Challenge of personalized health care: To what extent is medicine already individualized and what are the future...

Walter Fierz

Medical Science Monitor International Medical Journal of Experimental and Clinical Research

© Med Sci Monit, 2004; 10(5): RA111-123
PMID: 15114285

WWW.MEDSCIMONIT.COM
Review Article

Received: 2003.09.15
Accepted: 2004.01.05
Published: 2004.05.01

Challenge of personalized health care: To what extent is medicine already individualized and what are the future trends?

Walter Fierz

Institute for Clinical Microbiology and Immunology, St. Gallen, Switzerland and Institute of Health Policy and Management, Erasmus University Medical Center, Rotterdam, The Netherlands

RA

Summary

Personalized medicine: is it hype or revolution? In any case, there is not only real demand for it, but it also has a history. As it is, the personal aspects of health care have been partly neglected in the current era of evidence-based, scientific medicine. We now know that a 'one fits all' type of treatment has its limits. Medicine needs to be (re-)personalized. The time is right: the post-genomic era provides the necessary molecular tools, but does it provide for the risks involved? Privacy, protection of minorities, and prevention of discrimination are at stake. Regulations are required. The health-care process needs redesigning to render personalized medicine effective. Information and communication management is challenged to handle the wealth of personal information and link to global medical knowledge. But the goal is magnificent: personal health planning, early diagnosis, the right drug for the right patient, and predictable side effects.

key words: **personalized medicine • pharmacogenomics • infectomics • patient-centered health care • information management**

Full-text PDF: http://www.MedSciMonit.com/pub/vol_10/no_5/4161.pdf

Word count: 7114
Tables: 1
Figures: 7
References: 89

Author's address: Dr. Walter Fierz, LogoLab AG Ottikerstr.36, CH-8033 Zürich, Switzeland, e-mail: walter.fierz@logolab.ch

BACKGROUND

Health care has always been individual – or has it? Before the advent of scientific medicine a century ago (see below), the emphasis on customizing medicine to the needs of the patient was probably one of the success factors of health care because the lack of standardization made individualizing medical treatment easy, though the results were questionable, as Shapiro concludes in his critical history of medicine 'From Ancient Priest to Modern Physician' [1] (p.60). Since a large part of the treatment effects was based on the patient's faith into the healer [1] (p.58), it was mandatory for the physician to take into account the personal needs and values of the patient in order to be successful. Later, such early medical treatment was attributed to the so-called placebo effect [1]. The term 'placebo', having its origin in the Latin verb placere, meaning to please, expresses the personal aspect of such type of medicine. Such considerations still play a very important role, particularly in alternative medicine [2–5], but also in the professional sector. However, the efficacy of placebo treatment is being debated [6].

At the end of the 19th century, with Claude Bernard's (1813–78) introduction of the scientific method into medicine [7] – founded on observation and proved by experiments – the personal aspects of treatment started to become endangered. Particularly the concept of randomization and the double-blind procedure introduced into clinical trials in the 20th century is inconsistent with the individual aspects of treatment. For the scientific approach it is pivotal to level-out all the unknown, non-accountable variations of individual responses to treatment. Evidence-based medicine is asking for a standardized application of therapy that has little room for idiosyncrasy. But treatment effects are highly variable and, of course, as a patient one would be interested to know whether one belongs to the 80% of patients that are expected to respond to a particular therapy or to the 20% of unfortunates that do not respond or, even worse, whether one belongs to the group that will experience unfavorable side effects. Until recently that wish could not be satisfied. Although, 'interpatient variability in response to drug therapy is the rule, not the exception, for almost all medications' [8], 'pharmaceutical medicine today is geared around taking statistical information about the general population and applying it to the individual' [9].

So, the challenge is to regain individualism on a scientific basis. Personalized medicine is on the agenda of many research groups and pharmaceutical companies. But the challenge is immense. Individualized medicine is to be based on evidence. Laboratory tests have to be designed for biomarkers that identify subgroups of patients with a particular disease that can be targeted by specific drugs. Drugs have to be specifically designed for such subgroups. Newly developed drugs have to be tested on various subgroups of patients. For rare variants of individual biomarker profiles it might be difficult to find enough patients for a trial [10], or it might be too expensive to design a new drug. Groups of patients characterized by less-profitable genotypes are at risk of becoming therapeutic 'orphans' [11]. Ethical problems concerning minorities that carry certain biomarkers or have a particular ethnic background may emerge [12,13], and regulations may be necessary to maintain equity and privacy protection [14–16].

Nevertheless, in certain areas personalized medicine is already an established fact. For instance, let us take customized treatment with antibiotics according to the resistance pattern of the infecting microbe or anti-retroviral therapy on the basis of HIV-genotyping of resistance. Individualizing treatment and the study of the underlying pharmacogenetics is reflected in the scientific literature from the 1960s onwards, and the number of articles published with these terms in the title was fairly constant until 1996 (see Figure 1). Since 1997, the main driver, however, of individualized medicine has probably been pharmacogenomics [17]. Figure 1 demonstrates the recent growth in the number of publications that contain the terms 'personalized medicine', 'pharmacogenetics', and 'pharmacogenomics' in the title or abstract.

The term 'personalized medicine' actually does not occur in the headings of articles before the advent of pharmacogenomics. Among 60 articles published so far with the term 'personalized medicine' in the title or abstract, 43 also contain the term 'pharmacogenetics or pharmacogenomics' in the text.

According to the exponentially growing number of published articles in this new field of pharmacogenomics-based personalized medicine, it is to be expected that sooner or later the new knowledge and the new techniques will start to change several aspects of health care. A particular challenge will be to information and communication technology (ICT), which will have to handle the accruing individual information. Similarly, other questions about social, ethical and regulatory issues will also have to be tackled.

In this article, the question is raised as to what the concepts of personalized medicine are and to what extent these concepts are already developed in the area of infectious diseases and clinical immunological disorders. What is the impact of personalized medicine on the health-care process and what developments are to be expected in the future? Other areas of medicine, such as oncology, and other types of therapy, such as surgical intervention or psychotherapy, are not within the scope of this article nor are the individual aspects of nursing or alternative medicine.

ANALYSIS

Concepts of personalized medicine

The term 'personalized medicine' is relatively new and mainly used in the context of pharmacogenomics (see Figure 1). However, this view is rather narrow, and for this analysis a much wider perspective shall be taken. Personalized medicine can been conceptualized along several dimensions [18–21]. Here, the six dimensions of disease, environment, genes, medication, healthcare, and information are discussed. First, three of the dimensions are integrated into a conceptual space [22]:

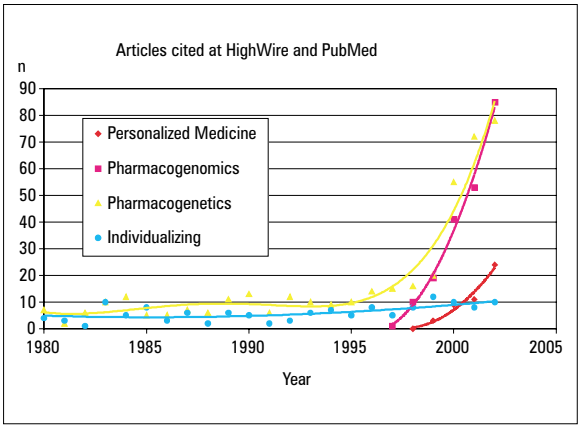

Figure 1. Number of publications about personalized medicine and pharmacogenomics.

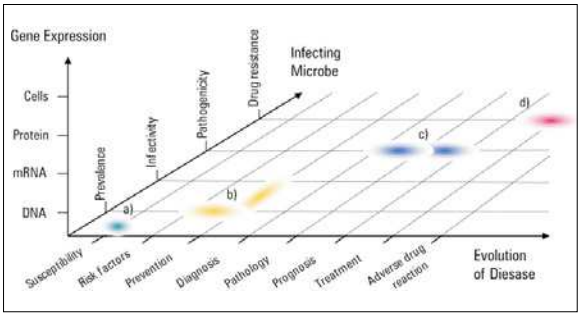

Figure 2. Concepts of personalized medicine can be represented in a multi-dimensional space. Here the first three dimensions are depicted.

disease progression, environment (microbe), and gene expression (Figure 2).

