Overview of personalized medicine in the disease genomic era

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Mini Review

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 wide spread 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.

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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 life style 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 of 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.

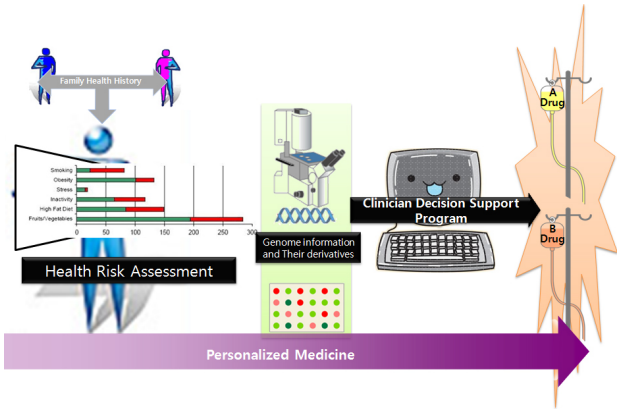

Fig. 1. Illustration of the fundamental components of personalized medicine.

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.

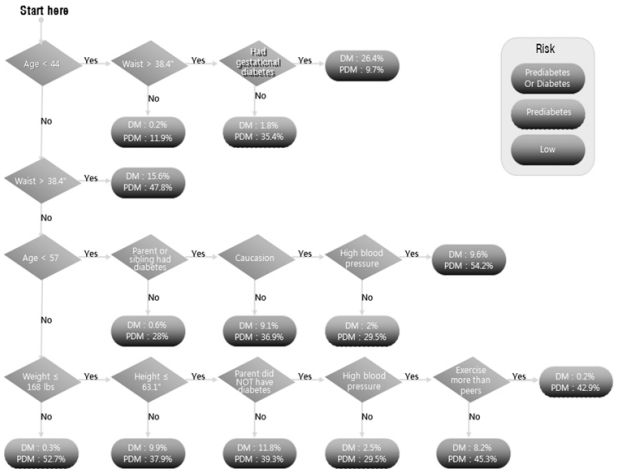

Fig. 2. Classification tree for detection of pre-diabetes or undiagnosed diabetes (5).