



Quo vadis personalized medicine?



Gualberto Ruano MD, PhD
President and CEO,
Genomas, Inc.,
67 Jefferson St, Hartford,
CT 06106, USA
Tel: +1 860 545 3773;
E-mail: g.ruano@genomas.net

'Personalized medicine introduces a daunting foray into the complexities, wonders and paradoxes of modern healthcare'

Welcome to the real world. Medicine has always attempted to be personalized. The patient–doctor relationship, both extolled and beleaguered, has historical aspirations and cultural roots in healing each person. The recent excitement in healthcare has been created by the prospect of personalizing medicine with genomic knowledge. The launch of this new journal, *Personalized Medicine*, heralds the time to integrate: for medicine, to adapt genomic tools; and for genomics, to delve into healthcare delivery. While there are multiple challenges on both the genomic and healthcare fronts, it is the latter that will be discussed here.

Five years ago we would have needed to address the complexity and cost of genotyping and raise concerns about the privatization of genomic information. Today, we can thank the biotechnology industry for quantum leaps in engineering that allow genotypes to be simpler and less expensive to measure than many serological factors. And thanks to the efforts of the Human Genome Project and the International HapMap Consortium, there is a wealth of sequence and polymorphism data readily accessible in comprehensively designed websites.

'We should reconsider the balance between preclinical research and clinical activities to derive knowledge from both, in a synergistic fashion'

Here, six trends will be detailed that need to be confronted, exploited and conquered as genomic science goes beyond drug discovery and controlled clinical trials into the real world of practicing physicians and healthcare consumers, formerly referred to as patients. Personalized medicine introduces a daunting foray into the complexities,

wonders and paradoxes of modern healthcare. My attempt within this paper is to provide a global perspective in terms of the challenges that personalized medicine will face while also expounding on the various controversies, accompanied by an opinionated assessment of methods that can be employed in order to move forward. Finally, by utilizing a case study on drug metabolism, we can assess firsthand what has limited the field thus far, and practical ways of moving it into clinical practice.

'Genomic markers for personalized medicine should be discovered to pinpoint individuals at high risk of the more common side effects or with a high probability of non-response'

Medicine and clinical discovery

Where does the knowledge for personalized medicine come from? We should reconsider the balance between preclinical research and clinical activities to derive knowledge from both, in a synergistic fashion. The current drug 'pipeline' concept is linear and does not incorporate the feedback that personalized medicine requires. The paradigm of Phase I to III clinical trials is already being reassessed if for no other reason than the most practical: the heterogeneity of response renders efficacy for a single indication difficult, especially with complex diseases, such as obesity and depression.

The pursuit of retrospective analyses of large clinical trials that search for 'active populations' that are responsive to a given drug *vis á vis* controls similarly matched according to genetic markers, has great potential to advance personalized medicine. The formalistic conundrum of prospective validation of such retrospective analyses is a major challenge that both industry and regulatory agencies need to address. One could argue that two totally non-overlapping subgroups sharing the same markers can be found in large trials, and that similar responses on both would constitute proof of efficacy. But the question of independent observation clearly remains, which

could be ascertained in subsequent targeted trials. One can, therefore, envision various feedback cycles generating value from past clinical development and thus delivering target populations for already approved drugs. One of the most valuable insights from such interactive clinical development could come from the distribution of side effects in patient populations.

Side effects and lessons from variability

Relevant biological insight can be gathered from the extremes of human response to a drug treatment. Genomic markers for personalized medicine should be discovered to pinpoint individuals at high risk of the more common side effects or with a high probability of non-response. Such individuals could then be treated with alternatives, either with other drugs or through preventive means, including diet and exercise, and managed with more elaborate scrutiny.

‘The utilization of genomic data for drug surveillance constitutes a powerful application of personalized medicine, which is now feasible with the advent of array technologies’

There has been an understandable tendency to rule out side effects as necessary by-products of therapy. Furthermore, all but the most serious are ascribed to innocuous human variability and even subjectivity. In personalized medicine, every side effect is scrutinized and the paradigm that they are unavoidable is simply unacceptable. Admittedly, these goals are lofty and even grandstanding. To date, personalized medicine uses human titration, therapeutic index ratios and therapeutic drug levels to assess such safeguards against the common side effects. In some specialties – notably, oncology and psychiatry – it is common to provide prophylaxis to the patient for drug-induced disease. For example, hormones to stimulate hematopoiesis or immunity are typically given in cancer therapies, and anticholinergic agents, such as benzotropine, are given as prophylaxis against the parkinsonism induced by antipsychotics in psychiatry. With new genomic tools, this kind of double prevention, arresting both the primary and the drug-induced diseases simultaneously, can be implemented precisely. As part of personalized medicine, double-preventive strategies could be applied to other diseases for their treatment and prophylaxis of drug side effects.