Dimension 1: Disease

The first dimension goes along the path of disease evolution. Individuals carry different susceptibilities for disease and different predisposing factors. Such personal risk profiles might lead to personal preventive measures, such as vaccination, and personalized health planning, such as regular screening procedures for particular diseases allowing for early diagnosis. Also pathology and disease progression depend on personal factors. Eventually, these individual characteristics influence the response to treatment with regard to drug efficacy as well as adverse drug reactions (ADRs). Consequently, appropriate choice and dosing of medication based on the individual characteristics of the patient is the hallmark of personalized medicine [23–25].

Dimension 2: Environment

The second dimension characterizes the environment - for the intent of this analysis, the infecting microbe. The actual prevalence of a microbe depends on the epidemiological situation that is given for a particular person. Geographical and seasonal factors as well as life style and sexual behavior influence the prevalence of particular microbes in the personal environment, and with that the risk of infection. Microbes are characterized by various properties that are summarized by their infectivities and pathogenicities, which might also depend on host factors [26–28]. Pivotal for personalized medicine is the sensitivity of the infecting microbe for the drug used to treat the patient.

Dimension 3: Genes

The third dimension characterizes the molecular traits and mechanisms underlying the individual characteristics of both the patient and the microbe. These are defined by the personal and microbial genes (genome) and their actual expression at the mRNA (transcriptome), protein (proteome) [29,30], and cell (cytome) levels [31]. One can distinguish stable molecular markers, such as genetic traits, single nucleotide polymorphisms (SNPs) and haplotypes [32], and dynamic biomarkers that depend on environmental factors, such as mRNAs, proteins, and their interaction at the cellular level [33].

Properties along these three dimensions are not independent from each other. They build a conceptual space, as depicted in Figure 2 [22].

Prototypic concepts in personalized medicine are focused in specific areas of this conceptual space (see Figure 2), for example:

a) personal genetic counseling [34] is localized in the lower left corner, defined by *susceptibility* [35] and genomic *DNA*.
b) individual *prevention* by vaccination is defined by personal *risk factors*, such as traveling plans or occupational risk, and by the *prevalence* of microbes, perhaps depending on pre-existing antibody levels (*proteins*). *Prevention* by personal hygienic measures is defined by the *prevalence* and *infectivity* of possible microbes.
c) individual *diagnosis* of an infectious disease is done at the *DNA* (microbial genome), *proteins* of both the microbe (antigens) and the host (antibodies), and the cellular (bacterial cultures, T-cell response of the host) levels. *Pathology* and *prognosis* of an infection are defined by individual host factors at the genome level (immune response genes) and gene expression at the protein and cellular levels (immune response) as well as the *pathogenic* factors of the microbe.
d) individual response to treatment is defined by the *drug efficacy* expected on the basis of the drug resistance of the microbe and of pharmacogenetic host factors or possible drug interactions. *Adverse drug reactions* (*ADRs*) are defined at the levels of *DNA* (toxicogenomic markers) or *proteins* and *cells* (allergies).

Dimension 4: Medication

A fourth dimension of personalized medicine goes along the path of drug development [8,9,17,36,37]. Pharmacogenomic studies will permit the development of therapeutic agents targeted to specific, genetically identifiable subgroups of the population. Genetic variation in drug targets (e.g. receptors) can have not only a profound effect on the efficacy of existing drugs, but its analysis is also likely to influence drug discovery in the future. In addition to drug targets, genetic polymorphisms can

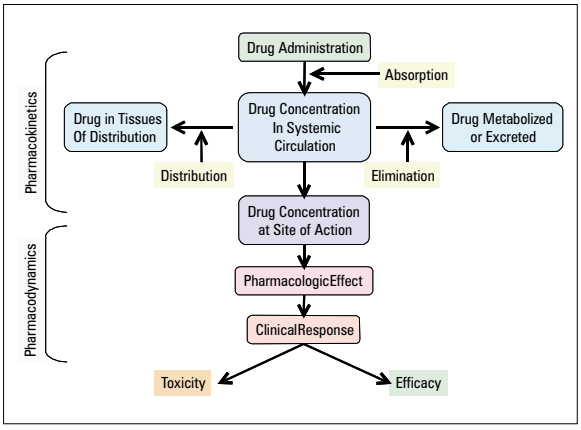

Figure 3. Dimension 4 of personalized medicine. Drug response in terms of efficacy and toxicity is governed by personal factors influencing the absorption, distribution, and elimination of that drug.

affect drug response at several levels (see Figure 3). Pharmacogenomics promises to allow for identification of individual factors influencing drug absorption, distribution, metabolism, and excretion. Pharmacologists distinguish two pathways of drug metabolism, phase I reactions (e.g. oxidation, reduction, and hydrolysis) and phase II, conjugation reactions (e.g. acetylation, glucuronidation etc.). Polymorphisms of the genes coding for cytochrome P-450 enzymes are important examples of phase I effects, and polymorphisms of the *TMPT* gene affecting the metabolism of the thiopurine drugs mercaptopurine and azathioprine are important examples of phase II effects [37].

A pivotal role in regulating absorption, distribution, and excretion of drugs is taken by drug transporters [38]. One example is P-glycoprotein, a member of the ATP-binding cassette family, encoded by the human *ABCB1* gene (also called *MDR1*) that is responsible for the efflux of drugs and other xenobiotics from the cell [39, 40]. For instance, a single-nucleotide polymorphism of this gene has been associated with better CD4 cell recovery in HIV-infected patients who are treated with anti-retroviral agents [41]. Thus, drug efficacy is governed by personal factors that can be screened using SNP diagnostics. Apart from drug efficacy, drug toxicity and hypersensitivity reactions can now also be predicted from genetic traits. Again, in HIV treatment, for example, a specific MHC haplotype is associated with hypersensitivity to the anti-retroviral abacavir, a reverse transcriptase inhibitor [41].

When testing drugs in clinical trials it is now also taken into account that individuals might respond differently. Knowing the genotypes of participating patients is getting more and more important [42,43]. Many pharmaceutical companies are already genotyping volunteers for polymorphisms of drug metabolizing enzymes in phase I studies. Also, in phase II-III clinical trials patients are starting to get genotyped to correlate drug efficacy with genetic markers or to exclude those individuals who will not benefit from or tolerate therapy due to genetic differences in drug metabolism or lack of the right target phenotype. In treating infectious diseases, not only the patient, but also the infecting microbe is genotyped. In hepatitis C or HIV infection, genotyping of the virus in therapy monitoring is already standard for anti-viral therapy.

Dimension 5: Health care

A fifth dimension for conceptualizing personalized medicine is the health-care process. Possibilities for individualization can be found throughout the health-care process.

- genetic counseling [34];
- patient education [44];
- evaluating risk profiles;
- medical decision making [45];
- monitoring of treatment;
  - surveillance of compliance;
  - drug-level measurement;
- privacy issues, patient empowerment [14];
- regulatory issues.

A more detailed discussion of the health-care dimension follows in a subsequent section.

Dimension 6: Information management

Health care is to a large extent an information-management endeavor. Two types of medical information can be distinguished: patient-specific and knowledge-based [46]. Personalized medicine is about connecting these two types of information and acting on them [45]. A key issue in personalized medicine is the gathering and management of patient-specific, personal information. Personal information is documented on several levels, commonly referred to as patient records or health records.

Some especially conspicuous personal medical documents, which are already in use to various extents in different countries, include the personal emergency card, the mother-child record, and the vaccination certificate. The type of information stored on such documents is variable and their usefulness is limited. Nevertheless, they serve as prototypes for the lifelong health record, and as such they have a certain symbolic value.

A potentially more valuable, but less conspicuous and largely under-exploited source of personal medical information, is the accumulated data stored in the electronic information systems of clinical microbiology and immunology laboratories. Although not lifelong, the time-scale of such stores is usually equivalent to the lifetime of a laboratory information system, i.e, 5–10 years. Unfortunately, neither the patient nor the treating physician is much aware of this treasure. This is a particularly urgent subject for health-care integration (see below).

