Genomic Med. (2007) 1:95–104
DOI 10.1007/s11568-007-9013-6

REVIEW

From evidence-based medicine to genomic medicine

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Received: 19 November 2007 / Revised: 26 November 2007 / Accepted: 28 November 2007 / Published online: 18 December 2007

Abstract The concept of 'evidence-based medicine' dates back to mid-19th century or even earlier. It remains pivotal in planning, funding and in delivering the health care. Clinicians, public health practitioners, health commissioners/purchasers, health planners, politicians and public seek formal 'evidence' in approving any form of health care provision. Essentially 'evidence-based medicine' aims at the conscientious, explicit and judicious use of the current best evidence in making decisions about the care of individual patients. It is in fact the 'personalised medicine' in practice. Since the completion of the human genome project and the rapid accumulation of huge amount of data, scientists and physicians alike are excited on the prospect of 'personalised health care' based on individual's genotype and phenotype. The first decade of the new millennium now witnesses the transition from 'evidence-based medicine' to the 'genomic medicine'. The practice of medicine, including health promotion and prevention of disease, stands now at a wide-open road as the scientific and medical community embraces itself with the rapidly expanding and revolutionising field of genomic medicine. This article reviews the rapid transformation of modern medicine from the 'evidence-based medicine' to 'genomic medicine'.

Keywords Genetics · Genomics · Evidence-based medicine · Genomic medicine · Personalised medicine · Pharmacogenetics · Pharmacogenomics · Nutrigenomics

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Introduction

The philosophy behind the practice of 'evidence-based medicine' (EBM) is not new. Its philosophical origins date back to the mid-19th century Paris or even earlier (British Medical Journal 1996). Since then it has been hotly debated by clinicians, public health practitioners, health planners and commissioners, politicians and the public. It has now established a central position in the medical practice. The recent upsurge and interest about EBM was triggered in 1991 at the McMaster University in Canada (Guyatt 1991) that led to the North American initiative for EBM (Evidence-Based Medicine Working Group 1992) and establishment of the British centres for evidence-based practice in Oxford and York with the Cochrane Collaboration (Grahame-Smith 1995; Lancet 1995). The importance of EBM was quickly appreciated leading to the launch of a dedicated journal—*Journal of Evidence Based Medicine* (Davidoff et al. 1995). The importance of the evidence-based practice and teaching is reflected in its incorporation in the policy planning and implementation in both undergraduate and postgraduate medical teaching and training (Evidence-Based Medicine Working Group 1992; British Medical Association 1995; SCOPME 1994; General Medical Council 1994). Since its early days the evidence-based practice has evolved as the widely acknowledged paradigm for the health care providers and consumers (Haynes 2002).

The British health community and the public became interested in 'evidence-based medicine' when several articles and official government policy on medical education and training were published (British Medical Association 1995; General Medical Council 1994; House of Commons Health Committee 1995). It was followed by several key articles (Grahame-Smith 1995; Weatherall

1994) and supporting the launch of a dedicated journal (Davidoff et al. 1995). Its popularity is reflected in several undergraduate and postgraduate courses and seminars that followed since publication of the first report. Various databases and resources are now available on 'evidence-based clinical practice' including the Agency for Health Care Research and Quality, Evidence-Based Practice, the Cochrane Library, the National Guidelines Clearinghouse, the National Institute of Clinical Excellence, and various other practice guidelines developed by the British Royal Medical Colleges and academic medical societies (Go et al. 2004).

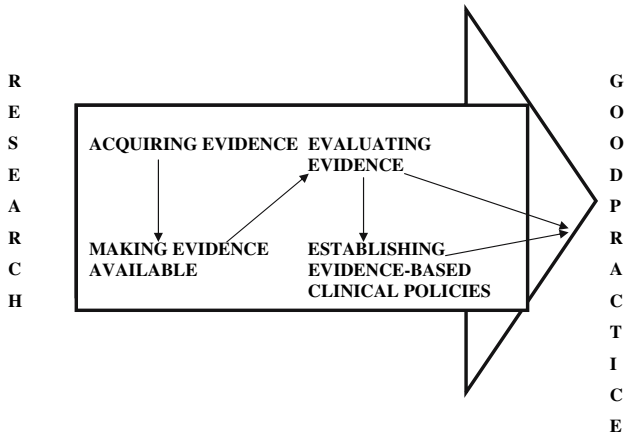

Fig. 1 Steps in 'evidence-based practice' (modified from Donaldson and Donaldson 2003)

The practice of 'evidence-based medicine'

From the time of Hippocrates and to the present day all medical students are diligently taught to elicit individual patient's family history, past medical history and corroborate this with clinical symptoms and signs. This individual evidence is collated with the external evidence based on the outcome of a number of laboratory and imaging investigations. Thus essentially 'evidence-based medicine' is truly the 'personalised medicine'. It is the acceptable form of 'good medical practice'.

