Overview of personalized medicine in the disease genomic era

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Sir William Osler (1849-1919) recognized that “variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no two individuals react alike and behave alike under the abnormal conditions we know as disease”. Accordingly, the traditional methods of medicine are not always best for all patients. Over the last decade, the study of genomes and their derivatives (RNA, protein and metabolite) has rapidly advanced to the point that genomic research now serves as the basis for many medical decisions and public health initiatives. Genomic tools such as sequence variation, transcription and, more recently, personal genome sequencing enable the precise prediction and treatment of disease. At present, DNA-based risk assessment for common complex diseases, application of molecular signatures for cancer diagnosis and prognosis, genome-guided therapy, and dose selection of therapeutic drugs are the important issues in personalized medicine. In order to make personalized medicine effective, these genomic techniques must be standardized and integrated into health systems and clinical workflow. In addition, full application of personalized or genomic medicine requires dramatic changes in regulatory and reimbursement policies as well as legislative protection related to privacy. This review aims to provide a general overview of these topics in the field of personalized medicine. [BMB reports 2010; 43(10): 643-648]

INTRODUCTION

Traditionally, medical doctors focus on the clinical signs and symptoms of patients in accordance with their medical history. However, traditional methods are not always the most effective as each person has a different genetic architecture (1). Recent advances in medical and human genetics have enabled a more detailed understanding of the impact of genetics in disease (2). Genome-wide association studies over the past 5 years have identified several hundred genetic risk factors for common diseases such as cancer, diabetes, coronary artery disease, etc (3). The discovery that genetic factors are common in disease will undoubtedly lead to greater insights as well as provide additional therapeutic and prevention strategies. In addition, an enormous number of genetic variations in humans have been identified through the human genome project, international HapMap project and personal genome sequencings (2). Especially, newly developed efficient tools for the detection of genetic variations have allowed us to better understand individual differences while challenging new fields of personalized medicine.

The concept of personalized medicine was anticipated by Sir William Osler (1849-1919), a well-known Canadian physician during his time. He recognized that “variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no two individuals react alike and behave alike under the abnormal conditions we know as disease”. Personalized medicine has rapidly advanced the prediction of disease incidence as well as the prevention of incorrect drug prescription based on a person’s clinical, genetic and environmental information. The goal of personalized medicine is optimizing the medical care and outcomes for each patient. To achieve this, there needs to be multidisciplinary healthcare systems developed that educate health providers and patients about customized disease prevention, detection and treatment. For the purpose, the Personalized Medicine Coalition (PMC) was formed as a nonprofit umbrella organization consisting of pharmaceutical, biotechnology, diagnostic and information technology companies, healthcare providers and payers, patient advocacy groups, industry policy organizations, major academic institutions and government agencies. The PMC provides a foundation for achieving consensus positions among these stakeholders on crucial public policy issues, a role which will be vital to translating personalized medicine into widespread clinical practice (4).

Currently, there are many pressing issues in the field of personalized medicine, such as whether or not genomic achievements are sufficient for the prediction or diagnosis of disease, whether review systems to validate the effectiveness of applications in personalized medicine are established, and whether practicing clinicians understand how such tests fit into current models of care and risk assessment. This review provides a general overview of these issues.
Fundamental components of personalized medicine

There are four fundamental components of personalized medicine (Fig. 1). As the first component, personalized medicine requires standard health risk assessment (HRA) tools capable of evaluating an individual’s likelihood of developing a certain disease. One well-known HRA tool is the Diabetes Risk Calculator (5), the objective of which is the calculation of the probability that an individual has either diabetes or pre-diabetes. The Calculator includes questions on age, waist circumference, gestational diabetes, height, race/ethnicity, hypertension, family history and exercise habits (Fig. 2). The diabetes risk can be tested at a public website: http://www.diabetes.org/diabetes-basics/prevention/diabetes-risk-test/. However, the sensitivity, specificity and positive and negative predictive values for diabetes are limited to 75%, 65%, 49% and 85%, respectively, without genetic risk factors, which were recently established in a genome-wide association study (6). Since many predictive genetic markers have been validated across many populations, they should be incorporated into HRA to increase the predictive values.