The ultimate goal of personal information documentation is the lifelong electronic health record. From the fragmented, distributed, and hard-to-access patient records of various hospitals and physicians' offices there is still a long way to go to achieve an integrated, widely

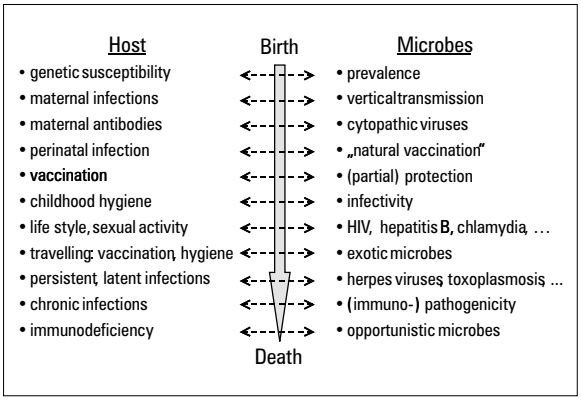

Figure 4. Time line of personal interactions between individual and microbes.

accessible, and comprehensive electronic health record. The speed of this development may well depend on the grade of involvement of the patient's interest in such an endeavor. A catalytic factor for patient involvement and for the success of personalized medicine in general is patient education and patient consent.

Having easy access to personal information is just the beginning. The challenge for ICT is to link such personal information with information from global medical knowledge [45,47]. Such information is deposited in digital libraries that can be searched by services such as Pubmed (National Library of Medicine) [48] or Highwire (Stanford University Library) [49] for scientific literature and the comprehensive search and retrieval system 'Entrez' (National Center for Biotechnology Information) [50] for databases of nucleotide and protein sequences, protein structures, complete genomes, taxonomy, and others. A list of databases is given in Appendix II. Their scope ranges from pharmacogenomic databases [51,52], and gene ontologies [53], to clearing houses for medical guidelines. Eventually, decision support tools will be able to automatically access this global knowledge in a patient-specific way [45].

The 6-dimensional conceptual space of personalized medicine

Properties along these further dimensions of personalized medicine are not independent from the other dimensions; all six dimensions build together a conceptual space for personalized medicine. For illustration, a regulatory decision (D5) might have to be taken for HIV-infected patients (D1, D2) whether to perform MHC typing (D1, D3) before treatment with abacavir (D1, D4), and a corresponding guideline has to be distributed (D6) [41]. Such problems in personalized medicine involve all six conceptual dimensions.

The individual character of infectious diseases

How far are the concepts of personalized medicine already developed in the area of infectious disease?

The interaction of genes with the environment is fundamental to health and to the development of disease, particularly for infections. In this case, the interactive experience between host and microbes is very individual and it builds up from the beginning of life until death (see Figure 4).

This individuality is based on the genetic makeup inherited from the parents and the prevalence of microbes in the environment. But not only genes are inherited from the mother, but also viruses and protective antibodies are vertically transmitted via the placenta. Under this individual protective umbrella of maternal antibodies, the first peri- and postnatal infections are attenuated but are still contributing to the personal microbial experience as a kind of 'natural vaccination' [54]. Artificial vaccination follows and, together with the personal hygiene in childhood, it defines the result of further microbial encounters. Personal life style, sexual behavior, traveling, etc. defines the spectrum of microbes that will lead, later in life, to acute, chronic or persistent infections and concomitant diseases, which eventually, under the weakened influence of an aged immune system, might end in death.

The intricate relation between microbe and host is particularly well exemplified by large, DNA-containing viruses that have acquired host genes encoding cellular homologues which mimic or counteract key molecules of the host immune system [55–57]. In latent infections with these viruses, which replicate their genome with the genome of the host cell, the distinction between microbe and host gets blurred, and the virus contributes to the personal characteristics of the host. As a result, infections with latent viruses contribute significantly to the personal phenotypic profile of the host.

With the help of modern genomic tools it is now envisaged to undertake screening on a comprehensive scale for personal phenotypes of infection and to choose treatment afterwards [58]. However, even before the post-genomic time, the individual characters of infectious diseases were evident. It has always been known that not every encounter with a microbe leads to infection and not every infection with a pathogenic microbe leads to clinical disease or to the same pathology, and not every clinical infection can be treated in the same way. Hence, the management of infectious diseases has for a long time been individual. Successful therapy requires knowledge about the infecting microbe, the sensitivity pattern of it towards antibiotics, and the choice and dosage of antibiotics according to some individual characteristics of the patient, such as drug allergies, renal function, or the results of drug-level measurements.

In this way, single focus points in the two-dimensional conceptual space defined by microbial infection and evolution of disease have been identified, and risk evaluation, diagnosis and treatment can be tailored to the individual characteristics of the patient and the infecting microbe. What is new in the development of personalized medicine is a refinement in the third dimension with the advent of molecular technology. For each characteristic trait of the patient, and of the microbe, molecular causes are being sought and analyzed, and tailored drugs are being developed specifically targeted at molecular structures.

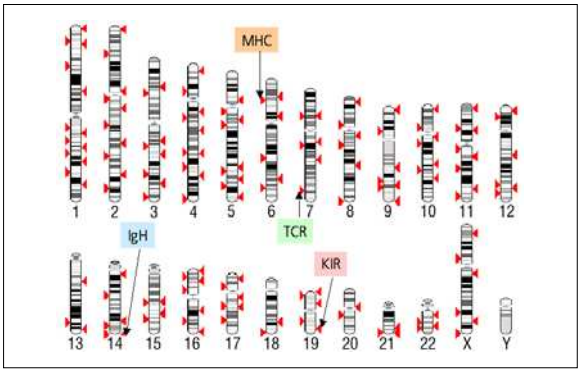

Figure 5. Immune response genes. Chromosomal position of genes categorized under the term 'immune response' of the Gene Ontology™ [53]. *(extracted from http://www.ensembl.org).*

To illustrate how far the molecular search for pathogenic microbial and host factors has gone already, the example of streptococcal infection can be given. It has been reported that the outcome of infections with the common group A streptococci (GAS; *Streptococcus pyogenes*) depends to a large extent on an intricate interaction of microbial and host factors. The risk of acquiring a severe and often deadly systemic disease like toxic shock syndrome or necrotizing fasciitis instead of a simple pharyngitis or scarlet fever is basically given by the serotype M1 of the GAS and its ability to secrete streptococcal pyrogenic exotoxins (SPES) on the one side and by the HLA haplotype of the patient on the other, apart from the protective effect of pre-existing anti-streptococcal antibodies. This interaction between SPES and HLA type can well be explained on the molecular level by the super-antigenic property of SPES which results in a devastating inflammatory response after its binding to and bridging of particular HLA molecules with T-cell receptors [59].

Beyond the reductionist approach, a new dimension has now opened with the possibilities of studying the whole genome and proteome comprehensively, in one go. On both sides, i.e. of the microbe and the infected host, the individual genome expresses itself as a particular proteome, depending on the interaction between the infecting microbe and the host (each representing their corresponding environments). The genomes of many bacteria [60] and viruses have been sequenced completely and, based on that knowledge, techniques have been developed to analyze the expression of complete genomes at the mRNA, protein, and cell levels. During infection, the global changes of the proteomes of both the microbe and the host have recently been termed 'infectome' [61]. Infectomics studies the characteristic genomic or proteomic patterns that correlate with the particular evolution of disease, even when the functions of the genes and proteins involved are not yet known. Such global approaches lead to a fundamental shift from reductionist towards holistic strategies in managing infectious diseases [62].

The individual character of immune responses

How far are the concepts of personal medicine already developed in the area of clinical immunology?

On the host side, the interaction of genes with the environment, which is characteristic for infectious diseases, involves the immune system in particular. When discussing the immune system, one has to distinguish the innate immune system from the adaptive immune system. The former provides the first line of defense based on 'hard-wired', genetically defined mechanisms, whereas the latter develops its functionality adaptively during encounters with infecting agents. On the genetic level, both systems show a very high degree of polymorphism, and immunogenetics has been an important subject of study for a long time [63,64]. Starting from transplantation immunology, immunogenetics has developed into an important discipline for understanding individual differences in the defense against infecting microbes. Whilst immune-related genes are found throughout the genome (see Figure 5), several clusters of highly polymorphic immune-response genes have been identified, including the major histocompatibility complex (MHC, in humans HLA), the T-cell receptor loci (TCR), the immunoglobulin heavy-chain region (IgH), and, recently, the killer Ig-like receptor loci (KIR). In fact, the MHC has been one of the first and most extensively studied stretches of DNA in mammals.