The practice of clinical medicine at a given time depends on several factors. The modern medicine evolved during the early 19th century and had to forcibly separate itself away from medieval practices that were largely influenced by several social, cultural and spiritual practices and beliefs.

Essentially evidence-based medicine is a process of lifelong, self-directed learning aimed at providing the best possible patient care using the clinically important available information about diagnosis, prognosis, therapy, and other clinical and health care issues (Sackett et al. 2000). The important elements of evidence-based practice include—(a) collection of evidence; (b) categorise the level of evidence (Table 1); (c) critically appraise the evidence for its validity and applicability; (d) applying results of appraisal in clinical practice; and (e) clinical outcome.

The practice of 'evidence-based practice' in health care includes several stepwise procedures that are essential in achieving the desired goal (Go et al. 2004). These procedures need to be coordinated, controlled, regularly revised and reviewed (Fig. 1). Although in general there may be some regional variation, in principle these procedures should include:

(1) The development of an appropriate, focused, and clear measurable question from observations made during the patient encounter;
(2) Completion of literature searches;
(3) Determination of the quality of designs;
(4) Assessment of the comparability of source populations of cases and control studies;
(5) Recognition of whether controls for potential confounding factors and measurement errors were included;
(6) The search for evidence of any difference in effect y age, gender, or subsites of disease.

The success of evidence-based clinical practice depends up on the robustness of translational research. This is applicable to all kind of applications that exist today. It is well known that several clinical applications did not stand the test of time as these were not properly evaluated through the process of adequately regulated translational

Table 1 Categories of evidence

Ia	Evidence from meta-analysis of randomised controlled trials
Ib	Evidence from at least one randomised controlled trial
IIa	Evidence from at least one controlled study without randomisation
IIb	Evidence from at least one other quasi-experimental study
III	Evidence from descriptive studies, such as comparative studies, correlation studies and case-control studies
IV	Evidence from expert committee reports or opinions or clinical experience pf respected authorities or both

Source: Eccles et al. (1998) Br Med J 316:1232–1235

process. Several promising basic and clinical science discoveries are 'lost in translation' (Lenfant 2003). The translation of scientific discoveries into clinical practice and the discovery of population-level health benefit have always been slow and difficult. It is estimated that only about 5% of the most valued and impressive research findings are actually licensed for clinical use and on average only about 1% remain in clinical practice (Contopolous-loannidis et al. 2003). It is thus essential that the whole process of translational research is properly managed to ensure delivering reliable and clinically relevant outcomes. Khoury et al. (2007) recommend a framework for the continuum of multidisciplinary translation research to utilise previous research outcomes in genomics and related areas of health and prevention. The whole process includes four phases and revolves around the development of evidence-based guidelines. Phase 1 translation (T1) research seeks to move a basic genome-based discovery into a candidate health application, such as a genetic test or intervention. Phase 2 translation (T2) research assesses the value of genomic application for health practice leading to the development of evidence-based guidelines. Phase 3 translation (T3) research attempts to move evidence-based guidelines into health practice, through delivery, dissemination, and diffusion research. Phase 4 translation (T4) research seeks to evaluate the "real world" health outcomes of a genomic application in practice. It is important to appreciate that the whole process of translation research leading to evidence-based guidelines is a dynamic process with considerable overlap between different stages. The process should be able to accommodate new knowledge that will inevitably arrive during translation research.

Although evidence-based health practice is generally welcomed by clinicians, health professionals, health planners and health managers, it is not yet fully incorporated in all spheres of the medical and health profession. This is because of multitude of problems. One of the major hurdles is faced by clinicians on daily basis is selecting the best available evidence. It has been widely recognised that the clinical staff cannot be expected to undertake this evaluation themselves prior to undertaking clinical decisions across a busy practice. Increasingly, databases and information systems have been developed to provide topic-based summaries of research evidence which can be made available to health professionals. One of the established is the Cochrane Collaboration based in Oxford, England which now works with other international networks. The Cochrane Collaboration (http://www.cochrane.org/index.htm) prepares, maintains and disseminates systematic reviews of research, usually focussing on randomised controlled trials. One of the few initiatives on the corporation of genetics and genomics into EBM is the EGAPP (Evaluation of Genomic Applications in Practice and Prevention; http://www.egappreviews.org/about.htm) from the Centers for Disease Control and Prevention in the USA. EGAPP seeks to establish an independent, systematic, evidence-based process for assessing genetic tests and other applications of genomic technology as these procedures transition from research to clinical and public health practice. This process yields summaries of the effectiveness of treatments and other interventions in particular fields of care. In this way the clinician can obtain the information. The widespread use and the availability of the Internet facilities are extremely helpful in developing, teaching and promoting the evidence-based practice of medicine. The state sponsored organisations are equally effective in this approach. These institutions and organisation can examine the evidence and prepare clinical guidelines that could be useful to clinicians and health commissioners. In the United Kingdom the setting up of the National Institute of Clinical Excellence (http://www.nice.org.uk) has been a significant step in this direction. There are several clinically useful guidelines and protocols now available on the public domain of this institution that are regularly reviewed and updated.