The second component is family health history (FHH), which is a complex combination of shared genetic, environmental and lifestyle risk factors (7). FHH has tremendous potential for improving preventive healthcare in a personal manner. The American Health Information Community’s (AHIC) Family Health History Multi-Stakeholder Workshop (8) developed “My Family Health Portrait 2.0 (http://family-history.hhs.gov)”, which incorporates the AHIC standards. The program was designed as an open source platform in order to enable sharing interoperability with multiple health information systems.

Regarding the third component, personalized medicine needs to integrate information on genomes and their derivatives, such as the transcriptome, proteome and metabolome. Upon completion of the reference human genome sequence, sequence variation was discovered among individuals, and it is estimated that 10-15 million common sequence variants (minor allele frequency > 5%) are polymorphic in humans (9). In addition, there are countless rare variants present in only a few individuals, which are mostly accessible by direct genome sequencing of these individuals. Variations in the genome can have several different effects on gene expression, thus contributing to the likelihood of disease. Even though as many as 500 disease markers were recently identified and validated by genome-wide association studies, few of these variations are integrated with mRNA and protein expression, not to mention physiological variance (10).

The fourth component is the clinical decision support (CDS) system. CDS systems are interactive computer programs designed to assist clinicians in their decisions about disease care, and they are defined as “Clinical Decision Support systems link health observations with health knowledge to influence health choices by clinicians for improved healthcare”. A known CDS, the ReMINE project (http://www.remine-project.eu), is currently being used to develop a high performance prediction, detection and monitoring platform for managing Risks against Patient Safety (RAPS) (11). The overall platform structure assumes the presence of an “info-broker patient safety framework” connected with the Hospital Information System, which supports the collection, aggregation, mining and assessment of related data, distributing alerts and suggesting actions to avoid the occurrence of RAPS.

Genetic & genomic application

During the progression from a healthy state to disease state (Fig. 3), there are many important time points at which genomic information can be applied to personalized healthcare.
Disease susceptibility and risk can be quantified and anticipated when one is healthy by assessing DNA, which does not change. In order to be cost-effective, the current paradigm of strategic health planning should be shifted from disease treatment to disease prevention. Women who carry mutations in either BRCA1 or BRCA2 have a high risk for breast and ovarian cancer (12). Therefore, it is recommended that women with a family history of breast or ovarian cancer undergo genetic testing for the BRCA mutation in order to make decisions about disease susceptibility when healthy. If positive, women should be monitored periodically. Similarly, subjects with familial history of colon cancer can undergo genetic testing for MLH1 and MSH2 gene variations, which make the risk for colon cancer as high as 60% (13).

In addition, whole-genome expression data can be used to identify subtypes of cancer not clearly diagnosed by traditional methods. For example, whole-genome expression profiles have been utilized to identify a new subclass of Burkitt’s lymphoma from diffuse B-cell lymphoma without prior knowledge of the classes (14). Thus, genomic information redefines disease phenotypes as well as therapeutic strategies.

**Pharmacogenomics**

Pharmacogenomics uses genomic tools to understand the genotype effects of relevant genes on the behavior of a drug, as well as the effects of a drug on gene expression. The best example of successful pharmacogenomic application is warfarin treatment (15). The oral anticoagulant warfarin is prescribed for the long-term treatment and prevention of thromboembolic events. More than 21 million patients are prescribed warfarin in the United States alone, but a variety of complications are associated with its treatment, even after dose adjustment according to age, gender, weight, disease state and diet. An investigation of the pharmacokinetic and pharmacodynamic drug properties of warfarin indicated the additive involvement
of two genes when determining the dosage. One of these genes encodes CYP2C9, which is responsible for the metabolic clearance (~80%) of the pharmacologically potent S-enantiomer of warfarin. There are three allele types, CYP2C9*1, *2 and *3, and both CYP2C9*2 and *3 cause a reduction in warfarin clearance. A ten-fold difference in warfarin clearance was observed between groups of individuals having the genotype of the highest metabolizer (CYP2C9*1 homozygote) and lowest (CYP2C9*3 homozygote). However, it is estimated that CYP2C9 variants account for only 10% to 20% of the total variation in warfarin dosage, which implies that additional genetic and environmental factors play even larger roles in dose determination. The second gene identified as a predictor of the dosage is vitamin K epoxide reductase complex protein 1 (VKORC1). The VKORC1 genotype together with the CYP2C9 genotype and covariates, such as age and body size, are estimated to account for 35% to 60% of the variation in warfarin dosage. The U.S. Food and Drug Administration (FDA) has acknowledged the importance and potential of genotyping CYP2C9 and VKORC1 during warfarin therapy, such that the drug label was amended accordingly in August 2007.