Important for the concepts of personalized medicine, however, is the ability of the immune system to adapt to the environment by learning and remembering. Through this adaptive process, the phenotype of the immune system is even more polymorphic than the genotype and, consequently, the immune response to a given antigen is highly individual. To illustrate this point, Figure 6 displays herpes simplex-specific antibodies of various individuals analyzed by separating single antibody clones with isoelectric focusing on a pH gradient. Actually, such variability can sometimes pose severe problems in standardizing serology (measurement of antibodies to infectious agents) as a diagnostic tool [65]. A similar diversity of the immune response can be found at the level of T-cell receptors.

Partly because of the overwhelming complexity of the immune system resulting from the high genotypic and phenotypic variability, personalizing the prevention and treatment of immune-based disorders has developed only slowly. There are some notable exceptions, however. Allergies, for instance, are amenable to treatment with desensitization procedures that are based on a personal hypersensitivity profile and, more importantly, individuals can prevent allergic attacks by avoiding exposure to allergens to which their immune system is overreacting. This knowledge has led to one of the most commonly recognized concepts of personalized medicine: the prototypic role of allergies in the discussion of personal risk profiles. Whenever personal health-care cards are discussed, the leading example taken to illustrate the usefulness of such cards is the documentation of allergies. Similarly, the personal vaccination profile is a prototypic example of documenting personal risks. The vaccination document probably represents the first rudimentary instance of a lifelong medical record. Useful as this is, the more astonishing is the fact that even a slight extension of this document by inclusion of records about immunity

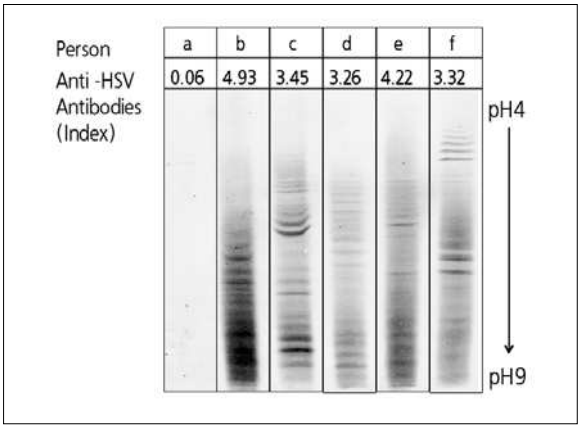

Figure 6. Individual Anti-HSV antibodies. Sera (a-f) of six persons with different levels of anti-HSV antibodies (indicated as test index) were separated by isoelectric focussing (IEF) on a pH gradient and blotted on a nylon membrane covered with HSV antigen. Clones of antibodies that recognize HSV are identified by immunostaining for human IgG. Individual patients' immune responses produce different oligoclonal IgG to the same viral antigen.

acquired from pervious infections and about infections with persistent microbes, such as herpes viruses or toxoplasmosis, has hardly been accomplished.

On the other hand, immune-based treatment of infectious diseases or autoimmune disorders is only marginally touched by personal medicine. Although the diagnostic possibilities to characterize individual patterns of immune reactions against infecting agents or against auto-antigens are extensive, there are hardly any immune-specific therapies available that would take advantage of the knowledge about personal immune patterns.

The impact of personalized medicine on the health-care process, with emphasis on the clinical laboratory

The realization of personalized medicine and, particularly, its corollaries in pharmacogenomics will certainly have bearing on the way health care is delivered [66]. Social, ethical, and regulatory issues need to be discussed and decisions taken as to the redesign of health-care systems based on personalized medicine [67]. Obviously, one wonders first how personalized medicine is related to patient-centered health care.

Patient-centeredness is a new key word in discussions of modern health care systems. In a recent report from the Institute of Medicine (IOM) about 'A New Health System for the 21st Century', six aims for improvement were formulated, one being patient-centeredness - next to safety, effectiveness, timeliness, efficiency, and equity. Patient-centeredness is understood as having 'qualities of compassion, empathy, and responsiveness to the needs, values, and expressed preferences of the individual patient' [68] (p.48). Hence, at first sight, one might have the impression that personalized medicine and patient-centered care are defined on completely different grounds – molecular genetics on the one hand and empathy on the other. However, these different perspectives do not necessarily contradict each other. On the contrary, they are likely to be mutually supportive. Here the question is asked how far personalized medicine supports or even necessitates patient-centered strategies.

Integration

One dimension of patient-centered care is coordination and integration of care [68] (p.49). In this context, the tenet to be proposed here is that personalized medicine cannot be successful when health-care processes are fragmented. The various bits and pieces of prevention, diagnosis, treatment, and care will have to be integrated in order to leverage personalized medicine.

One example of evolving strategies for integration is the development and employment of personalized diagnostic (Dx)–therapeutic (Rx) 'tandem combination' products [69]. The pharmaceutical industry will only embark on the development of personalized drugs if it has control of the diagnostic tools that are necessary to identify the target population to treat. The individualization of drug treatment based on genetic profiling may even require that regulatory approval of a drug for a specific subgroup of patients include the diagnostic test specifications. Henceforth, DxRx tandem products will increasingly be marketed by the industry [20]. Already, a new term, 'theranostics' (therapy-specific diagnostics), has been coined to refer to laboratory tests that help direct therapeutic intervention [70]. Some of the diagnostic tools will be point-of-care diagnostics (POCT) in order to shorten the time for reaching a decision about an individual drug regiment [71]. These integrating developments will have a significant effect on how future diagnostic laboratories function. From bedside diagnostics and application of drug-related diagnostic tools to highly specialized molecular procedures done in a reference laboratory, the hospital laboratory will have to integrate all the individual fragments into a coherent picture [72].

Information

A second dimension of patient-centered care is information, communication, and education [68] (p.50), which is also pertinent to personalized medicine (dimension 6). Personalizing prevention and medication requires detailed knowledge about a large amount of information. To find the right drug for the right patient one needs the right information [45]. In fragmented systems, comprehensive information is not readily available. This poses a challenge not only to information management, but to health-care management as a whole. A long sought-after solution for the provision of timely and comprehensive personal medical information would be the lifelong electronic patient record. There, all personal medical data that have accumulated during the lifetime would be stored and made accessible when to medical decision is needed [73] (see Figure 7A).

However, before this dream becomes reality [74,75], there should be other tools available to connect such

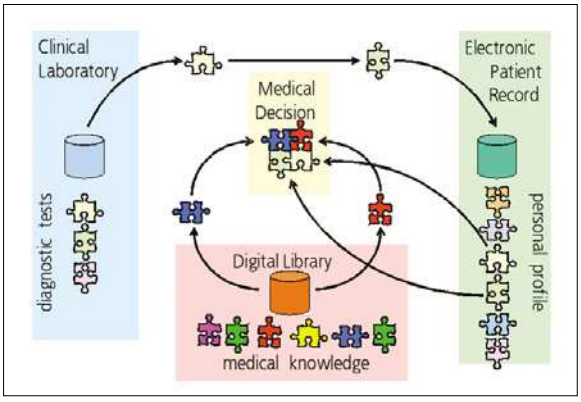

Figure 7A. Electronic support of medical decision making by connecting personal profile with digital library: The comprehensive model. Data from the personal profile are connected with information from digital libraries and knowledge databases.

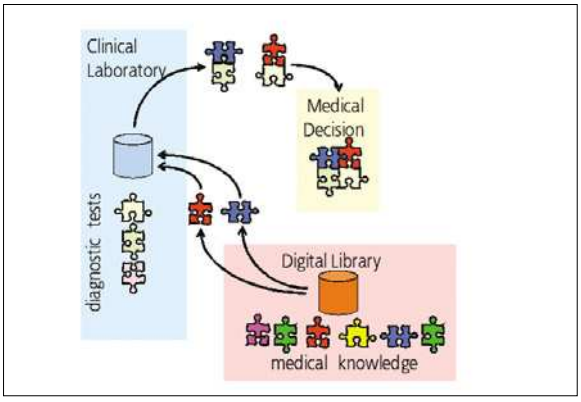

Figure 7B. Electronic support of medical decision making by linking diagnostic data with digital library: An alternative model. Laboratory results are annotated with information gathered from digital libraries and databases.

personal information with medical knowledge residing in digital libraries [76]. A special role could be played in this context by the clinical laboratory. Since many of the personal data items relevant for personalized medicine are produced by the clinical laboratory, and since clinical laboratories are the first actors in the health-care process that have all of the patient's data in electronic form, often even cumulatively over time, it is natural to propose that the clinical laboratory take over an active position in establishing electronic links between patient data and digital libraries (see Figure 7B).