The role of genetics and genomics in 'evidence-based medicine'

One of the fundamental principles of 'evidence-based medicine' includes scientific understanding of anatomy and physiology in both holistic terms and as well as in individual parts. The human body is organised into organ systems, tissues, cells, and cell components that are reduced to genetic and genomic profile. The structure–function relationship in biological terms is ultimately dependent upon the genotype. The molecular dissection at the genome or gene level is thus fundamental to understanding the morbid variation in terms of anatomy, physiology and biochemistry. The scope of molecular and cell biology in medicine is unlimited as this encompasses practically whole of genetics and genomics. Genetics conventionally relates to specific genes in relation to a number of different traits and characteristics whilst genomics encompasses the whole genome including all genes, DNA polymorphisms, RNA and its varied forms, and all other polymorphisms that might have current or evolutionary biological relationships. Thus it is not surprising to encounter plenty of evidence around in support of the role of genetics and genomics in the understanding of both normal structure and pathologic changes in relation to practically all aspects of clinical medicine ranging from the most uncommon disorders to the most common medical diseases that afflict the humans.

The pharmacotherapeutic approach has always been the centre point of medical or even surgical treatments. Even in

ancient times, drug administration, whether in the form of herbal or mineral preparation or a combination, was tailored according to age, body size and gender. In a crude sense this was a personalised approach. This concept has evolved and is now firmly established as tremendous progress has been made over several hundred years. Knowledge gained from the personalised approach has also been successfully applied in the public and population health as evident by the use of vaccines, infection control, and nutrient supplementation to safeguard prevention and control of communicable diseases and to some extent control the rapid rise of non-communicable diseases like obesity, diabetes mellitus, coronary heart disease, and some form of cancer. With the completion of the human genome project and full sequencing of several other genomes, the medicine now has the best opportunity to take the treatment prospects to extreme limits, what is being enthusiastically described as genomic medicine (Fig. 2; Go et al. 2004). Medical practice now comprises health promotion and disease prevention and is on the verge of transformation as the scientific and medical communities move from evidence-based medicine to genomic medicine.

There is now enormous amount of genomic data available on various public domains. Information on the genetic basis of rare and common disease phenotypes can be found relatively freely on Medline and OMIM. The focus is now understandably on common medical diseases that are termed complex diseases as the underlying pathogenesis is not usually fully understood but generally perceived to involve multiple factors including the pathogenic effects of polygenes, oligogenes, genetic polymorphisms, single nucleotide polymorphism (SNPs) and the copy number variations (CNVs). Thus evidence that has now accumulated from the genomic research is plentiful and powerful in clarifying the biological understanding of a number of complex diseases. This information is now rapidly harvested in designing new diagnostic tools and as well as those in making pharmaco-therapeutic decisions and predicting the outcome. In this context, genome-wide measures of gene expression derived from DNA microarray studies has the potential of providing information to the analysis of biological phenotypes (Nevins et al. 2003). One of the most successful applications of this kind of data has been in the characterisation of human cancers, including the ability to predict clinical outcomes. Gene expression studies using the microarray genomic technology have been used in defining the broad group distinctions as another mean to define traditional risk factors. However, this approach is less successful in making accurate predictions in individual patients due to considerable heterogeneity within these broadly defined groups. This can be possibly resolved using multiple gene expression patterns and combining this with individual characteristics and predicting outcomes. Thus it is envisaged that combining both genomic and clinical data would most effectively characterise individual patients and provide strong evidence in predicting the clinical outcomes (West et al. 2006).

