environmental forces, diet and lifestyle habits, and that treatment should focus on patient care (prevention) and prognosis (prediction)[1]. Ironically, the status of current medical practice is rather different and focuses on symptomology and a correlated diagnosis as well as specific disease treatment. While there has been significant enhancements in patient care over the past century, this latter approach has led to ever increasing healthcare costs and has had limited impact on the prevention, prediction, accurate diagnosis and treatment of both acute and chronic diseases. In addition our limited understanding of causal mechanisms for onset, progression and treatment of many 21st century diseases has led to a growing awareness for paradigm change. Current medical practice seeks to treat disease post-onset, whereas, in contrast, personalised medicine attempts to identify disease prior to clinical pathology and pre-onset at the molecular level. Furthermore, it seeks to carefully classify disease and sub-types of disease such that appropriate therapies can be optimised to a patient's unique molecular profile and physiology. In this article we discuss the current status of healthcare and some of the factors fuelling change, evolution of tools and technologies that were necessary for the advent of personalised medicine, as well as survey the current status of this emerging sector of medicine.

Current healthcare

Historically, our understanding of disease aetiology and pathobiology was predicated on simple observation of physiological changes and homeostatic imbalance. More recently this concept has been replaced with an understanding that disease causality and onset is a complex multi-component process. For example breast cancer is now categorised into at least five distinct subtypes and there may indeed be many other unique molecular types[2]. Likewise, it has been well documented with identical twins that one individual may develop a genetically predisposed disease while the other sibling may never exhibit the disease or express any symptoms of that particular disease[3]. In part, this may be explained by the fact that "although DNA is relatively simple and well understood chemically, the human genome's structure is extraordinarily complex and its function is poorly understood. Only 1-2% of its bases encode proteins, and the

full complement of protein-coding sequences still remains to be established[4]."

Our inability to unravel the complexity of disease onset, progression and ensuing treatment has led to escalating healthcare costs. In turn this has had a concomitant impact on all strata of society, but particularly it has negatively affected the poor and elderly. For example there are now 48.3 million uninsured Americans (~15% of the nation's population)[5]. In addition the percentage of income growth consumed by out-of-pocket expenses has risen from 39% in 2001 to 65% in 2006[6]. In other words the cost of healthcare is expanding more rapidly than income growth per capita. In 2005, according to the Hoover Institute, the United States as a "nation spent $2 trillion" on healthcare or approximately $6,697 per capita[7]. If this trend continues, it is estimated that by the year 2015, 20% of US GDP or approximately $4 trillion will be spent annually on healthcare[8]. While the percent of GDP spent on healthcare has increased from 5.1% to 15.3%, (200% increase) during the period 1960-2005, life expectancy in the USA has only increased 11% from 70 to 78 years in the same period (see **Figure 1**)[9]. It is even more disturbing to note that the death rate due to malignant neoplasms has gone from 170 to 187 deaths per 100,000 during the period 1960-2005[9]. In other words you are more likely to die after diagnosis of cancer today then you were over forty years ago despite a significant increase in healthcare spending. Cardiovascular disease is still the number one cause of premature death in the USA. However, as shown in **Figure 1**, there has been a noticeable decrease in mortality of patients suffering from cardiovascular disorders. This has resulted in a decline in mortality from 632 to 223 deaths per 100,000 (1960-2005)[9]. However, much of that improvement has been primarily attributable to changes in lifestyle and diet, and not as a direct result of new therapeutic treatments. Thus a three-fold increase in percent GDP allocated to healthcare has not translated into better therapies and treatments for some of the most common diseases in the United States as shown in **Figure 1**.

Rising healthcare costs are also influenced by ever-increasing drug discovery and development costs as well as the limited efficacy and safety of such commercially available drugs. For example R&D expenditures by pharmaceutical companies have increased from $2 billion in 1980 to $55.2 billion in 2006[10]. Furthermore, the average cost of developing commercial drugs (including launch costs) has increased from $1.1 billion (1995-2000) to more than $1.7 billion in 2000-2002[10]. More
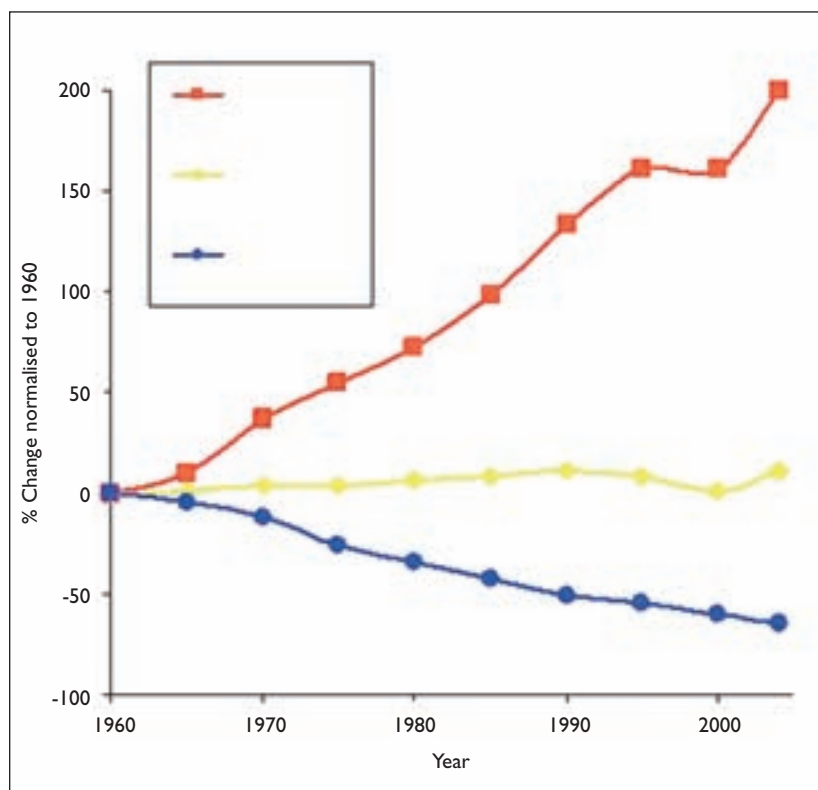
Personalised Medicine

recently the Paralexel Report states that the general consensus for the developmental cost of just a new molecular entity is $1.4 billion[10]. The cost is driven in part by a long and tedious timeline to develop the new compound which can take as long as 15 years[11]. Unfortunately, the increase in expenditure has not translated into either increased product output or practical developments such as innovative therapeutics. For example, the number of new chemical entities reached a peak in the mid-1990s and has declined by more than a factor of two[10,12]. In addition, the number of compounds reaching late stage clinical trials has decreased during this same time period[12]. According to the FDA critical path initiative, the number of phase I compounds that will ultimately be marketed has dropped from 14% to 8% over a 15-year time span[13]. Additionally, the number of drugs that fail after reaching the costly phase III clinical trial stage has increased from 20% to 50% over a 10-year timespan[13]. Increased costs resulting in fewer products is in part responsible for the rise in healthcare costs as pharmaceutical and biotechnology companies look to consumers to recapture some of the shortfall[8].