Another practical driver for the study of phenotypic variation is the realization that the extremely rare and catastrophic side effects that require drug withdrawals from the market may be tractable for formal study. The process would include monitoring the epidemiological occurrence of the adverse events and correlating the cases with a higher frequency of certain genetic markers, which result from genome-wide screens. The utilization of genomic data for drug surveillance constitutes a powerful application of personalized medicine, which is now feasible with the advent of array technologies. By focusing on both common and rare side effects, the practice of personalized medicine should boldly accept the challenge of drug safety and, in the process, could relieve some of that burden from the clinical trial process. A bonus is generated for the pharmaceutical industry, as personalized medicine will expedite the regulatory approval and market launch of new drugs.

Multigenic effects and array diagnostics

Single-gene effects are the basis of inherited errors of metabolism and other ‘genetic diseases’. In the world of common medical care, partial penetrance of single genes is the rule and any clinical use of genetic information for such practical applications must rely on multi-gene information. The pathways of physiology in personalized medicine are multigenic, as they rely on networks of genes and not on single receptors and enzymes. With the advent of gene arrays, parallel processing of gene expression and gene variability is practically possible at the pathway level, and soon could be feasible on a genome-wide basis.

‘The practice of personalized medicine will bring together separate sectors of the healthcare industry’

Analytical barriers plague this field. The concept of ‘average response’ and ‘deviation from the mean’ are ingrained in pharmaceutical development and in physician thinking. Learning from variability in response, and translating that into predictive diagnostics for personalized medicine is going to be a great challenge. Positioning each individual along a continuum of response or vulnerability to a drug is the goal of array technology. There is a major need to couple the

engineering advances in highly parallel genomic screens with statistical tools to derive valid information from pattern-recognizing algorithms. The practical consequence is that by learning from variability and not depending on means and standard deviation, we can expect reduced sample sizes in clinical studies and, most importantly, the ability to discover the markers and implement them in practice for prototyping and clinical validation.

‘Clinical management in personalized medicine must interplay genetic factors with lifestyle and demographic factors for each person’

The practice of personalized medicine will bring together separate sectors of the healthcare industry. For one, it will require a much greater integration with laboratory medicine than has previously been seen. For another, it will require embracing information technologies that have, to date, been underutilized in medicine. It may be that it is the genetic information in personalized medicine that finally brings digital literacy to mainstream medicine. The precedence for these technologies is imaging advances that reinterpret electromagnetic energy variations and gradients as images recognizable to the human eye. Analogous interpretative software will be required for personalized medicine once arrays are standard elements of diagnostics. While powerful, none of these advances should be presumed to be self-sufficient and must be integrated with existing medical practice.

Primary care and the environment

In the world of medicine, genetics has not entered common medical practice, and this is another challenge for personalized medicine. Part of the uncertainty lies in the perennial ‘nature-versus-nurture’ argument; the colossal battle on how deterministic genetic information is *vis á vis* the environmental influences overwhelming it. Personalized medicine must seek to integrate both sources of information. It has been surmised that gene–environment interactions are too complex for genetic analysis. Personalized medicine actually benefits from these interactions when the environmental trigger can be identified, which is the case in most treatments – notably, drug administration. Clinical management in personalized

medicine must interplay genetic factors with lifestyle and demographic factors for each person. A realistic way of beginning this integration is to incorporate baseline levels of function, ‘nurture’, with genetic predictors of response, ‘nature’, to obtain quantitative assessments on the relative value of diverse therapies for the individual.

In concert with the development of models of function through pathways, we can now create hybrid algorithms interfacing physiology and genetics where various genetic traits coalesce into the development of treatment responses. Individual traits by themselves are lacking specificity and sensitivity. Such systems analysis will cross over the existing specialty areas in organized medicine and redefine the layout of the medical professional landscape, with a return to the expertise of the general practitioner and internist.

In addition, we must also examine the role of precedent in the adoption of new technologies and new procedures. There is a tendency to believe that any diagnosis or treatment plan with genetic information of one kind or another is a new entity in healthcare. Nothing is farther from the truth. Blood and tissue typing are perhaps the best examples on the use of precise genetic data for patient management, and most individuals know their blood type. In my assessment, testing drug metabolism is next for implementation in such a routine manner.