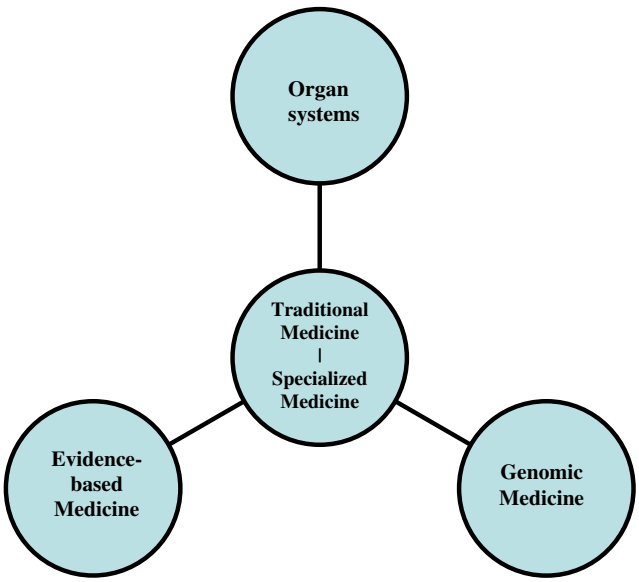

Fig. 2 Evolution of traditional clinical practice to genomic medicine (modified from Go et al. 2004)

Several disease groups have attracted the attention of researchers employing a number of genomic approaches. The treatment of cardiovascular disease and cancer is among the top few. In the treatment of cardiovascular disease the current strategies include relying on using a cocktail of drugs of proven efficacy. In some cases, consideration of age, body size, gender and ethnic origin is taken into account in choosing the drug. Most patients benefit from only a few of the five or so drugs that are commonly prescribed. Although positive effects are seen in most, negative side effects are seen in some patients. Examples include a broad range of beta-blockers and statins. Undoubtedly the clinician would welcome any evidence-based approach in selecting the appropriate drug with the maximum efficacy and minimum side effects. Genomic researchers are actively engaged in collecting this kind of evidence and resolving ways in dealing with the complexity of enormous data (West et al. 2006).

Some tentative progress has been made in this direction. Several genetic polymorphisms have been identified that appear to influence the response to pravastatin, one of the several statins currently in use for the treatment of hyperlipidemia (Jukema 1999). Among these Taq1B polymorphism of cholesteryl ester transfer protein (CETP), which has a key role in the metabolism of high density lipoprotein, has been reported to show a dose dependent correlation with severity of coronary atherosclerosis and

predict the response to treatment with pravastatin (Kuivenhoven et al. 1998). Patients with the B1B1 genotype (homozygous for the restriction site for Taq1) demonstrated more severe disease phenotype and responded better to pravastatin compared to those patients who were homozygous with the B2B2 genotype; this observation received support with intermediate response among those with the B1B2 genotype. In the same context, patients with heart failure harbouring the Ile164β_2 adrenergic receptor polymorphism demonstrate a more rapid progression of their disease (Liggett et al. 1998). The presence of this genetic polymorphism arguably alters the function of the receptor as it reduces the binding affinity of the receptor for catecholamines and certain β receptor antagonists thus reducing the basal and adenyl cyclase activity and agonist stimulated sequestration of the receptor (Liggett et al. 1998). While these observations and such evidence is exciting, Wilkins et al. (2000) caution on relying heavily on the genetic or genomic data in prescribing and point out that the patient's genotype should not be used in isolation but in conjunction with other well established medical and ethical guidelines as part of making therapeutic decisions.

Clinical oncology is another field where evidence-based approach has been in practice in defining the clinical outcomes, choosing the chemotherapeutic regimens, and predicting the response to treatment. It is often argued that in some cases the treatment selected is somewhat harsh and aggressive, and on the other hand in some cancers an aggressive approach should be adopted from start to achieve the best possible clinical outcomes. For example, a woman diagnosed with early stage breast cancer will normally undergo surgery for removal of the tumour and then, typically, be treated with adjuvant chemotherapy. It is possible that some of these women could be spared the harsh reality of chemotherapy should reliable and precise predictors of better longer-term clinical predictors were available. Traditional clinical risk factors, such as tumour size, patient age, regional lymph node spread and estrogen receptor status are commonly used in predicting the disease progression and the prospects of recurrence. However, information derived from these parameters is often unreliable in identifying patients who will respond better with therapy from others who might end up with poor outcome and recurrences. In the same context, some patients might not require the unpleasant chemotherapy and could be spared from this and avoid unnecessary morbidity. Genomic information, in the form of gene expression profiles within tumour samples together with individual's genomic profile (SNPs and CNVs), has in recent years demonstrated the capacity to identify characteristics that reflect tumour behaviour and that relate to disease progression and outcomes, including cancer recurrence. Tumour-based gene expression data from DNA microarrays adds immense detail and complexity to the information available from traditional clinical and pathological evidence. The gene expression profile in a particular tumour reflects the total somatic gene activity and provides the complex and detailed evidence on both the inherent genetic state of the patient and on the current characteristics of the tumour and disease state (Ramaswamy et al. 2001; Singh et al. 2002; van'T et al. 2002; van de Vijver et al. 2002; West et al. 2001). This approach has the potential in to categorise breast cancer patients into high-risk and low-risk categories in the context of long-term recurrences. Patients categorised into high-risk would be likely to have more recurrences and long-term morbidity with probably higher mortality. This type of evidence helps in achieving broad patient stratification that together with traditional clinical risk factors would add tremendous power in making accurate clinically valid predictions (Nevins et al. 2003).