These factors continue to add pressures to an already overburdened healthcare system. In part this has stirred debate and discussion such that sci-

entists and physicians are no longer content in simply treating disease from the classical 'trial and error protocol'. A growing understanding of the limitations of this approach coupled with the emergence of new analytical and information technologies as well as systems biology (described below) has captured the scientific and medical world's imagination and is being translated into the paradigm of personalised medicine. However, as with any new idea, change occurs slowly and is often greeted with scepticism. For example a number of individuals predict that personalised medicine may be as far as 20 years out with more optimistic projections in the neighbourhood of 10 years[14,15]. Yet others have pointed out that in reality personalised medicine may have already arrived in some respects and when fully implemented may dramatically shift the paradigm of healthcare[15].

Technologies and personalised medicine

During the 20th century we have experienced an unparalleled expansion in scientific knowledge. This has been particularly pronounced in technology associated with the computational and life sciences. This explosive growth started with Turning and the first computer[16] as well as the elucidation of the structure of DNA by Watson, Crick, Franklin and Wilkins[17]. The resulting consequences were the creation of the personal computer industry and the advent of 'Silicon Valley' as well as the beginnings of the Biotechnology sector, pioneered by Berg, Boyer, Cohen, Gilbert and others[18]. In molecular biology Kary Mullis devised the polymerase chain reaction (PCR) which allowed a limited number of copies of DNA to be amplified to create a virtually unlimited supply of analyte[19]. More recently, at the turn of the 20th century, we witnessed the completion of the monumental task of sequencing the first human genome[20]. This concurrent and often independent development of technology, computational tools and life science understanding converged in the 1990s with the advent of the Omics revolution, consisting primarily of genomics, proteomics and metabolomics[21].

Despite the recent advances in omic technologies and analyses there was still a limitation in such approaches when applied to complex biological processes. In part, the inefficiency is due to the inability to produce an integrative unified methodological approach to study, for example, human disease causality. For example, it can be argued that biology occurs at the expression level and beyond. Genomics alone, which has produced a plethora of new information, fails to fully

account for phenotypic expression of disease which can be significantly affected by factors such as epistatic mechanisms. Thus this failure to integrate various omic platform technologies has, in part, caused a limited development of new disease insight and understanding.

Recognition of these limitations as well as the confluence of technologies and information from the emerging fields of genomics, proteomics and metabolics resulted in an integrative approach (systems biology) for characterising biological organisms. Systems biology is also referred to as "pathway, network, integrative or new biology[22]" and can be thought of as a more holistic, big-picture approach to the study of organisms with an attempt to understand how one cascade of molecular events in an organism relates to another. It has been defined as "..the study of all the elements in a biological system (all genes, mRNAs, proteins, etc) and their relationships to one another in response to perturbations[23]". Simply put, it is a new scientific field accompanied by a varied tool kit assembled from methods developed in a variety of fields including biology, biochemistry, analytical chemistry, molecular biology, bioinformatics and statistics. The end product of systems biology characterisation is a more systematic and accurate representation of an organism's complex biochemistry and physiology.

Previously we have lacked the necessary technological prowess to develop approaches such as systems biology due largely to deficiencies computational and analytical equipment and strategies. For example, it is now possible to compute increasingly complex algorithms and to generate thousands of gigabytes of data[24]. Many new tools are being developed such as the ability to process and store this voluminous data in a cost-effective manner. Additionally, advancements in analytical chemistry such as condensed-phase separation strategies as well as mass spectrometry (MS) have now made it possible to analyse incredibly complex protein mixtures as well as to characterise ever lower amounts of analytes[25]. The confluence of all of these technologies and experimental concepts has laid the foundation for the advent and development of personalised medicine.

Definitions of personalised medicine

As with any new emerging field of endeavour, clear definitions are often a work in progress. In the case of personalised medicine it is complicated by the fact that it is often used as an umbrella term to cover a number of other sub-specialties. Hence, the term personalised medicine as well as the concept of how personalised medicine is practised has broad interpretations. Francis Collins recently 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: personalised medicine."[26] The Personalised Medicine Coalition defines personalised 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"[15]. As described, personalised medicine is more of an umbrella term encompassing predictive medicine, preventative medicine, molecular medicine, pharmacogenetics, pharmacogenomics and pharmacotherapeutics.

Predictive medicine is defined as "the detection of changes in a patient's disease state prior to the manifestation of deterioration or improvement of the current status"[27]. 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 personalised 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 personalised 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 physician may then prescribe a statin in order to delay or even completely eliminate the onset of disease.

The American Board of Preventive Medicine defines preventative medicine as "Preventive medicine is 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."[28]. 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 utilises general holistic principles for healthy living.

Indeed, for individuals as well as society to fully benefit from personalised medicine they must take advantage of preventative medicine. Currently it is the most underutilised tool to combat disease and illness in the developed world.

The Royal Society of Medicine defines the term 'pharmacogenetics' as an "emerging science that seeks to determine how people's genetic make-up affects their response to medicines"[14]. Essentially, pharmacogenetics is a relatively mature field that seeks to determine the genetic role in drug response differences between individuals[29]. The National Center for Biotechnology Information (NCBI) defines 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"[30]. The paradigm shift to pharmacogenomics coincides with the advent of the 'omics revolution where emphasis is placed on studying "the whole"[29]. For example, because drugs interact with multiple proteins involved in multiple cellular processes, a more comprehensive characterisation is required. Indeed, it has even been suggested that pharmacogenomics may "include all –omics disciplines applied to drug therapy"[29]. In that respect, the term is similar to molecular medicine; however, generally molecular medicine encompasses a broader range of topics. Essentially, pharmacogenomics seeks to tailor treatments to a person's unique molecular make-up.