For example, a microbiology lab could deliver, as an added value together with the results of the identification of an infecting microbe, a list of links to pertinent information on that microbe and its treatment. Likewise, a genetic lab could provide links to pharmacogenomic knowledge about a detected mutation. DxRx tandem concepts, as mentioned above, will support this alternative model of connecting patient data with digital libraries. Even if this idea seems to be straightforward, there will be hurdles in implementing such a service in view of the necessity to find and approve a financing model to recompense the laboratory for the added value.

However, information alone is not enough. Personalizing medicine also means evaluating, planning and acting with a common goal within an integrated strategy. This means that information needs to be accessible and that the information has to be communicated. Furthermore, the information needs to be understood. Patient education as well as education of the professionals is a prime success factor for personalized medicine. Only on these grounds will all the available information about the patient's personal constitution be used fruitfully to tailor medicine to personal needs and values.

Regulation

Last but not least, there are also ethical, legal, and social issues involved. The more detailed and personal information is becoming, the more privacy issues will play a role. This is particularly relevant when stable molecular markers such as genetic traits or chronic diseases are considered [16,77]. Early in the Human Genome Project it was recognized that the Project also had ethical, legal, and social implications (ELSI), and the ELSI program was established and is still a key objective in the vision for the future of genomics research [78,79]. One proposal of how to safeguard privacy advocates three major pillars on which to base protection for pharmacogenetic testing [66,80]: informed consent, trusted intermediaries, and legal protection.

The notion of **informed consent** is well known from clinical studies, but its application for the protection of privacy in diagnostics is not well established. Guidelines for informed consent should be adjusted to the diagnostic risk. For example, in the guidelines of the Swiss Federal Office of Public Health about HIV-testing it is declared mandatory to ask the patient for informed consent before performing an HIV test [81], whereas for less critical tests an unspoken agreement can be assumed. The 'Medical-ethical Guidelines for genetic investigations in humans' of the Swiss Academy of Medical Sciences asserts that 'The decision to carry out, continue or stop the [genetic] investigation rests exclusively with the patient, who will also decide whether and to what extent he wishes to be informed of, and to draw conclusions from the result of the investigation' [82].

Trusted intermediaries are proposed as 'firewalls' between genetic tests and medical records to hold DNA samples and test results. These intermediaries would release genetic information about a person only to those who need access to it and only when that person specifically has requested it. Such intermediaries may become important not only in research settings, but also in clinical settings in which multiple tests are run on the same DNA sample, or whenever full genetic profiles on individual patients are obtained [80]. The clinical laboratory would be predestined to fulfill such a role as a trusted intermediary.

Legal protection is the third weapon to protect privacy. At the time of writing, the Swiss Federal Assembly is introducing a new law about genetic tests in humans [83] with the aim of protecting human dignity and personality, of preventing improper genetic testing and improper use of genetic data, and of guaranteeing the quality of genetic tests and the interpretation of their results. The basic principles of this legislation are:
- prohibition of discrimination;
- informed consent;
- right of not knowing;
- protection of genetic data;
- licensing of genetic testing.

In the accompanying commentary of the government to the legislation, an overview of European law is given: Until now, only Norway and Austria have a general regulation for genetic testing. Other countries have only regulations about particular aspects of genetic testing.

A further social concern is the **protection of minorities**. A population with a particularly critical high risk of being affected by personalized medicine is the group of genetic minorities. On one hand, they might strongly benefit from future drugs that are tailored to their special genetic makeup, whereas they have been underprivileged so far in the 'one fits all' era. On the other hand, minorities are at high risk of becoming therapeutic orphans in that it might not be profitable for the industry to develop special drugs for them.

A very critical issue for the social acceptance of personalized medicine is the danger of **discrimination** on the grounds of genetic testing [84]. Anderlik and Rothstein [16] tried to distinguish rational from irrational discrimination. Irrational discrimination results from decision making on the basis of faulty or incomplete data, or misinterpretation of the implications of genetic test results for morbidity and mortality. Whereas this type of discrimination is certainly to be banned, there is a debate about the social acceptability of rational, scientifically sound and empirically supported discrimination. It already has become common use by insurers to engage in risk classification based on characteristics such as age, sex, individual and family health histories, health status, occupation, serum cholesterol, alcohol and tobacco use, and HIV status. Personal genetic profiles are just an extension of this risk evaluation, and with the success of personal medicine, such profiling becomes more precise. Yet whatever society considers permissible in this respect, the real danger will lie in the difficulty to discriminate rational from irrational.

Discussion

Personal medicine was lost with the advent of scientific, evidence-based medicine. This loss is deplored by many patients and is one of the reasons for the attractiveness of alternative medicine. Now, medicine needs to be re-personalized on a scientific basis. In the recent years of the post-genomic era, a new thriving of personalizing medicine can be observed. Molecular diagnostics based on comprehensive and high-throughput genetic testing promises to revolutionize medicine.

However, individualized medicine is not new. In clinical microbiology and immunology the personal aspects of susceptibility, prevention, infection, immune defense, and response to treatment are inherent properties of medical care. New are the dimensions of molecular diagnostics and pharmacogenomics. With their advent, a new name has been coined: personalized medicine.

Personalized medicine can be conceptualized in a 6-dimensional space along the axes of disease, environment, genes, medication, health care, and information management. The concepts, potentials, and hazards of personalized medicine are located within this 6-dimensional conceptual space. Prototypic concepts are localized in specific areas of this space. The individual character of infections and immune defense, based on the genomic makeup of the microbe and the host, makes them prototypic examples of the personal evolution of disease. Drug development, health-care decisions, and information management are to be targeted at these personal characteristics. Pharmacogenomics is one of the main drivers of this new development.

Within the health-care process, personalized medicine and patient-centered care are mutually supportive. A special emphasis has to be put now on the integration of disparate personalized medical approaches and on the integration of fragmented personal records. A focal point for individualized health care is personalized information management. It is proposed that before lifelong electronic health records become a reality, the clinical laboratory should provide electronic links between personal laboratory data and electronic information from digital libraries and databases.

The new tools of genetic and molecular medicine are powerful, but so are the social and ethical risks. Several personal values are at stake: privacy, protection of minorities, and prevention of discrimination. Regulations about informed consent in the diagnostic process are needed. Clinical laboratories could take the role of trusted intermediaries guarding the DNA and personal profiles resulting from laboratory tests. Genetic minorities carry a high risk of either profiting from or losing out on personalized medicine. Social mechanisms have to be developed to handle these risks. Some discrimination on the grounds of genetic testing might be considered acceptable when it concerns rational risk classification by insurers. Nevertheless, misuse of personal risk profiles is a real danger for the success of personal medicine and requires legal regulation.

Overall, personalized medicine is very promising. Old dreams of being treated individually might be fulfilled on a scientific basis. The success depends on redesigning the health-care process and information management.

Conclusions

Humans are individual, so medicine must be. From the analysis of the current state of personalized medicine and its foreseeable development, the following tenets can be put forward:

1. Personalized medicine is not new but acquires a new dimension with the comprehensive molecular analysis of genes and gene expression.
2. Personalized medicine can be conceptualized along 6 dimensions: disease, environment, genes, medication, health care, and information management.
3. Personalized medicine requires patient-centered healthcare, particularly with the dimensions integration and information.
4. Clinical microbiology and immunology provide prototypical examples of personalized medicine. Chronic and latent infections and the corresponding immune response add to the genetically defined character of an individual.
5. Personalized medicine depends on personalized information management and asks for lifelong electronic patient records that interface with the digital libraries.
6. The clinical laboratory should play a pioneering role in electronically connecting patient-specific information with global medical knowledge.
7. Personalized medicine also has ethical, legal, and social implications. Several personal values are at stake: privacy, protection of minorities, and prevention of discrimination.
8. The clinical laboratory could play the role of a trusted intermediary between genetic testing and clinical application.

The hopes and promises of personalized medicine are high. The challenge is to adapt the health-care process to the needs of personalized medicine and to cope with its social risks.

Acknowledgments

This article was written as an assignment for the first module of the master's course on Health Information Management taught at the Institute of Health Policy and Management of the Erasmus University Medical Center in Rotterdam [85]. Encouraging critique by Bert Huisman is gratefully acknowledged and Leslie Bisset's professional editorial help is thankfully appreciated.