Personalised or individualised medicine

Among the several exciting opportunities that have been explored and discussed, the concept and argument for personalised health care have attracted the maximum attention. Is it a reality or hype? How far this is a valid option? Above all, what does it actually mean? These are some of the inevitable questions that have been addressed and argued in numerous reports and publications (Fierz 2004; Weatherall 2006; Kumar 2007). Whatever may be the argument in favour or against personalised medicine or individualised medical care, this is what is expected by the patient and this is what every clinician is professed to deliver. Starting from the initial days of medical school, all medical students and trainee doctors are taught the art of clinical medicine that includes collecting details of patient's personal and past history in the context of relevant family and social history. This is then put together in the context of presenting symptoms and signs and the outcomes of various radiological and laboratory investigations. Thus the fundamental approach is essentially individualised. So what is different now, in particular following the completion of the human genome sequence and other advances in genome science and technology?

For any disease, there is a causative factor, the manner by which the body or a particular organ system reacts to the causative factor, modifying environmental factors, the institution of most appropriate therapy, the outcome to the therapeutic intervention, and the long-term prognosis. All these parameters are intricately related and the outcome in the form of morbidity and health implications is to large extent individualised. Essentially every individual carries the inherent biological predisposition to react or behave to

a causative factor, the capacity to withstand the unwanted effects of the causative factor, making the best use of the available environmental factors including the pharmacological agents, and contributing to the prevention of progression of the particular disease or disorder.

Developments in genetics, in particular human genetics, over the last 50 years have led to recognised medical specialties that are now an integral part of modern health care. Genetic medicine and molecular medicine are interchangeable terms. Both these specialist fields require a thorough understanding of functioning of genes, molecules, metabolic pathways and immunological processes. The practice of medical or clinical genetics is exclusively confined to dealing with the diagnosis, the risk assessment and communication, and to some extent taking part in the management which is largely of preventive nature.

The practice of modern medicine in the genome era, which is appropriately called Genomic Medicine has the advantage of assimilating all that is known so far and as well as the opportunity to acquire information on individual's genomic profile (Kumar 2007). This is probably more relevant in the context of microbial diseases where the knowledge of genomic profile of the pathogenic organisms (Pathogenomics) can be utilised in establishing the susceptibility or protective ability to the particular pathogen. On the other hand genomic profiling can provide the evidence that the individual is more likely to positively or negatively respond to a particular anti-micobial agent. This has been shown in a number of microbial diseases (Peacock and Jamiesson 2007).

Perhaps the best application of the genomic evidence would be in non-communicable diseases that commonly result from interaction of multiple causative factors and complex environmental factors. These are also referred to as complex disorders, for example bronchial asthma, diabetes mellitus, coronary artery disease, bipolar depression and some common cancers. The individual genomic profiling, which is now possible with the use of variety of microarrays, can enable identification of individuals who are at higher risk of developing the disease and those who can receive bespoke advice on life-style modification, avoidance of contributing environmental factors, and institution of short-term and long-term pharmacotherapy.