Another successful example is trastuzumab, a monoclonal antibody drug that specifically targets breast cancers overexpressing the HER2/neu gene. Trastuzumab is marketed solely for the subset of breast cancer patients overexpressing HER2/neu (~10%) (16). As trastuzumab was developed for marker-positive individuals who comprise a rather low proportion of breast cancer patients, trastuzumab therapy may be one of the best examples of a genomic technology paving the way for personalized medical treatment.

Personal genomics

The automated Sanger method has dominated the sequencing industry for the last two decades, including a number of monumental accomplishments such as the human genome project. However, this method is not suitable for the routine sequencing of human genomes, for example several hundreds or even thousands of personal genomes in a short period, which establishes a need for new technologies. The automated Sanger method is considered as a ‘first-generation’ technology, while newer methods are referred to as next-generation sequencing (NGS). These newer technologies constitute various strategies that rely on a combination of template preparation, sequencing and imaging, and genome alignment and assembly methods. In Table 1, various NGS platforms are listed (17). The major advantage offered by NGS is the cost-effective production of an enormous volume of data in a short time. Since personal genome sequencing is a fast-moving area that leads technological development, dramatic improvements in sequencing technology will soon reduce the cost to $1,000 per human genome (18). In addition to personal genome sequencing, advances in...
single-nucleotide polymorphism (SNP) technology have allowed genotyping of most of the variations in our personal genomes at low cost. Several companies such as Navigenics and 23andMe offer sequencing or genotyping services for the purpose of disease risk susceptibility as well as information on one's ancestry (Fig. 4). Therefore, it will not be long before a patient can bring along a report of his/her entire genome to a physician and ask for guidance, even though some in the medical community have called personal genome scans premature and ill advised (19).

Policy issues

Although scientific findings are making their way from the genome into the clinic, the full application of genomic and personalized medicine to healthcare requires that several policy issues such as the discrimination against genetic information, the ethics in research as well as industry, guidelines for the genotype tests and drug development, and the reimbursement of patient's cost are to be solved.

In 2008, the U.S. congress finally passed the genetic information non-discrimination act (GINA), which ensures that all genetic information will be protected against misuse by health insurance companies and one's employer (20). Persistently, proactive and important steps have been taken in the U.S. that embrace the emerging practice of personalized medicine (Table 2). Drug companies are encouraged to provide molecular data to the FDA for the evaluation of drugs in development. Further, relevant government offices continuously issue guidelines regarding the standard protocol of genetic testing while recommending drug firms for clinical trials aiming for certain molecularly defined patients' population.

The number of diagnostic tests listed on the labels of drugs approved by the FDA is ever growing, as is the number of pharmaceutical products with package inserts recommending genetic testing for the determination of prescription selection or dosage. So far, more than 200 product labels either recommend genetic testing or recognized the influence of genetic variation on drug response or safety (21). Since genetic tests are also increasingly available for use in a traditional clinical setting, the need for guidance regarding their appropriate use is encouraged. For this purpose, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative commissions evidence-based reviews and develops recommendations for informed decision-making regarding the implementation of genetic tests and other genomic technologies into clinical practice (22). A critical component of this analysis involves the identification and appropriate weighing of relevant health outcomes of genetic testing.

One of the most important factors influencing the integration of personalized medicine is the high cost of testing and treatments and whether or not public and private insurers will reimburse those costs. If larger insurers start paying for genetic tests for the purpose of guiding the prescription of companion drugs or the prevention or management of chronic disease, then personalized medicine should steadily increase (23).

CONCLUSION

Personalized medicine is only beginning to achieve its goal of "the right treatment to the right person at the right time". Even though many discoveries related to genetic variations, transcription, protein expression and sequencing have been made in genomic studies, they are still being evaluated for the applicability to patients. Regardless, genomic data is the driving force behind personalized medicine. Personalized medicine will not change traditional medicine but instead will make healthcare more safe and effective for individual patients.

Acknowledgements

This work was supported by the Basic Science Research Program through a National Research Foundation of Korea (NRF) grant funded by the Korea government (MEST) (2010-0012080).

REFERENCES