APPENDIX I: GLOSSARY

Person-related terms

Placebo

'A placebo is any therapy (or that component of any therapy) that is intentionally or knowingly used for its non-specific, psychological, or psychophysiological, therapeutic effect, or that is used for a presumed specific therapeutic effect on a patient, symptom, or illness but is without specific activity for the condition being treated.' [1] (p41).

Individualization/personalization

There seems to be no strict separation of the meaning of the two terms. They could be used synonymously, expressing the act of making something more individual/personal. Nevertheless, it can be observed that the two terms are not used in the same context and/or by the same scientific community. As shown in Figure 1, the number of articles using the term 'individualizing' remains fairly constant over the last twenty years, whereas the use of the term 'personalized' has been exponentially increasing in the last five years. 'Individualization' is more often used when describing non-genetic patient profiles, and when adjustment of pre-existing treatment to individual needs and pharmacogenetic factors is discussed. The use of 'personalization', on the other hand, is strongly related to the new term 'pharmacogenomics', where a more encompassing view on tailored drugs based on genomic patient profiles is discussed.

Patient-centered health care

The Institute of Medicine (IOM) adopts in 'A New Health System for the 21st Century' Gerteis' conceptualization of patient-centered care with six dimensions: 1) respect for patients' values, preferences, and expressed needs; 2) coordination and integration of care; 3) information, communication, and education; 4) physical comfort; 5) emotional support; and 6) involvement of family and friends.

The -omes and -omics

We have entered the 'omic' era in biology and medicine [86]. The suffix '-ome' in biology has the function of directing attention to a holistic abstraction of molecular or functional parts of a population defined by the -ome term, whilst the suffix '-omics' designates the study of the respective -ome. A glossary of –omes and –omics currently lists almost 100 of such terms (*http://www.genomic-glossaries.com/content/omes.asp*). The -omic terms most frequently used in scientific literature are genome, proteome, and transcriptome (*http://bioinfo.mbb.yale.edu/what-is-it/omes/*). The oldest term, biome, was coined in 1916.

Pharmacogenetics/pharmacogenomics

The two terms are closely related, but 'pharmacogenetics' is the traditional term used from the beginning of the 1960s to describe hereditary influences on the response to drugs. 'Pharmacogenomics' could be defined in the same way, but Kalow [25] proposes the additional element that 'genomic knowledge is used to search for new drugs'. The emphasis is on the influence of a whole set or complement of genes summed up in a genetic profile. With Kalow [25] one could argue that pharmacogenetics is concerned with drug safety and pharmacogenomics with improving drug efficacy. In addition, whereas pharmacogenetics is concerned with the effect of genes on drug response, pharmacogenomics also studies the effect of drugs on gene function.

Infectomics

Infectomics encompasses the genomics and proteomics of microbial infections. The global phenotypic changes (infectomes) in microbes and their hosts during infection are encoded by the genomes of microbial pathogens and their hosts, expressed in certain environmental conditions devoted to specific microbe-host interactions [61].

Toxicogenomics

Toxicogenomics describes the measurement of global gene-expression changes in biological samples exposed to toxicants, with the possibility of assisting in the detection of compounds with the potential to cause adverse health effects earlier in the development of pharmaceutical and chemical products [87].

Theranostics (therapy-specific diagnostics)

'Theranostics is the term coined by PharmaNetics [Ltd] to describe rapid diagnostics that influence the physicians' therapy decisions in treating patients. By melding the separate disciplines of diagnostics and therapeutics, physicians are effectively empowered to bring the hospital laboratory in real time to the patient's bedside, facilitating the selection of the right drug, in the right dose, at the right moment.' [88,89]

Genetic variability

Genetic polymorphisms/allelic variants

The two terms are used synonymously, expressing sequence variations among individuals for a given gene. Most of the genetic variability is in the form of single nucleotide polymorphisms (SNPs).

SNP/haplotype analysis

The analysis of single nucleotide polymorphisms (SNPs) is the basis for personal genotyping. On average, two unrelated people differ at about 1–3 bases in every 1'000 of the 3 billion or so bases in their genome, so any individual will have about 3–10 million SNPs.

'Nonsynonymous SNP' is an SNP within a coding region that changes the amino acid that is encoded.

The SNP Consortium (TSC) is a public/private collaboration that has to date discovered and characterized nearly 1.8 million SNPs [51].

Haplotypes are defined as groups of nearby alleles (SNPs) that are inherited together. It is thought that about 65 to 85% of the human genome may be organized into haplotype blocks that are 10'000 bases long or larger. Therefore, the number of SNPs required to examine the entire genome for association with a phenotype should be reduced from the 10 million SNPs that exist to roughly 500,000 tag SNPs. An effort has been launched recently by an international research consortium to create a haplotype map of the complete human genome (*http://www.hapmap.org/index.html.en*) in the next three years (*http://genome.gov/10005336*). The HapMap promises to facilitate research into genetic risk factors underlying diseases or health conditions.

Appendix II: Databases.

Resource	URL	Content
Ensembl	*http://www.ensembl.org*	Access to DNA and protein sequences with automatic baseline annotation
Entrez (National Center for Biotechnology Information)	*http://www.ncbi.nlm.nih.gov/Entrez/*	Retrieval system for searching several linked databases, including PubMed
Ethical, Legal, & Social Issues (ELSI)	*http://www.ornl.gov/hgmis/elsi/elsi.html*	Information, articles, and links on a wide range of issues
GeneClinics GeneTests	*http://www.geneclinics.org/* *http://www.genetests.org/*	Authoritative synopses of disorders that have a significant genetic component
Gene Ontology™ Consortium	*http://www.geneontology.org/*	Dynamic controlled gene vocabulary
GeneSNPs Environmental Genome Project web resource	*http://www.genome.utah.edu/genesnps/*	Genetic data related to environmental exposure
Human Genome Epidemiology Network	*http://www.cdc.gov/genomics/hugenet/*	Epidemiologic information on the human genome
HighWire Press, Internet Imprint of the Stanford University Libraries	*http://highwire.stanford.edu/*	Literature Search for HighWire-hosted journals and Medline, with many free full-text articles
National Cancer Institute's CancerNet	*http://www.cancer.gov/cancerinfo/prevention-genetics-causes*	Authoritative information about cancer genetics
National Center for Biotechnology Information (NCBI)	*http://www.ncbi.nlm.nih.gov/genome/guide/*	Views of chromosomes, maps, and loci; links to other NCBI resources
National Guideline Clearinghouse™ (NGC)	*http://www.guideline.gov/*	Evidence-based clinical practice guidelines
OMIM	*http://www.ncbi.nlm.nih.gov/Omim/*	Information about human genes and disease
Pharmacogenetics Research Network and Knowledge Base	*http://www.pharmgkb.org/*	Genomic data, molecular and cellular phenotype data, and clinical phenotype data
SNP consortium	*http://snp.cshl.org*	Query for SNPs in the human genome
The Institute for Genomic Research (TIGR) Comprehensive Microbial Resource (CMR)	*http://www.tigr.org/*	Access to all of the bacterial genome sequences completed to date

REFERENCES:

1. Shapiro AK, Shapiro E: The Powerful Placebo: from ancient priest to modern physician. Baltimore and London: The Johns Hopkins University Press, 1997
2. White A, Slade P, Hunt C et al: Individualised homeopathy as an adjunct in the treatment of childhood asthma: a randomised placebo controlled trial. Thorax, 2003; 58(4): 317-21
3. Linde K, Vickers A, Hondras M et al: Systematic reviews of complementary therapies - an annotated bibliography. Part 1: Acupuncture. BMC Complement Altern Med, 2001; 1(1): 3. Available from: URL: *http://www.biomedcentral.com/1472-6882/1/3*
4. Linde K, ter Riet G, Hondras M et al: Systematic reviews of complementary therapies – an annotated bibliography. Part 2: Herbal medicine. BMC Complement Altern Med, 2001; 1(1): 5. Available from: URL: *http://www.biomedcentral.com/1472-6882/1/5*
5. Linde K, Hondras M, Vickers A et al: Systematic reviews of complementary therapies - an annotated bibliography. Part 3: Homeopathy. BMC Complement Altern Med, 2001; 1(1): 4. Available from: URL: *http://www.biomedcentral.com/1472-6882/1/4*
6. Hrobjartsson A, Gotzsche PC: Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. N Engl J Med, 2001; 344(21): 1594-602
7. Conti F: Claude Bernard: primer of the second biomedical revolution. Nat Rev Mol Cell Biol, 2001; 2(9): 703-08
8. McLeod HL, Evans WE: Pharmacogenomics: Unlocking the Human Genome for Better Drug Therapy. Annu Rev Pharmacol Toxicol 2001; 41(1): 101-21
9. Marshall A: Laying the foundations for personalized medicines. Nat Biotechnol, 1997; 15(10): 954-57
10. Palmer LJ, Silverman ES, Drazen JM, Weiss ST: Pharmacogenomics of Asthma Treatment. In: Licinio J, Wong M-L, editors. Pharmacogenomics: The Search for Individualized Therapies. Weinheim: WILEY-VCH, 2002: 215-34
11. Rothstein MA, Epps PG: Ethical and legal implications of pharmacogenomics. Nat Rev Genet, 2001; 2(3): 228-31
12. Cooper RS, Kaufman JS, Ward R: Race and Genomics. N Engl J Med, 2003; 348(12): 1166
13. Burchard EG, Ziv E, Coyle N et al: The Importance of Race and Ethnic Background in Biomedical Research and Clinical Practice. N Engl J Med, 2003; 348(12): 1170
14. Vaszar LT, Cho MK, Raffin TA: Privacy issues in personalized medicine. Pharmacogenomics, 2003; 4(2): 107-12
15. Moldrup C: Ethical, Social and Legal Implications of Pharmacogenomics: A Critical Review. Community Genetics, 2001; 4(4): 204-14
16 Anderlik MR, Rothstein MA: Privacy and Confidentiality of Genetic Information: What Rules for the New Science? Annu Rev Genom Hum Genet, 2001; 2(1): 401-33
17. Evans WE, Relling MV: Pharmacogenomics: Translating Functional Genomics into Rational Therapeutics. Science, 1999; 286(5439): 487
18. Meyer JM, Ginsburg GS: The path to personalized medicine. Curr Opin Chem Biol, 2002; 6(4): 434-38
19. Ginsburg GS, McCarthy JJ: Personalized medicine: revolutionizing drug discovery and patient care. Trends Biotechnol, 2001; 19(12): 491-96
20. Ross JS, Ginsburg GS: The integration of molecular diagnostics with therapeutics. Implications for drug development and pathology practice. Am J Clin Pathol, 2003; 119(1): 26-36
21. Jain KK: From molecular diagnostics to personalized medicine. The IBC Workshop, London, UK, 1st May, 2002. Expert Rev Mol Diagn, 2002; 2(4): 299-301
22. Gärdenfors P: Conceptual Spaces: The Geometry of Thought. Cambridge MA, London: The MIT Press, 2000
23. Mancinelli L, Cronin M, Sadee W: Pharmacogenomics: the promise of personalized medicine. AAPS Pharm Sci, 2000; 2(1): E4. Available from: URL: *http://www.aapspharmsci.org/ps0201/ps020104/ps020104.pdf*
24. Liotta LA, Kohn EC, Petricoin EF: Clinical Proteomics: Personalized Molecular Medicine. JAMA, 2001; 286(18): 2211
25. Kalow W: Pharmacogenetics and personalised medicine. Fundam Clin Pharmacol, 2002; 16(5): 337-42
26. Moxon R, Tang C: Challenge of investigating biologically relevant functions of virulence factors in bacterial pathogens. Philos Trans R Soc Lond B Biol Sci, 2000; 355(1397): 643-56
27. Martinez JL, Baquero F: Interactions among Strategies Associated with Bacterial Infection: Pathogenicity, Epidemicity, and Antibiotic Resistance. Clin Microbiol Rev, 2002; 15(4): 647-79
28. Wilson JW, Schurr MJ, LeBlanc CL et al: Mechanisms of bacterial pathogenicity. Postgrad Med J, 2002; 78(918): 216
29. Tyers M, Mann M: From genomics to proteomics. Nature, 2003; 422(6928): 193-97
30. Gerling IC, Solomon SS, Bryer-Ash M: Genomes, Transcriptomes, and Proteomes: Molecular Medicine and Its Impact on Medical Practice. Arch Intern Med, 2003; 163(2): 190
31. Valet GK, Tarnok A: Cytomics in predictive medicine. Cytometry 2003; 53B(1): 1-3. Available from: URL: *http://www.biochem.mpg.de/valet/cellclas.html*
32. Guttmacher AE, Collins FS: Genomic medicine a primer. N Engl J Med, 2002; 347(19): 1512-1520. Available from: URL: *http://content.nejm.org/cgi/reprint/347/19/1512.pdf*
33. Hanash S: Disease proteomics. Nature 2003; 422(6928): 226-32
34. Weil J: Genetic counselling in the era of genomic medicine: As we move towards personalised medicine, it becomes more important to help patients understand genetic tests and make complex decisions about their health. EMBO Reports 2002; 3(7): 590-93
35. Burgner D, Levin M: Genetic susceptibility to infectious diseases. Pediatr Infect Dis J, 2003; 22(1): 1-6
36. Evans WE, McLeod HL: Pharmacogenomics – Drug Disposition, Drug Targets, and Side Effects. N Engl J Med, 2003; 348(6): 538-49. Available from: URL: *http://content.nejm.org/cgi/reprint/348/6/538.pdf*
37. Weinshilboum R: Inheritance and Drug Response. N Engl J Med, 2003; 348(6): 529-37. Available from: URL: *http://content.nejm.org/cgi/reprint/348/6/529.pdf*
38. Tirona RG, Kim RB: Pharmacogenomics of Drug Transporters. In: Licinio J, Wong M-L, editors. Pharmacogenomics: The Search for Individualized Therapies. Weinheim: WILEY-VCH, 2002: 179-213
39. Fromm MF, Eichelbaum M: The Pharmacogenomics of Human P-Glycoprotein. In: Licinio J, Wong M-L, editors. Pharmacogenomics: The Search for Individualized Therapies. Weinheim: WILEY-VCH, 2002: 159-78
40. Schwab M, Eichelbaum M, Fromm MF: Genetic Polymorphisms of the Human MDR1 Drug Transporter. Annu Rev Pharmacol Toxicol, 2003; 43(1): 285-307
41. Telenti A, Aubert V, Spertini F: Individualising HIV treatment – pharmacogenetics and immunogenetics. Lancet, 2002; 359(9308): 722-23
42. Murphy MP: Current pharmacogenomic approaches to clinical drug development. Pharmacogenomics, 2000; 1(2): 115-23
43. Shi MM, Bleavins MR, de la Iglesia FA: Pharmacogenetic Application in Drug Development and Clinical Trials. Drug Metab Dispos, 2001; 29(4): 591. Available from: URL: *http://dmd.aspetjournals.org/cgi/reprint/29/4/591.pdf*
44. Visser A, Deccache A, Bensing J: Patient education in Europe: united differences. Patient Educ Couns, 2001; 44(1): 1-5
45. Fierz W: Information management driven by diagnostic patient data: right information for the right patient. Expert Rev Mol Diagn, 2002; 2(4): 355-60
46. Hersh WR: Medical informatics: improving health care through information. JAMA, 2002; 288(16): 1955-58
47. Hersh WR: Information Retrieval: A Health and Biomedical Perspective. 2nd ed. New York: Springer-Verlag, 2003
48. McEntyre J, Lipman D: PubMed: bridging the information gap. CMAJ, 2001; 164(9): 1317. Available from: URL: *http://www.cmaj.ca/cgi/reprint/164/9/1317.pdf*
49. Anonymous: HighWire Press Is 5 years old. J Biol Chem, 2000; 275(15): 10717. Available from: URL: *http://www.jbc.org/cgi/reprint/275/15/10717.pdf*
50. Tatusova TA, Karsch-Mizrachi I, Ostell JA: Complete genomes in WWW Entrez: data representation and analysis. Bioinformatics, 1999; 15(7): 536. Available from: URL: *http: //bioinformatics.oupjournals.org/cgi/reprint/15/7/536.pdf*
51. Thorisson GA, Stein LD: The SNP Consortium website: past, present and future. Nucl Acids Res, 2003; 31(1): 124. Available from: URL: *http://nar.oupjournals.org/cgi/reprint/31/1/124.pdf*