Clinical models of genomic medicine

A search for suitable paradigms for genomic medicine requires a fundamental view of the chief facets of the pathogenic process that is reflected as a disorder or disease. It is not always possible to provide a satisfactory distinction between a disease and disorder. Both are interchangeable terms or likely to be an expression metaphor. A disease can be specific to an organ or related to a particular functional aspect. On the other hand a disorder may involve more than one body systems or organs reflecting in sequence of patho-physiological events all leading to the morbid state. Thus for a disease or disorder to become apparent there should be significant disturbance in the body's internal environment or *milieu interior*. The external factors that are capable for disturbing the internal metabolic environment include diet and microbial infection. The five decades of advances and developments in genetics have provided ample evidence for metabolic and molecular bases of human disease (Scriver et al. 2001). A number of genes, gene polymorphisms and genomic sequences of unknown functions govern the internal metabolic environment. Thus essentially almost all human disorders or diseases will have some form of direct or indirect genomic bases. Some one argued that all human disorders will have a genetic explanation except for trauma. But this is now discounted as several inherent factors are known to make an individual react in severe pathological manner to mild trauma whilst other person can withstand the impact of severe trauma, such as severe crush injury or burns (Garrard et al. 2007). The list is endless and rapidly expanding. It is not possible to review all aspects and provide examples. However, the role of diet is looked at in the genomic perspective, which is fast gaining recognition as a distinct discipline of *nutrigenomics*. The second major aspect of genomic medicine is pharmacotherapy in the genomic context. The broad term of *pharmacogenomics* has been used which is appropriately discussed along with *pharmacogenetics*. These two models are discussed in this review.

Genome, genes and clinical nutrition—nutrigenomics

Since the World War II several dietary recommendations have been made to improve health and disease prevention, in particular chronic diseases including cancer. The US Department of Health and Human Services approved *Dietary Guidelines for Americans* as a science and evidence-based guide on diet and physical activity, providing advice and recommendations to promote a healthier lifestyle and reduce the risk for chronic diseases. These are widely supported by several other international agencies including World Health Organisation. In this context it is widely recognised that there is marked inter-individual variation that modulates the true effect of dietary intervention or modification. This variation is fundamentally related to the genetic makeup of the individual. The individual genetic make up and variation is reflected either in the form of genetic predisposition or protection.

This is perhaps a major factor influencing dietary effects in cancer risk through the genomic–nutrient and metabolic–phenotype interactions (Go et al. 2005). However, an individual's overall phenotype, including health status, is achieved and maintained by the combination of metabolic activities under differing circumstances at different stages of the life cycle and the complex interactions among genotype, metabolic phenotype, and the environment. This approach and concept are likely to receive a major boost in the current phase of rapid high-throughput technology developments in genomics, proteomics and metabolomics that analyse DNA sequences, RNA transcripts, proteins, and nutrient-metabolic pathways. These advances have transformed biological studies on nutrient–gene interactions that are crucial in our holistic understanding of complex metabolic processes through functional genomic and metabolic profiling. Perhaps one of the major benefits of the gene–nutrient–metabolism approach could be the development of individualised dietary recommendations to reduce cancer risk. Figure 3 provides a diagrammatic representation of how the genetic/genomic profiling can be harnessed in the future in developing individualised nutritional guidelines for a wide range of chronic diseases.

The evidence collection in nutritional genomics is based on two separate approaches. Firstly, the traditional hypothesis approach that specific nutrient influences the expression of certain genes and proteins through its effect at a particular point in the biochemical pathway following the accepted steps of DNA to mRNA and protein. Secondly, a thorough understanding of functioning of all the inter-related systems that either depends upon or is influenced by the particular nutrient. This approach is now discussed under the broad term of systems biology. This approach allows examination of the evidence starting from genes, proteins, and metabolites that together form the functional metabolic unit influenced by the specific nutrient. Various terms are being used for this are nutritional genetics, nutrigenetics and nutrigenomics. The latter is preferred by the majority as individual genomic signatures are the final determinants in the outcome of genotype–nutrient–metabolic inter-relationships. It is argued that nurigenomics is by far the best model of genomic medicine as it satisfies all the criteria for holistic style of clinical medicine.

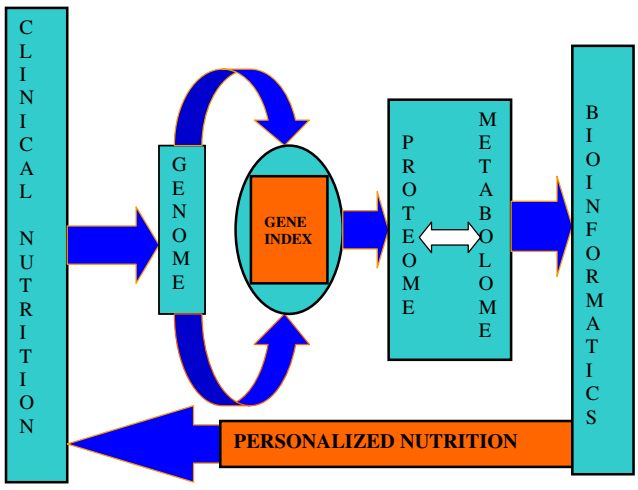

Fig. 3 The application of genomic science in clinical nutrition (Go et al. 2004; reproduced with permission from The Journal of Nutrition)