‘The intimacy and trust inherent to the doctor–patient relationship is the ideal setting in which to divulge and discuss genetic data’

Ethics and the stratification of consent

Personalized medicine relies on the doctor–patient relationship for implementation. The intimacy and trust inherent to the doctor–patient relationship is the ideal setting in which to divulge and discuss genetic data. No subject matter will rely more heavily on this relationship than genetic privacy and genetically guided treatments.

Personalized medicine will require safeguarding the privacy of genetic information beyond the doctor–patient relationship, however. For this purpose, my proposal to the ethics community would be to develop a stratification or staging of informed consent for its use in personalized medicine according to a triage

process. For treatment purposes, the ethical 'risks' of various types of genetic information should be practically differentiated; for example, pure diagnosis of intractable genetic disease poses the greatest ethical risk, and profiling of drug metabolism holds the least. In this triage, consent for diagnosis of disease would require full professional genetic counseling, while consent for drug metabolism genotyping may only require that the information regarding its intended use be provided to the patient by the physician. The gathering of pharmacogenetic data in personalized medicine could be anchored by references to family history, and by presenting such information to the patient as the contemporary level of resolution based on the inherited material itself, DNA.

'There will be a need for moving research funding into actual pilots of personalized medicine to prove that it works'

The collection of genetic data will challenge the current racial definitions of ancestry based on 'race' and demonstrate their anachronistic obsolescence. It will instill an appreciation and respect for one's genetic legacy with the ultimate intent of empowering, not stigmatizing, the individual. In countries with widely heterogeneous populations, such as the USA and UK, diversity of ethnogeographic origin poses a particular limitation to the existing definitions of 'race', which will trigger reassessment of population groups defined with genetic markers.

One concern that has been frequently voiced is that personalized medicine will be too expensive and that, even if affordable, it may be limited to the social groups that are the most frequently studied. This will invariably be the ones with the most income in the countries with the most wealth, at the expense of those individuals that have not yet been studied for whatever economic or political reason. Yet, all of healthcare is fraught with these same concerns. We have orphan populations in contemporary medicine, and those are not likely to be treated suddenly with personalized medicine either. I believe that in the long run the treatment of orphan populations bears a better chance of success with a personalized medicine paradigm, than a 'one-size-fits-all' healthcare model.

Much progress in the field has been maligned by fears of intrusion into one's life by the

read-out of the genetic material. One approach to deal with this legitimate concern is to limit the genetic read-out to the markers required for a given treatment choice or diagnosis to be collected, and to discard the sample afterwards. We do not know how to interpret the entire genomic complement of a person at this time. And even if we did, medical intervention utilizes the data it needs and regards everything else as an incidental finding. In the context of preventive care, one may desire as comprehensive a read-out as possible, but that presumably would have been the reason for the depth of the analysis in the first place, where all observations are germane and none are incidental. Whether the search for markers is targeted or comprehensive, it has to address a medical reason, and once it serves it, there is no reason to archive the genetic material, especially as the costs of re-reading the genetic transcript become less onerous than the storage and safeguarding of the entire genetic complement. The urgent quest for improved treatments should be the engine propelling the use of genetic data, especially in this environment where the optimized allocation of healthcare resources is paramount.

'Personalized medicine may well spell the end of intellectual property based on single genes and individual markers, which so far has encumbered the growth and medical acceptance of the molecular diagnostics sector'

Health economics and the law

Moving personalized medicine into the world of living people, practicing doctors and decrepit healthcare systems is pronounced as the ultimate death knoll on the field, even before it has been launched. There will be a need for moving research funding into actual pilots of personalized medicine to prove that it works. The demonstration of economic value to assure reimbursement may actually have a salubrious effect on outmoded outcomes models that are strictly based on morbidity and mortality. A related concern is that personalized medicine would introduce unexpected insurance burden liability on the individual in the case where an untreatable disease is diagnosed. Here, once again, a primary intention to treat, heal and prevent disease will come a long way in explaining

the primary value of personalized medicine in the real world.

Other trends concern the law. Personalized medicine may well spell the end of intellectual property based on single genes and individual markers, which so far has encumbered the growth and medical acceptance of the molecular diagnostics sector. Once individual genes and markers are rendered elements of a composite, it will become clear that novel intellectual property concepts similar to patent pooling adapted in other industries will be required for the commercialization of the inventions of personalized medicine. It will also be impossible for any company to hold intellectual property captive, since redundancy of physiological pathways and the multiple components of array diagnostics may well compensate for the absence of a specific gene in the ensemble.