52. Hewett M, Oliver DE, Rubin DL et al: PharmGKB: the Pharmacogenetics Knowledge Base. Nucl Acids Res, 2002; 30(1): 163-65. Available from: URL: *http://nar.oupjournals.org/cgi/reprint/30/1/163.pdf*
53. Consortium TGO: Creating the Gene Ontology Resource: Design and Implementation. Genome Res, 2001; 11(8): 1425. Available from: URL: *http://www.genome.org/cgi/reprint/11/8/1425.pdf*
54. Zinkernagel RM: On natural and artificial vaccinations. Annu Rev Immunol, 2003; 21: 515-46
55. Alcami A: Viral mimicry of cytokines, chemokines and their receptors. Nat Rev Immunol, 2003; 3(1): 36-50
56. Chaston TB, Lidbury BA: Genetic 'budget' of viruses and the cost to the infected host: a theory on the relationship between the genetic capacity of viruses, immune evasion, persistence and disease. Immunol Cell Biol, 2001; 79(1): 62-66
57. Haig DM: Subversion and piracy: DNA viruses and immune evasion. Research in Veterinary Science, 2001; 70(3): 205-19
58. Cummings CA, Relman DA: Using DNA microarrays to study host-microbe interactions. Emerg Infect Dis 2000; 6(5): 513-525. Available from: URL: *http: //www.cdc.gov/ncidod/eid/vol6no5/pdf/cummings.pdf*
59. Kotb M, Norrby-Teglund A, McGeer A et al: An immunogenetic and molecular basis for differences in outcomes of invasive group A streptococcal infections. Nat Med, 2002; 8(12): 1398-404
60. Loong CV: Bacterial Genomes and Infectious Diseases. Pediatr Res, 2003; 01
61. Huang SH, Triche T, Jong AY: Infectomics: genomics and proteomics of microbial infections. Funct Integr Genomics, 2002; 1(6): 331-44
62. Aujame L, Burdin N, Vicari M: How Microarrays Can Improve Our Understanding of Immune Responses and Vaccine Development. Ann NY Acad Sci, 2002; 975(1): 1-23
63. Geraghty DE: Genetic diversity and genomics of the immune response. Immunol Rev, 2002; 190: 5-8
64. Hill AVS. Immunogenetics and genomics. The Lancet 2001; 357(9273): 2037-41. Available from: URL: *http://pdf.thelancet.com/pdfdownload?uid=llan.357.9273.editorial_and_review.16672.1&x=x.pdf*
65. Fierz W: Basic problems of serological laboratory diagnosis. Mol Biotechnol, 1999; 13(2): 89-111
66. Robertson JA, Brody B, Buchanan A et al: Pharmacogenetic challenges for the health care system. Health Aff (Millwood), 2002; 21(4): 155-67
67. Austin MJF, Kreiner T: Integrating genomics technologies in health care: practice and policy challenges and opportunities. Physiol Genomics, 2002; 8(1): 33-40. Available from: URL: *http://physiolgenomics.physiology.org/cgi/reprint/8/1/33.pdf*
68. Committee on Quality of Health Care in America (Institute of Medicine). Crossing the Quality Chasm: A New Health System for the 21st Century. Washington, D.C: National Academic Press, 2001
69. Poste G: Molecular diagnostics: a powerful new component of the healthcare value chain. Expert Rev Mol Diagn, 2001; 1(1): 1-5
70. Picard FJ, Bergeron MG: Rapid molecular theranostics in infectious diseases. Drug Discovery Today, 2002; 7(21): 1092-101
71. Gouget B, Barclay J, Rakotoambinina B: Impact of emerging technologies and regulations on the role of POCT. Clin Chim Acta, 2001; 307(1-2): 235-40
72. Friedman BA: The Total Laboratory Solution: A New Laboratory E-Business Model Based on a Vertical Laboratory Meta-Network. Clin Chem 2001; 47(8): 1526-35. Available from: URL: *http://www.clinchem.org/cgi/reprint/47/8/1526.pdf*
73. Grimson J: Delivering the electronic healthcare record for the 21st century. Int J Med Inf 2001; 64(2-3): 111-27
74. Haux R, Ammenwerth E, Herzog W, Knaup P: Health care in the information society. A prognosis for the year 2013. Int J Med Inf, 2002; 66(1-3): 3-21
75. Berg M: Patients and professionals in the information society: what might keep us awake in 2013. Int J Med Inf, 2002; 66(1-3): 31-37
76. Humphreys BL: Electronic Health Record Meets Digital Library: A New Environment for Achieving an Old Goal. J Am Med Inform Assoc, 2000; 7(5): 444-52
77. Collins FS: Medical and Societal Consequences of the Human Genome Project. N Engl J Med, 1999; 341(1): 28
78. Clayton EW: Through the Lens of the Sequence. Genome Res, 2001; 11(5): 659
79. Collins FS, Green ED, Guttmacher AE, Guyer MS: A vision for the future of genomics research. Nature, 2003; 422(6934): 835-47
80. Robertson JA: Consent and privacy in pharmacogenetic testing. Nat Genet, 2001; 28(3): 207-09
81. Swiss Federal Office of Public Health: HIV – aktuelles Wissen zu Test und Diagnostik, 2000. Available from: URL: *http://www.suchtundaids.bag.admin.ch/imperia/md/content/aids/6.pdf*
82. Swiss Academy of Medical Sciences: Medical-ethical Guidelines for genetic investigations in humans, 1993. Available from: URL: *http://www.samw.ch/content/Richtlinien/e_Gen.pdf*
83. Bundesversammlung der Schweizerischen Eidgenossenschaft: Bundesgesetz über genetische Untersuchungen beim Menschen, 2002. Available from: URL: *http://www.admin.ch/ch/d/ff/2002/7481.pdf*
84. Breithaupt H: The future of medicine: Centralised health and genetic databases promise to increase quality of health care while lowering costs. But to get there, many legal and social obstacles will have to be overcome to prevent abuse. EMBO Reports, 2001; 2(6): 465
85. Aarts JECM, Berg M, Huisman E: Health Information Management Education at the Institute of Health Policy and Management of the Erasmus Unversity Medical Center. In: Haux R, Kulikowski C, editors. Yearbook of Medical Informatics, 2003. Stuttgart: Schattauer Verlagsgesellschaft GmbH, 2003: 179-83
86. Greenbaum D, Luscombe NM, Jansen R et al: Interrelating Different Types of Genomic Data, from Proteome to Secretome: 'Oming in on Function. Genome Res, 2001; 11(9): 1463. Available from: URL: *http://www.genome.org/cgi/reprint/11/9/1463.pdf*
87. Orphanides G: Toxicogenomics: challenges and opportunities. Toxicology Letters, 2003; 140-141: 145-48
88. Funkhouser J: Reinventing pharma: The theranostic revolution. Curr Drug Discovery, 2002; 8: 17-19. Available from: URL: *http://www.currentdrugdiscovery.com/pdf/2002/8/Funkhouser%20.pdf*
89. Bogdanovic S, Langlands B: Theranostics: Commercial Opportunities for Diagnostic and Pharmaceutical Companies. Westborough: D&MD Publications Inc, 2001

Index Copernicus

Global Scientific Information Systems for Scientists by Scientists

www.IndexCopernicus.com

INDEX COPERNICUS INTERNATIONAL

EVALUATION & BENCHMARKING

PROFILED INFORMATION

NETWORKING & COOPERATION

VIRTUAL RESEARCH GROUPS

GRANTS

PATENTS

CLINICAL TRIALS

JOBS

STRATEGIC & FINANCIAL DECISIONS

Index Copernicus integrates

IC Scientists

Effective search tool for collaborators worldwide. Provides easy global networking for scientists. C.V.'s and dossiers on selected scientists available. Increase your professional visibility.

IC Virtual Research Groups [VRC]

Web-based complete research environment which enables researchers to work on one project from distant locations. VRG provides:

- customizable and individually self-tailored electronic research protocols and data capture tools,
- statistical analysis and report creation tools,
- profiled information on literature, publications, grants and patents related to the research project,
- administration tools.

IC Journal Master List

Scientific literature database, including abstracts, full text, and journal ranking. Instructions for authors available from selected journals.

IC Patents

Provides information on patent registration process, patent offices and other legal issues. Provides links to companies that may want to license or purchase a patent.

IC Grant Awareness

Need grant assistance? Step-by-step information on how to apply for a grant. Provides a list of grant institutions and their requirements.

IC Conferences

Effective search tool for worldwide medical conferences and local meetings.

IC Lab & Clinical Trial Register

Provides list of on-going laboratory or clinical trials, including research summaries and calls for co-investigators.