It is beyond the scope of this article to discuss all facets of nutrigenomics. However, evidence that is available in relation to the prevention of cancer by dietary modifications in the genomic context can be examined. Cancer is now considered a chronic disease of the genome that may be influenced at many stages in its natural history by nutritional an metabolic factors that affect not only the prevention but also the progression and treatment of this devastating disease (Go et al. 2005). The cancer phenotype is the complex interaction of both genetic and environmental factors as indicated by numerous studies on humans and as well as experimental animals. Perhaps the strongest evidence for environmental factors in carcinogenesis is that of dietary factors. It is estimated that about 80% of colon, breast, and prostate cancer cases and approximately one-third of all other types cancers may be caused by dietary and associated life-style factors. All classical nutrient categories consist of bioactive dietary compounds, including carbohydrates, amino acids, fatty acids and structural lipids, minerals and vitamins. In addition, there is a long list of non-nutrient compounds, such as phytochemicals, that may also have anticancer activity. Phytochemicals are plant-based chemicals that carry anticarcinogenic and antimutagenic properties (Harris and Go 2005). An estimated 25,000 chemical compounds exist in fruits, vegetables, and other plants that are consumed by humans. Examples include carotenoids, falvonoids, organosulfur compounds, isothiocyanates, indoles, monoterpenes, phenolic acids and chlorophyll. Most of these nutrients can influence gene expression of steps along the genotype–phenotype continuum (Davis and Milner 2004). There is plenty evidence supporting the view that dietary factors play a crucial role in different stages of development, probably more important during intra uterine phase of the development. The rapid development in genomics and application of new genomic technologies will allow us in collecting more evidence for nutrient–gene interactions that could then be applied in understanding the pathogenesis and prevention of chronic late-onset diseases like cancer (Zeisel et al. 2005).

Genome, genes and drug development and drug response—pharmacogenetics and pharmacogenomics—examples from cardiovascular pharmacogenomics

In the latter part of the sixth decade Arno Motulsky and other workers drew attention to individual-specific drug response. This led to the beginning of pharmacogenetics. Although, several genetic diseases and some genetic polymorphisms are now known that influence the pharmacologic response to a given drug or a group of pharmacologic agents, this was not enough to have a significant impact on the practice of clinical medicine. It was chiefly hampered due to the lack of a satisfactory explanation to the perceived 'drug–gene' relationship. It was not clear how the gene-mutation or a genetic polymorphism could be factor. Several possibilities were enlisted including other modifying genes or genetic polymorphisms, specific genes regulating the drug transport or impact on the drug-target. It was widely accepted that the drug response was heavily influenced by the individual's genetic profile which obviously became more relevant in relation to a specific genetic disorder. The completion of the human genome project in 2003 and subsequent rapid growth in the genome science and technology have opened the way forward in analysing the individual genomic profile. This powerful development together with highly sophisticated tools in bio-informatics are now the mainstay in the drug discovery, development, assessing drug response, conducting clinical trials and monitoring adverse or positive drug response. All these aspects of pharmacology and pharmaceutical science form the major domains of pharmacogenomics. Pharmacogenomics differ from pharmacogenetics as this is not confined to a particular genetic disorder or genetic polymorphism in humans alone. This new field encompasses genomic information drawn from all sources that might be relevant to any aspect of drug discovery, development, and response (Penny and McHale 2007).

One of the major aspects of pharmacogenomics is assessing the interpatient variability in the response to drugs. It is well known that while some patients achieve the desired therapeutic response from their drug therapy others do not. In addition, some patients not only fail to show desired therapeutic response, they suffer from adverse effects, which can range from unpleasant symptoms to life-threatening complications. Whilst this is applicable to all system-disorders, pharamcotherapeutics in cardiovascular medicine is probably most challenging due to marked variability of the drug response. This is more relevant as a broad range of pharmacologic agents are used in cardiovascular medicine. Inevitably the interpatient variable drug response is hugely dependent upon the age, gender and the specific disease.

There are two broad aspects of pharmacogenomics that are applicable to new drug discovery, development and evaluation of the drug response. The first aspect deals with the identification of potential drug targets using the available genomic information. This concept is based on the simple fact that drug targets are widely distributed and exist in the form of peptide molecules encoded by specific genes belonging to specific gene–protein families. It is estimated that there are about 5,000–10,000 potential drug targets. However, currently all the drugs used today only represent about 500 different drug target genes. Thus there is huge potential of novel drug targets for future development of new drugs (Johnson and Cavallari 2005). Whilst this approach has been used in developing new drugs in cancer therapeutics, no marketed cardiovascular drugs have been discovered using the drug target gene approach. Undoubtedly this approach has tremendous potential in developing new drugs which is actively being exploited by the pharmaceutical industry.