The world of liability is part of the fractious nature of medical practice today, and it would be naive not to expect personalized medicine to be affected by it. There is the possibility of incurring liability for not adopting personalized medicine as the standard of care, or at least implementing it to prevent adverse reactions. Yet, improvement of the standard of care is what modern medicine is all about, and personalized medicine should hardly be driven by liability concerns and malpractice. Outcomes research and pilot testing should bear the burden of proof that the fruits of personalized medicine do indeed improve patient wellbeing and reduce healthcare costs.

Case study

The history of pharmacokinetics and the cytochrome P450 (CYP) system illustrates several of these challenges. The CYP system is a marvel of functional evolution. Its main role is to oxidize lipophilic substances into hydrophilic molecules that can be excreted by the kidneys in urine. The system metabolizes endogenous and exogenous substrates. In evolution, exogenous substances were mostly ingested or absorbed substances; most notably, foods and liquids. In our modern world, this also includes pharmaceutical compounds given as therapeutic drugs.

In order to allow survival for a heterogeneous panoply of environmental substrates, the CYP system has evolved into a gene family that has expanded into multiple chromosome loci, each with tandem arrays of genes, and each gene with substantial polymorphism. The

CYP system illustrates gene expansion, multi-gene families and allelic functional variation all at once. The study of functional variability began in the 1970s with assays for protein isoforms and gel electrophoresis isolation of individual isoproteins. Thirty years later, genomics has supplied a rich resource of gene mapping data, as well as individual variants in each gene at the single polymorphism and haplotype levels. It is now a routine part of pharmaceutical development to assess the main metabolic pathways for drug metabolism and derive clinical pharmacological correlations.

‘At present, there is an embarrassing dichotomy between the body of pharmacogenetic knowledge and its clinical application’

The variability of metabolism of debrisoquine and sparteine was discovered in the late 1970s (reviewed by Meyer and Zanger [3]) in what is now the classic example of phenotypic variability ascribed to isoenzymes, and which we now know result from gene polymorphisms. The metabolic variability could be traced to the CYP isoenzyme 2D6 gene, *CYP2D6*. This gene was found to be hypervariable, which required analysis of its haplotypes rather than individual polymorphisms, as well as of its deletion and duplication in some individuals. In what may be an example of adaptive evolution, hypervariability in this gene is potentially advantageous, which would be consistent with the need to process and detoxify several substances in various environments. We now have three decades of research in this gene. Phenotypic correlates to patterns of variation are now available. At least 70 alleles have been described, and the phenotypic characteristics of their diploid constitutions in humans have been ascertained [1]. The CYP system has now been distilled into four phenotypes: ultra-rapid, extreme, intermediate and poor metabolizers. The distribution and frequency of these phenotypes is dominated by reliance on ‘race’ for their determination. Estimates routinely offered point to ‘Caucasian’ populations having 10% frequency of the poor metabolizer phenotype while ‘Oriental’ populations have a frequency of only 1%. Intermediate metabolizers account for 40% of the ‘Caucasian’ population and are a significant clinical category to ascertain. Drug interactions

are now recognized that can effectively turn the intermediate metabolizer into a poor metabolizer phenocopy through the inhibition of *CYP2D6* expression. With more precise ethnogeographic resolution, it is pointed out in most texts that North African populations are enriched for ultra-rapid metabolizers because of gene duplication localized to that region.

These phenotypic characteristics can be utilized to adjust the dosage of psychotropic drugs. At least 25 drugs drawn from antidepressant and antipsychotic treatments are candidates for dosage adjustment according to metabolizer status [2]. For these, the required adjustment has been estimated as at least a doubling of dose for extensive metabolizers compared with poor metabolizers. Another example is the drug atomoxetine (Strattera®; Eli Lilly & Co.), a norepinephrine re-uptake inhibitor for attention-deficit/hyperactivity disorder, which is metabolized primarily through the *CYP2D6* enzymatic pathway. The drug bears the following statement on its label: "People with reduced activity in this pathway (poor metabolizers) have higher plasma concentrations of atomoxetine compared with people with normal activity (extensive metabolizers)... Laboratory tests are available to identify *CYP2D6* poor metabolizers... Coadministration...with potent inhibitors of *CYP2D6*, such as fluoxetine...results in a substantial increase in atomoxetine plasma exposure, and dosing adjustment may be necessary..." [101]. However, there are no such tests widely available in medicine except from selected academic centers, and FDA-approved kits for *CYP2D6* are under development but not in the market as of this writing. At present, there is an embarrassing dichotomy between the body of pharmacogenetic knowledge and its clinical application. Routine testing for *CYP2D6* is not yet part of the clinical practice of psychiatry. However, personalized medicine using *CYP2D6* to individualize drug therapy by choosing the best medication dosage should be possible by the decade's end. The stage is thus set for a systematic assessment of the clinical utility of *CYP2D6* genotyping, and we should expect data from various centers over the next five years. Beyond genotyping, the compilation of environmental aspects is also required to assess drug interactions and other modifiers of gene expression.