Molecular medicine should be viewed as an understanding of disease and its pathology at the molecular level. Examples include the levels of such molecules as DNA, RNA, proteins, and metabolites. Detailing the relationship of such molecules to aberrant cellular processes such as transcriptional, translational, or metabolic events is a goal of molecular medicine[31].

A broad aim of personalised medicine is to use a molecular characterisation approach to create a better system for disease classification. It is anticipated that this work will lead to earlier interventions and more specific treatments predicated on the individual's specific biochemical fingerprint. This is in stark contrast to current medical practice. The differences in approach can be symbolised in the form of an iceberg (**Figure 2**). Since the time of Hippocrates scientist and physician alike have viewed and interpreted disease at the 'visual' level, namely the organism, organ and more recently tissue[32,33]. Personalised medicine offers the alluring promise and potential of uncovering the largely
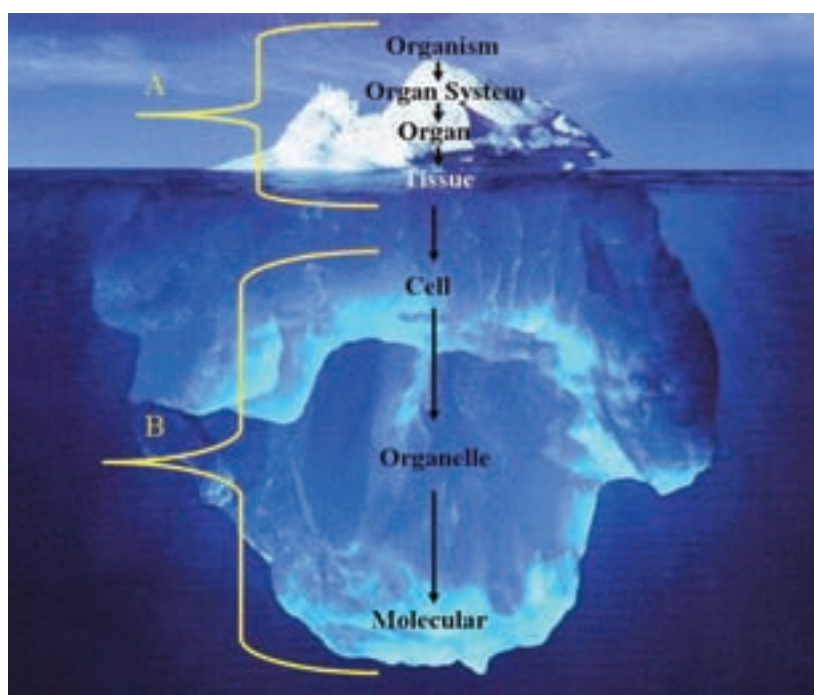
'unseen' details of disease causality, onset and progression. For example, while general disease phenotype is generally the same from patient to patient (tip of the iceberg), the picture is enhanced (eg stage of progression) by viewing disease at its onset and monitoring progression at the molecular and cellular level (hidden unseen mass) (see **Figure 2**)[34]. The degree of success in individualising medicine in this manner will depend on the degree to which the molecular aspects of the disease can be elucidated and measured.

Much of what is described above can be deemed conjecture. However, to date there are some specific examples of personalised medicine approaches currently utilised to benefit patient disease diagnosis and treatment.

Examples of personalised medicine
Breast cancer diagnosis and treatment
There are an estimated 210,000 newly diagnosed cases of breast cancer reported annually in the USA[35]. For much of the 20th century our understanding of breast cancer manifestation and progression was extremely limited and it tended to be regarded as a single disease. However, today it has been recognised that at least five different molecular sub-types of the disease exist[2]. This has prompted a reassessment of disease prognosis and treatment. The development of diagnostics and specific therapies for breast cancer make it an excellent example of a harbinger of personalised medicine.

Figure 2
Illustration of the characterisation of disease at various functional levels within an organism. The brackets highlight the time period at which useful medical information was obtained. (A) represents those levels for which traditional medicine has been successful originating in the 18th and 19th centuries. (B) represents the extended region accessible by personalised medicine. Such practices have emerged only recently (~1970)

Personalised Medicine

Molecular classification of breast cancer is essential to obtain the best possible treatment. Thus several diagnostic assays exist for more concise classification of cancer sub types. The five well-characterised subtypes include Luminal A, Luminal B, basal type, HER2 positive and unclassified which can all be distinguished by immunohistochemical (IHC) stain[2]. In addition, further categorisation exists providing more specifically characterised types of breast cancer. These include the progesterone receptor positive (PR) and estrogen receptor positive cases (ER); the latter is discussed below in the context of tailoring therapies. Of all cases of breast cancer, ~30% are characterised by the cell surface protein HER2, which is involved in the regulation of normal cellular growth[36]. However, a mutation in the gene that encodes the HER2 cellular surface protein can cause over-expression of the HER2 protein and abnormal cell growth. The over-expression of HER2 has been characterised as a very aggressive form of breast cancer and is associated with poor survival rates[37].

Currently there exist two tests that can confirm the diagnosis *in vitro* for the over-expression of the HER2 protein. They are the Fluorescence In Situ Hybridisation (FISH) and the Immunohisto Chemistry (IHC)[38]. Once the classification of the specific cancer subtype is found optimal therapy such as adjuvant therapy with the monoclonal antibody Herceptin® can be selected to combat the disease. The therapeutic is accompanied with the Hercep test diagnostic that confirms the use of the drug. The monoclonal therapy simply binds to cellular receptor HER2 protein. The binding inhibits cellular replication thus stopping the cancer in a targeted approach based upon the cancer molecular pathology. Treatment has fewer side effects and is a more efficacious approach to cancer treatment because it is based upon the tumour's molecular classification.