The second aspect of pharmacogenomics deals with the drug efficacy and toxicity in the individual's genetic and genomic context. As stated earlier, this was eluded in reference to pharmacogenetics which in a simple manner focuses on the variable drug response in relation to a pathogenic mutation or a genetic polymorphism. In the pharamcogenomic context this concept is expanded to include several loci and polymorphic variants dispersed throughout the genome. Among these genomic polymorphisms such as single nucleotide polymorphisms (SNPs) and copy number variations (CNVs) feature in several publications. There are several examples in the cardiovascular medicine which highlight variable efficacious or toxic drug response based on the individual genetic or genomic profile (Table 2) (Johnson and Cavallari 2005). This list is undoubtedly not complete as new drugs will be discovered, developed and evaluated using a whole range of genomic tools.

The progression of pharmacogenomic research to clinical practice requires several steps (Fig. 4). Several steps need to be followed starting from the identification of sequence variability, for example a single nucleotide polymorphism (SNP), in a candidate gene to clinical use. An important aspect of the pharmacogenomc research is establishing the clinical association of a given polymorphism. This often requires testing several normal healthy volunteers rather than the selected patient population. Although this approach is acceptable in most situations but this could be misleading in the absence of disease state, and is likely to be questionable on ethical and safety grounds. In practice, the clinical studies are best conducted in patient population in a manner that reflects the usual therapeutic practices.

Table 2 Genetic or genomic association in cardiovascular drug response

Drug/drug class	Gene(s) associated with toxicity or efficacy
β-agonists	β_2-receptors
β-blocker	β_1-receptor
	ACE
	Gs protein α subunit
	CYP2D6
ACE inhibitors	ACE
	Angiotensinogen
	AT_1 receptor
	Bradykinin B_2
Antiarrhythmics	Various congenital long QT syndrome genes
	N-acetyltransferase
	(Procainamide) CYP2D6
Antithrombotics	
Abciximab	Platelet glycoprotein IIIa
Aspirin	Platelet glycoprotein IIIa
Heparin	Platelet Fc receptor
Warfarin	CYP2C9
AT_1-receptor blockers	AT_1 receptor
Digoxin	*P*-glycoprotein
Diuretics	G protein β_3 subunit
	α-adducing
Hydralazine	*N*-acetyltransferase
Lipid-lowering drugs	
Statins	Apolipoprotein E
	Cholesterol ester transfer protein
	Stromelysin-1
	β-Fibrogen LDL receptor
	Lipoprotein lipase
	ACE
Gemfibrozil	Apolipoprotein E
	Stremelysin-1

ACE—angiotensin converting enzyme (adopted from Johnson and Cavallari 2005 with permission)

Conclusion

This brief review draws attention to the importance of 'evidence-based medicine', an established concept in the practice of modern clinical medicine. The purpose here is revisit the scope of 'evidence-based medicine' in the rapidly changing medical and health practices following the completion of human and other genomes. The new genome-based technologies and bioinformatics tools offer tremendous power for revolutionising the diagnosis and therapy in a number of human diseases. The genome-based evidence, made accessible to clinicians and health professionals, is robust, accurate and individualised or narrowed down to the small patient population groups. The future of medicine and public/population health looks promising as new opportunities shall emerge from powerful genomic technologies and pharmaco-therapeutic agents. The future clinicians and health professionals will need to be equipped with knowledge and skills in applying broad range of genomic-based diagnostic and therapeutic tools. The transition from the present day '*evidence-based*' approach to '*genomic-based*' approach is in process leading to *Genomic Medicine*.

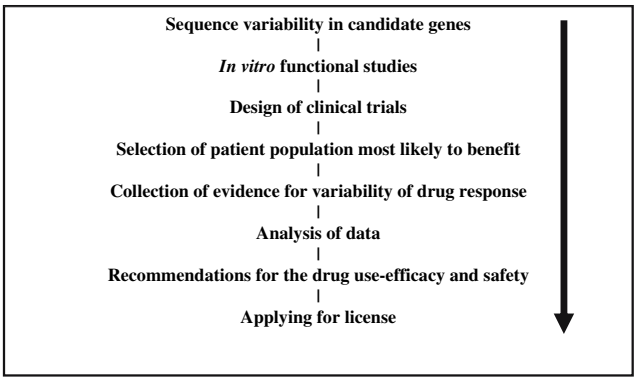

Fig. 4 Progression of pharmacogenomics to clinical practice (Johnson 2003)

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