The FDA has clearly identified *CYP2D6* as a valid biomarker, meaning that it would be ready for use in clinical trials and drug labels. In its

November 2003 Draft Guidance for Industry: Pharmacogenomic Data Submissions, the FDA states: "...the consequences for drug metabolism of genetic variation in the...*CYP450 CYP2D6* are well understood in the scientific community and are reflected in certain approved drug labels. The results of genetic tests that distinguish allelic variants of these enzymes are considered valid biomarkers..." [102]. Nonetheless, not a single drug, to date, has a label specifically identifying *CYP2D6* genotypes. Should we expect that this situation will change over the next 5 years? How clinically useful will *CYP2D6* genotyping prove to be? Will *CYP2D6* genotyping require genetic counseling? Who will pay for these tests whether available from certified reference clinical laboratories or from regulated laboratory systems and products? These are the challenges awaiting *CYP2D6* testing over the next few years.

'Personalized medicine should be regarded as an ongoing progression of healthcare, which is now advancing with genomic tools and markers'

Prospects

The opportunity for personalized medicine to prove itself as being beneficial to the pharmaceutical industry, to the healthcare system, to physicians and, most importantly, to patients may incorrectly appear to be only a distant possibility in the face of so many concerns disabling its practice. Its great potential represents an opportunity for industry, academia, philanthropies, and research-funding and regulatory agencies to work together. Driving personalized medicine increasingly into prevention may be an unexpected benefit of facing such real world pressures.

How best to advance personalized medicine into the clinic? From the perspective of a purist, it could be argued that prospective controlled trials of the benefit of genotyping for drug administration should be conducted where patients in the 'active arm' are prescribed according to genotype versus the 'control arm' where the patients are treated as per the usual mode of care without genotyping. The suggestion is to compare the rate of undesirable outcomes in one arm versus the other with regard to incidence of adverse drug reactions, side effects, expense of care, and protracted

therapeutic course. Yet a more practical approach is simply to examine a treated population in a clinic, and by retrospective genotyping assess which individuals by chance obtained the treatment that would have been suggested by genotyping versus those who got the wrong treatment. This research approach is well suited to most primary care and specialist clinics, and could generate invaluable data to demonstrate the value of pharmacogenomic testing. There is a clear need for funding sources to support this work. The recently announced Critical Path initiative of the FDA to advance translation of knowledge into medical products is one such program [103].

Personalized medicine should be regarded as an ongoing progression of healthcare, which is now advancing with genomic tools and markers.

Despite an increasing body of knowledge on variability of drug response phenotypes and their inherited genetic basis, the salient challenge is the translation to the practice of medicine. The realm of healthcare delivery is the modern challenge for personalized medicine and it involves far more than optimizing drug prescription. Interpretation, distribution, communication and reimbursement of the new genomic data, now managed as clinical information, is an urgent research imperative for the field to advance. Much can be learned by precedents established by other technologies in healthcare, ranging from imaging to minimally invasive surgery. Once proven clinically efficacious, accepted by physicians, and expected if not demanded by patients, personalized medicine will become the standard of care.

Bibliography

1. Bertilsson L, Dahl ML, Dalén P, Al-Shurbaji A: Molecular genetics of CYP2D6: clinical relevance with focus on psychotropic drugs. *Br. J. Clin. Pharmacol.* 53, 111-122 (2002).
 2. Kirchheiner J, Nickchen K, Bauer M *et al.*: Pharmacogenetics of antidepressant and the antipsychotics: the contribution of allelic variations to the phenotype of drug response. *Mol. Psychiatry* 9(5), 442-473 (2004).
 3. Meyer UA, Zanger UM: Molecular mechanisms of genetic polymorphisms of drug metabolism. *Annu. Rev. Pharmacol. Toxicol.* 37, 269-296 (1997).
- Websites
101. <http://pi.lilly.com/us/strattera-pi.pdf> Atomoxetine prescribing information.
 102. <http://www.fda.gov/cder/guidance/5900dft.pdf> FDA's Draft Guidance for Industry: Pharmacogenomic Data Submissions (November 2003).
 103. <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf> FDA's Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products (March 2004).