As mentioned above, one of the distinguishing characteristics of breast cancer subtypes is the ER+ case which has a diagnostic test allowing patients' physicians to determine the necessity of costly and painful treatments such as chemotherapy. The assay OncotypeDx is most beneficial for women who have ER+ cancer in stages one and two and have no lymph node involvement[39]. To date one problem with the current treatments of breast cancer is that in an effort to kill tumours, patients are given large doses of chemotherapeutics. Current cancer protocol calls for a one size fits all model of medicine. "We're giving a tremendous amount of chemotherapy in this country with very little benefit," according to Randy Scott,

CEO of Genomic Health. "Current treatment guidelines recommend chemotherapy for as many as 90% of breast cancer patients," he noted, "yet 85% don't need it, because their cancer isn't going to reoccur. Of the 15% that do, chemotherapy will only reduce the recurrence rate to 11%."[40] The test is a reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay that uses 21 previously identified cancer genes and can be used to place patients into a low, intermediate or high risk category for reoccurrence of cancer after initial treatment[41]. These categories can be used to "predict the likelihood of breast cancer recurrence in women with newly diagnosed, early-stage invasive disease and assesses the benefit from certain types of chemotherapy[40]".

To reiterate the aspects of personalised medicine already present with respect to breast cancer, the Oncotype DX and HER2 therapeutic/diagnostic allows for a more precise characterisation of the breast cancer based upon molecular characteristics. As mentioned above, in a real sense, personalised medicine is already here (or at least several aspects are). Currently there are a multitude of diagnostic tests and products that allow physicians and patients to customise their treatments to a component of the patient's personal biochemical profile. However, with information comes decision-making and this can be a complicated process that requires a clear diagnostic and treatment paradigm. This is outlined in **Figure 3** as a decision making tree for breast cancer treatment utilising a personalised medicine approach.

Gleevec

Chronic myelogenous leukemia (CML) accounts for approximately 13% of the 4,500 cases of leukaemia diagnosed each year in the United States[41]. Gleevec is a tyrosine kinase inhibitor which can used to treat both CML and also malignant gastrointestinal stromal tumours (GIST)[42]. The drug is indicated for use with Philadelphia chromosome positive tumours caused by the binding of an abnormal protein Bcr-Abl 12 which causes the uncontrolled replication of white blood cells[15]. The use of Gleevec can be confirmed as the appropriate treatment with a diagnostic that confirms the presence of the Bcr-Abl gene complex. The treatment is specific to patients with CML and uses a monoclonal therapeutic. Additionally, though not all patients respond to Gleevec, there now exists a test to exclude the ~5% of the patients that do not respond to Gleevec therapy. A test by Genzyme can further exclude non-responders to avoid unproductive therapies[43]. The drug is a success story due to
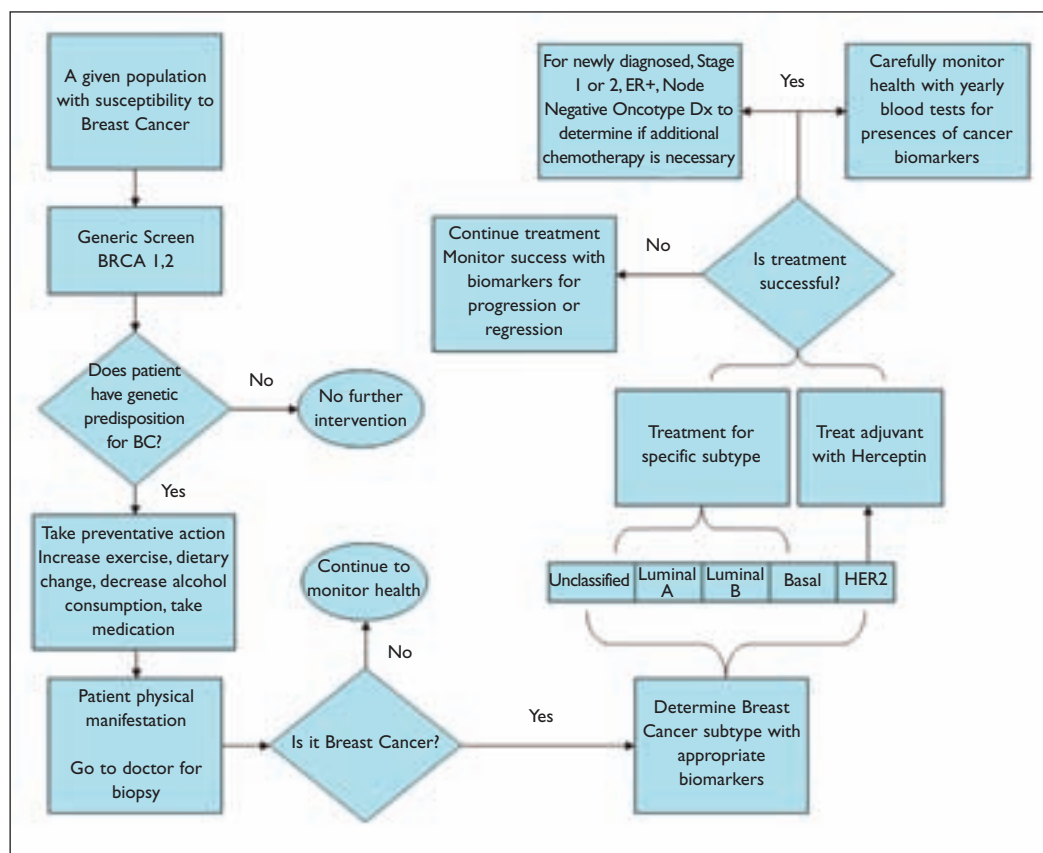
its 90% overall positive response rate of which many experience complete remission[15].

Warfarin genetic test
The correct dosage of the cardiovascular drug warfarin is difficult to determine for patients with thrombosis. The problem with prescribing warfarin is that the optimum dosage is different for every patient due to genetic differences in the approximately 60 different versions of the cytochrome P450 family of genes[44]. One of these is a variation in the gene encoding vitamin K epoxide reductase complex 1(VKORC 1) which is associated with the metabolism of warfarin[45]. If a patient receives too much of the drug there is a chance of death resulting from severe haemorrhaging. Conversely if not enough of the drug is administered there is risk of embolism in an arteriole and the occurrence of a stroke. Despite the risks, the drug has the potential to save the lives of many patients; patient compliance is absolutely necessary. The company Genelex currently provides a diagnostic service that screens for SNP variants in VKORC 1 and CYPR2C9[45]. With such information physicians are able to more efficiently adjust drug dosage in patients with the attenuated copies

of the mutant alleles. Thus dosage of warfarin can now be specifically tailored to an individual's genes coding for CYPR and VKROC1 rather than relying on an empirical determination. The result for patients is to optimise drug dosage quickly and effectively. This is in contrast to giving the patient a low-dosage of the drug, having the patient return some time later, and adjusting the dosage until it is correct. So patients can save costly, repeated trips to the doctor, have the benefit of the correct dosage right away and doctors do not have to rely on the patient's explanation to gauge whether the dosage is optimal.

Drug dosing chip
Roche Pharmaceuticals states on its website that it aims to "determine disease predisposition, provide information that can act upon to prevent or delay the onset of illness, and even monitor treatments". The company currently produces the AmpliChip, a DNA chip-based diagnostic test that aids in individualised drug dosing. According to Roche's website (www.roche.com) the CYP450 is "the world's first pharmacogenetic microarray-based test approved for clinical use. The AmplicChip CYP450 Test provides comprehensive coverage of

Personalised Medicine

References
1 Hippocrates. Encylopaedia Britannica. 2007 Encyclopedia Britannica Online. 25 Apr. (2007) (http://search.eb.com/eb/article-9040540).
2 Yang et al. Cancer Epidemiology Biomarkers & Prevention 16 (3): 439-443 Mar (2007).
3 Fraga, MF et al. Epigenetic differences arise during the lifetime of monozygotic twins. Proc. Natl. Acad. Sci. 102(30): 10413-10414 (2005).
4 Collins, F et al. A vision for the future of genomics research. Nat. 422: 835-847 (2003).
5 Center for Disease Control website; (http//www.cdc.gov).
6 Burill & Company. Personalized Medicine are we really ready for this revolution. Oct. 18, 2005 slide 20.
7 Hoover Institute. www.hooverinstitute.com (http://www.hoover.org/research/factsonpolicy/facts/5854746.html).
8 Washington Alliance for a Competitive Economy. November 17, 2006.
9 OEDC Health Database 2006. June 30, 2006. version 6/26/2006.
10 Accenture. The Pursuit of High Performance through Research and Development. Understanding Pharmaceutical Research and Development. accessed from http://www.phrma.org/files/Accenture%20R&D%20Report-2007.pdf June 17, (2007).
11 Innovation. http://www.innovation.org/index.cfm/InsideDrugDiscovery.
12 Galson, S. FDA. Center for Drug Evaluation and Research (CDER). Drug Regulation Update. Well-Characterization Biotechnology Products. "WCBP2006" 2006 CDER Update. January, 18 (2007).
13 FDA. Critical Path Initiative: History, Objectives, Approach, June 21 (2005) www.fda.gov/oc/critical path/presentations.
14 The Royal Society: Personalised medicines: hopes and realities. 1-50: September, (2005).

gene variations – including deletions and duplications-for the CYP2D6 and CYP2C19 genes, which play a major role in the metabolism of an estimated 25% of all prescription drugs. It is intended to be an aid for physicians in individualising treatment selection and dosing for drugs metabolised through these genes[14]. This is yet another example of a currently available personalised medicine approach which allows for a more quantified approach to medicine. This should ultimately encourage more patient drug compliance and if used on a broad scale has implications with respect to increasing the efficacy and safety of pharmaceuticals as adverse drug reactions are a major problem in the current system.

Personalised medicine companies

In this emerging new sector, private enterprise has already recognised the potential of personalised medicine to radically alter the landscape of patient care. In addition, since personalised medicine empowers the individual there are numerous ongoing efforts to provide personalised medicine services to the engaged and concerned consumer. They vary from companies which provide: 1. Home-brew testing kits; 2. Convenient testing services; 3. Predictive tools for determining health and wellness; 4. Websites for self education and diagnosis, innovative knowledge tools for better informed decision making and individual patient medical record keeping; 5. Check-in facilities for patients health and wellness programmes. 6. Advocacy and policy for personalised medicine. All these companies offer a broad range of services that provide the consumer with options to participate in determining and defining their own health and well-being. Listed below are representative examples of some of the companies and organisations involved in commercial activities in this rapidly emerging space.

1 Home-brew kits
DNA Direct, San Francisco, CA
www.dnadirect.com
DNA Direct provides a number of home-brew DNA test kits for a multitude of disease such as breast cancer, drug metabolism and cystic fibrosis. The test is completed by the consumer in his/her own home without any medical supervision and the kit is returned directly back to the company. Subsequently a report based on the data acquired from the testing of the consumers DNA is provided back to the customer, as well as his/her physician. At present this approach requires no regulatory and agency (FDA) oversight.

Sciona, Boulder, CO
www.sciona.com
Sciona is a personalised medicine company that, according to its website, is a leader in "nutrigenomics, the science of personalising your nutrition and lifestyle decisions". It offers "personalised health and nutrition recommendations based on an individual's diet, lifestyle and unique genetic profile". Sciona is another example of an existing company that offers health and wellness products directly to the consumer. The company is regulated under CLIA, the clinical laboratory improvement amendment passed by congress in 1988. It should be noted that CLIA, though less stringent than FDA regulations, certainly brings greater credibility to its testing services.

2 Convenient testing services
Lifeline Screening, Cleveland, OH
www.lifelinescreening.com
This is a company that offers a broad range of health services, primarily in preventive medicine. According to its website, it proposes "...to make people aware of an undetected health problem and encourage them to seek follow-up care with their physician. We are dedicated to providing the highest quality preventive screenings at an affordable rate." Preventative healthcare has tremendous potential to alter the paradigm of healthcare with a proactive approach that again allows consumers the ability to take charge of their own health. The company will test for various markers of disease that include blood sugar, C-reactive protein and a complete lipid panel. Additionally, it has ultrasound technology and specific disease screening strategies for stroke/carotid artery, abdominal aortic aneurysm, peripheral arterial disease and osteoporosis screenings.

BioPhysical250, Austin, TX
www.biophysicalcorp.com
Biophysical250 offers preventative medical services geared toward the health conscious consumer. The company's website states that it offers a test "...that combines more than 250 biomarkers used by cardiologists, oncologists, rheumatologists and other specialists that could indicate medical conditions and diseases, often before symptoms appear." The website states that its panel "is comprised of approximately 60 biomarkers commonly used in general medicine, 80 biomarkers used in 12 medical specialties and 110 biomarkers that are primarily used in medical research". Furthermore, customers will fill out a short medical questionnaire, and then schedule a blood draw with a phlebotomist at a predestinated location or even at a customer's office. The completed test is then mailed to customers and they offer

15 Personalized Medicine Coalition. The Case for Personalized Medicine. September, (2006).
16 Encyclopaedia Britannica. 2007. Encyclopaedia Britannica Online. http://www.britannica.com/eb/article-216035>. 18 June (2007).
17 Watson, JD and Crick, JHC. A Structure for Deoxyribose Nucleic Acid Nature 171, 737-738 (1953).
18 Biotechnology Hall of Fame. (http://www.chemheritage.org/exhibits/biotech/boyer.html).
19 Mullis, KB. Target amplification for DNA analysis by the polymerase chain reaction. Ann Biol Clin. ;48(8):579-82 (1990).
20 Human Genome Project. Facts About Genome Sequencing. (http://www.ornl.gov/sci/techresources/Human_Genome/faq/seqfacts.shtml).
21 Lederberg, J.and McCray, A. 'Ome Sweet 'Omics – A Genealogical Treasury of Words. The Scientist 15(7):8 April, 2 (2001).
22 Naylor, S. System Biology, information, disease, and drug discovery. Drug Discovery World. Winter (2004/5).
23 Hood, L. A personal view of molecular technology and how it has changed biology. J. Protome Res. I:300-409 (2002).
24 Kalyanaraman, A et al. Proceedings. 20th International Parallel and Distributed Processing Symposium 10 (2006).
25 Koeniger, S. An IMS-IMS Analogue of MS-MS. Anal. Chem. 78, 4161-4174 (2006).
26 Collins. Boston Globe. Personalized Medicine a New approach to Staying Well. July 2005. (http://www.boston.com/news/globe/editorial_opinion/oped/articles/2005/07/17/personalized_medicine/0.
27 Gunter, K and Tarnok, A. Cytomics in Predictive Medicine. Clinical Cytometry 53B: 1-3 (2003).

a second copy to customers and "encourage" customers to mail a copy to their physicians. The personalised test utilises primarily antibody-based technologies but "does not require approval by the Food and Drug Administration for diagnostic or clinical use". The current cost per test is listed at $3,400.

3 Predictive services
BioSignia, Durham, NC
www.biosignia.com

This company offers a variety of services and tools to patrons of personalised medicine. Most notability is its Know your Number (KYN)® service that according to the website "...puts physicians and healthcare providers on the same page with their patients". Additionally it is noted that "healthcare providers need a chronic disease health risk assessment and communication tool designed to promote good health". The service provides patients with a score for various diseases in a simple graph format. They offer a sample report on their website and it appears as if they use traditional biomarkers such as glucose testing, cholesterol levels and triglycerides that provides a percent probability for onset of diseases such as stroke and Type II diabetes.

Predictive Physiology and Medicine (PPM), Bloomington, IN
www.ppmone.com

PPM is currently developing a set of tools to provide consumers with a "Health and Wellness Index" based upon body fluid measurements employing its NetFit process. The index will be provided to consumers in report format and will include an indication of current health status as well as disease predisposition. Accessible via secure server, the customer can view their respective health reports. The report will offer patrons a view of their whole biochemical fingerprint which is the closest description of their phenotype, as opposed to DNA genotyping. A goal is to encourage patients to utilise the NetFit concept in combination with annual physicals where it is anticipated that the rapid results and ease of use will embolden patients to monitor their health more frequently.

4 Patient tools
Revolution Health, Washington, DC
www.revolutionhealth.com

Revolution Health is the current brainchild of Steve Case, former CEO of American Online. Case has noted that "… healthcare was in dire need of transformative change, and [I] decided to build another company that could be a change agent, with the goal of shifting power into the hands of people

themselves". Revolution Health is not actually a provider of direct medical services but is a critical information portal that embodies the principals of personalised medicine and seeks to create a new era of medical care. The website empowers consumers to rate doctors, hospitals, treatments and share ideas with other patients around the globe who are experiencing the same ailment. In addition, the website provides patients with a secure place to store there own medical records. There is even a way for consumers to fax hard copies of their medical records and have them digitalised. The significance of this opportunity for patients to cost effectively store their own up-to-date medical information has tremendous implications for the field of personalised medicine. For physicians to provide effective treatment at the personalised medicine level, it is vital that they have ready access to current and complete medical histories of patients.

5 Check in facilities for patients health and wellness programmes
MayoClinic, Rochester, MN
www.MayoClinic.com

Mayo Clinic, as a premier healthcare institution, has been at the forefront of promoting what it terms 'Individualised' medicine. It offers an award-winning website MayoClinic.com to help health conscious consumers learn about various ailments and conditions. The site offers a great deal of information and informative articles that are often linked on other sites such as Revolution Health. The site offers information on diseases and conditions as well as a section to make appointments at one of the three locations in Rochester, MN, Jacksonville, Fl, and Scottsdale, AZ. Additionally, there is information about correct therapeutic drug and nutritional useage, and a healthy living section with topics including health, fitness and nutrition. More recently, it announced the appointment of a Director of Individualised Medicine to promote its implementation of personalised medicine at Mayo Clinic/Foundation.

6 Advocacy and policy for personalised medicine
Personalised Medicine Coalition, Washington, DC
www.personalizedmedicinecoalition.org

The PMC is a non-profit advocacy group for the implementation of personalised medicine. It is actively involved in shaping the public policy on personalised medicine. Its website offers a plethora of information from slide presentations, links to personalised medicine articles and a vast number of corporate partners. In addition the PMC has published several key papers on the subject.

Currently many of the aforementioned companies

are leaders in the personalised medicine space. Several offer cutting-edge diagnostic tests, others use the current standard of care proactively to improve the current paradigm of healthcare in America. Overall the industry is still in its infancy with some interesting questions being played out. More recently, the regulatory agencies which oversee the diagnostic industry have taken a closer look at this industry and how it is interacting with the consumer. In particular, the Government Accountability Office recently held hearings over "direct-to-consumer genetic testing". It reported that its "investigators bought kits from four businesses: test-kit companies Suracell of Montclair, NJ; Genelex of Seattle, WA; Sciona of Boulder, CO; and Greensboro, NC-based internet marketing company Market America. All four advertise that they sample four to 19 genes to provide consumers with personalised diet and lifestyle recommendations[46]". The strongly worded GAO report concluded that "all the tests GAO purchased misled consumers by making predictions that are medically unproven and so ambiguous that they do not provide meaningful information to consumers[47]". Clearly, as company providers of personalised medicine continue to target the consumer then government agencies will provide critical oversight activity and ultimately additional legislation if needed.

There are clearly numerous issues to be considered in the personalised medicine space. Many of them, such as patient privacy and confidentiality of medical records, have already been addressed by current medical practice and legislation. That said, the latter examples showcase companies which offer services to the health conscious consumer in a thoughtful and scientifically credible manner. These examples demonstrate tools that have yet to be fully implemented and when accomplished stand to shift the paradigm of healthcare in a more positive direction. Particularly, the services that seek to involve consumers and encourage them to take a more proactive role in their own health stand to make a tremendous shift in the standard of care and have tremendous potential to lower healthcare costs in the United States and abroad.

Pharmaceutical industry and personalised medicine

As noted above, the average cost of bringing a therapeutic drug to market is estimated to be ~$1.4-1.7 billion[10]. In addition, the current business model employed by large pharmaceutical companies necessitates the continued launch of blockbuster drugs. By definition this requires annual market sales of >$1 billion per year, which are necessary to support their significant R&D budgets. It appears that under the current model it is unlikely that large pharmaceutical companies will embrace a personalised medicine model, where drugs are tailored more to the individual consumers genetic and omic profile. The blockbuster model appears at odds with such an extreme market-segmented model, based on R&D cost of individual pharmacotherapeutics, lack of ROI and potential huge liability issues. However, Steven Little in a recent *DDW* article[48] argued eloquently that there is the possibility for change in this industry. He listed four ways that personalised medicine can be practically utilised for both the benefit of the patient and industry: (1) The use of a diagnostic coupled with a targeted treatment can allow for "use of personalised medicine to differentiate a 'me-too' product in a crowded marketplace. (2) Obtain extended patent protection on the drug/diagnostic combination. (3) Reduce time to market by the use of orphan drug status. (4) Resist the threat of the diagnostics industry".

The pharmaceutical industry has yet to completely adapt to personalised therapies, but ironically there are "already targeted therapies on the market for cancer, allergies and rheumatoid arthritis, and many others are in development. The sooner Big Pharma gets behind personalised medicine, the sooner the industry will regain its ability to innovate"[49]. However, in spite of the hurdles faced by large pharma, there are compelling market forces under way to provide more focused therapeutic agents. "Boston Consulting Group reports that the hundreds of tiny biotechs, while responsible for only 3% of the drug industry's total R&D spending, can lay claim to 67% of the drugs in clinical trails. Almost all are personalised medicine drugs."[49] This is an area that will continue to attract considerable interest and investment. It has been said that "Pharma does not exist in a vacuum – there are many other stakeholders with an interest in the development of personalised medicine"[48]. Some of these stakeholders are going to cause changes independently of the pharmaceutical industry so when answering the 'what's in it for me?' question the industry needs to consider not only 'how can we use personalised medicine to sell more drugs?' but also 'how can the use of personalised medicines protect our existing sales against changes in the marketplace?'[48]

Conclusions

The current healthcare system is under siege. Escalating costs will reach unsustainable levels within the next eight years[8]. What can be done? Some argue that personalised medicine offers

28 American Board of Preventative Medicine. Booklet of Information. accessed on http://www.abprevmed.org/public/infobook.pdf. Feb. (2007).
29 Sadee, W. Pharmacogenomics: the implementation phase. AAPS PharmSci 4(2): 1-5 (2002).
30 National Center for Biotechnology Information (NCBI). Just the Facts: A Basic Introduction to the Science Underlying NCBI Resources. One Size Does Not Fit All: The Promise of Pharmagenomics. (http://www.ncbi.nlm.nih.gov/About/primer/pharm.html) accessed June, 21 (2007).
31 Human Genome Sequencing Center (HGSC). Baylor College of Medicine. HGSC Glossary. http://www.hgsc.bcm.tmc.edu/docs/HGSC_glossary.html.
32 Mann, RD. From Mithradatium to modern medicine: the management of drug safety. Journal of the Royal Society of Medicine. 81: 725-728 (1988).
33 Drews. J. Drug discovery: a historical perspective. Science. 287(5460): 1960-1964 (2000).
34 Prous, JR, Khurdayan, VK. The Story so far in R&D. Drug News Perspect. 20(1): 7-15 (2007).
35 National Cancer Society, Breast Cancer Facts & Figures 2005-2006. http://www.cancer.org/downloads/STT/CAFF2005BrF.pdf.
36 Mendard, S et al. Biologic and therapeutic role of HER2 in cancer. Oncogene. 22(42): 6570-6578 (2003).
37 Piccart-Gebhart, MJ et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Eng J Med; 353;1659-72. (2005).
38 Herceptin (trastuzmab) (Herceptin; www.herceptin.com).
39 OncotypeDx. (http://www.genomichealth.com/oncotype/).
40 Rawson, K. The RPM Report. Reimbursing Designer Drugs. Vol. 1, No. 10 Oct. (2006).

Personalised Medicine

41 Paik, S et al. A Multigene Assay to Predict Recurrence of Tamozifen-treated, Node-Neg. Breast Cancer. NEJM. 351(27): 2812-2826 (2004).
42 Jabbour et al. Current and Emerging Treatment Options in Chronic Myeloid Leukemia. Cancer; 109: 2171-2181 (2007).
43 Genzyme website (http://www.genzyme.com/) http://www.genzymegenetics.com/testmenu/tests/cancer/geneptestmenucantestBCRABL.as accessed May, 30, 2007.
44 Rider, M et al. Effect of VKORC1 Haplotypes on Transcriptional Regulation and Warfarin Dose. N Engl J Med. 352;22: 2285-2293 (2005).
45 Genelex. http://www.healthanddna.com/professional/pharmacogenetics.html.
46 Appleby, J. USA Today. GAO ounces on home DNA test to predict disease. July, 27 (2006).
47 United States Government Accountability Office. Testimony Before the Special Committee on Again, U.S. Senate. Nutrigenetic Testing. Test Purchased from Four Web Sites Mislead Consumers. GAO-06-977T Thursday, July 27 (2006).
48 Little, Stephen. Personalised Medicine What's in it for big pharma?. Drug Discovery World. Winter: 19-22 (2006).
49 Unknown. Business Week online. http://www.businessweek.com/magazine/content/04_42/b3904034_mz011.htm link . October 18, (2004).
50 http://www.cdc.gov/nchs/data/nvsr/nvsr54/nvsr54_19.pdf.

tremendous potential for reducing healthcare costs while at the same time providing more efficacious therapies for the individual consumer[15]. In addition there is a powerful grass-roots advocacy group in the form of the baby boomer generation who can be described as 'ageing activists'. Many of these individuals are interested in assuming more control over the quality of healthcare currently available and are demanding better treatments at lower cost. Additionally, economic factors will provide momentum for the development of personalised medicine as biotechnology and even pharmaceutical companies seek to capitalise on previously untapped markets as well as consumer enthusiasm.

Personalised medicine is a rapidly growing arena of activity and awareness. Current thought leaders recognise the potential of personalised medicine to reinvigorate the healthcare system as a whole. In addition, a small, but growing, number of companies are building business models around personalised medicine as opportunists and visionaries see the monetary potential of this new thinking. Examples of various companies and business models range from those that provide home-brew test kits to walk-in clinics where comprehensive preventative physicals can be performed. In essence, on one level or another, personalised medicine is utilised today. Perhaps the best illustration for successful personalised medicine is breast cancer where individually tailored therapeutics have been utilised over the past few years.

Personalised medicine is not just exuberant hyperbole! There is a growing trend in the use and understanding of personalised medicine. The concomitant increase in knowledge and information available about an individual's health and wellness and/or disease is providing a new paradigm focused on the molecular level which provides much greater detail than the macro level organism, organ tissue system. The potential of this approach in the future to restructure our understanding of individualised human health is significant. Such possibilities include (but are not limited to): the prevention of disease onset and progression, early detection of disease, the development of more safe, efficacious drugs and the determination of optimal drug dosage, and the elimination of costly and ineffective treatments.

Personalised medicine is still in its infancy – can it deliver and what is the timeframe? Some have argued it is 20 years away[14], however, it appears that personalised medicine is already here. Certainly there are numerous issues to address. For example, the role of the regulatory agencies is yet to be determined. Other issues include: who will

pay for personalised medicine? What protections need to be in place to protect people from genetic discrimination? How can we educate the next generation of physicians on personalised medicine in order to optimise its implementation? The answers to these questions and many others that arise during the development of personalised medicine make for an extremely interesting future. However, more so than ever before in the history of medicine it will be determined by the individual consumer and his or her needs. In the age of instant information and news, the individual now has tools available to help them determine, shape and influence their own health and wellness. Now, that's personalised medicine!   DDW

Adam W. Culbertson graduated from Indiana University with a Bachelors of Science in Biology and with a concentration in Chemistry. Additionally, he completed a certificate in the notable Managing in the Life Sciences Program from the Indiana University Professional Development Program. This programme won The 2006 Indiana Council for Continuing Education Statewide Award for best new programme. Mr Culbertson is the co-author of two manuscripts currently being written as well as the first author of a recently submitted article describing personalised medicine in the 21st century. Currently, he is working on the development of the PPM analytical platform focusing on areas such as sample acquisition and the development of high-throughput sample preparations protocols. This work involves the automation of plasma sample digestion and clean-up as well as digest analysis via electrospray ionisation (ESI) and mass spectrometry (MS).

Dr Stephen J. Valentine has extensive experience with the development of ion mobility spectrometry (IMS), mass spectrometry (MS) instrumentation resulting in 30 publications in the area. As the first employee of the biotechnology company Beyond Genomics, Dr Valentine led efforts to develop an IMS-MS instrument for proteomics analyses. Here he directed a group of design engineers, scientists, data acquisition experts and machinists to increase the overall resolution and sensitivity of IMS-MS instrumentation while decreasing construction costs. Additionally, he oversaw the transfer of the technology from the development site to the corporate headquarters and provided training to scientists regarding the use of the instrumentation for liquid chromatography (LC)-IMS-MS proteomics studies. During his time with PPM, Dr Valentine

has served as the principal investigator for a small business research innovation (SBIR) grant where he directed efforts to analyse human plasma using two-dimensional (2D) LC-IMS-MS techniques. From those studies, his team has been able to construct one of the largest annotated proteomes for human plasma. Currently Dr Valentine is heading up the proteomics analysis efforts for the Fairbanks Institute as part of a contract research project within PPM. He is also currently directing efforts within PPM to improve IMS-MS instrumentation for the molecular profiling of individual plasma samples which is central to the personalised medicine business concept currently pursued by PPM.

Dr Stephen Naylor has more than 20 years' experience in the health and life sciences, biotechnology pharmaceutical and university sectors. He is the former Chief Technology Officer (CTO) of Beyond Genomics, a Systems Biology company based in Waltham, MA, where in concert with his colleagues, he built the world's first integrated systems biology platform, consisting of both analyti-

cal, informatics and knowledge assembly capability. He held various professorial positions in the past, including: Professor of Genetics and Genomics at Boston University School of Medicine (Boston, MA), Faculty member in the Division of Biological Engineering and the Computational Systems Biology Initiative (CSBi) at MIT (Cambridge, MA), founding Director of the Biomedical Mass Spectrometry and Functional Proteomics Center at Mayo Clinic, Professors in Biochemistry and Molecular Biology, Molecular Pharmacology and Experimental Therapeutics, Clinical Pharmacology, and Biomedical Engineering at Mayo Clinic. He received his PhD from the University of Cambridge (UK) in biological mass spectrometry, and completed postdoctoral work at MIT (USA). He has published more than 225 research papers and book chapters, has filed a number of patents, and has made more than 600 presentations and seminars worldwide, in the area of analysis of complex biological mixtures, biomedical chromatography and mass spectrometry, and systems biology.