

## The Promise of Pharmacogenomics in Personalized Medicine

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The completion of the human genome sequencing has contributed tremendously to human genetic research. The application of the monstrous data set of DNA sequence variations in pharmacogenomics has/will help physicians to tailor treatments to individuals and their diseases. This powerful new capability is called personalized medicine. The ultimate goal of personalized medicine is to utilize all kinds of clinical and molecular information to optimize treatment and health outcomes for individual patients, to answer three key questions precisely: “Who should be treated?”, “How should we treat them?” and “When should we treat them?”

In many ways, physicians have already practiced “personalized medicine.” To understand a patient’s response to treatments, physicians routinely use diagnostic tests to learn more about the patient’s disease, and to choose treatment options and drug dosages based on the results of those tests, along with the patient’s family medical history and lifestyle factors. However, the traditional form of personalized medicine has been based on the observed manifestations of a disease or treatment, such as a tumor size on a mammogram, morphology of cells under a microscope, or a patient’s complaints of side effects (for example, dizziness) in response to a drug. Therefore, the traditional form of personalized medicine is symptoms-based. It is only in recent years that science has begun to provide physicians new powerful tools to understand individual patient or disease differences at the molecular or genetic level, enabling them to tailor treatment even more effectively. For example, knowledge of genetic variations can now help physicians optimize breast cancer therapy, or protein biomarkers in blood can be associated with an elevated risk of cardiovascular disease. The new molecular methods make personalized medicine possible to include testing for variations in genes, gene expression, protein expression, and metabolites, as well as new treatments that target molecular mechanisms. Test results are correlated with clinical factors such as states of disease, prediction of future disease states, drug response, and treatment prognosis to help physicians individualize treatment for each patient (see Figure 1).

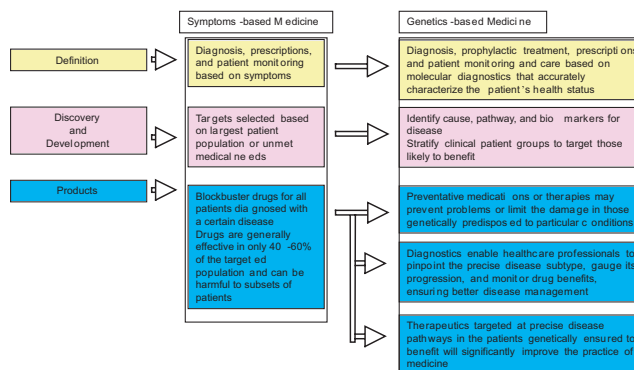


Figure 1. Comparison of symptoms-based and genetics-based medicine<sup>3</sup>






To date, much of the promise and many of the challenges of personalized medicine remain untested, and projection for its future is based on limited evidence<sup>1,2</sup>. In this review, we present evidence to illustrate that personalized medicine has already proven its value and will continue to grow in importance, while at the same time acknowledging that uncertainties remain about the full extent of its ultimate impact.

**Select optimal therapy**

Physicians have long recognized that patients response very differently to the same medication (see Table 1). For a given medication, some patients response positively, some negatively, while others suffer serious side effects. It is estimated that, on average, as much as forty percent of the medicines that individuals take every day are not effective. For certain medications the estimate of non-effectiveness is well over 50% (Table 2). For example, a statin drug used to lower cholesterol levels may work for only 30-70 percent of patients (Table 1).

In the United States, with annual spending on drugs totaling roughly \$150 billion, this implies that \$60 billion annually is ultimately wasted. In Japan, the second largest pharmaceutical market in the world, annual spending is roughly \$50 billion (US), implying a waste of \$20 billion annually on ineffective drugs. More importantly, millions of people are exposed to the problematic side effects of drugs while receiving little or no benefit.

Studies have linked differences in drug responses to differences in genes that code for the production of drug metabolizing enzymes, drug transporters or drug targets. Detection of these genetic differences provides the opportunities to use genetic or other forms of molecular screening approach to select optimal therapy for the first time and avoid a trial-and-error approach to prescribing.

Hypertension Drugs ACE Inhibitors	10-30%	
Heart Failure Drugs Beta Blocks	15-25%	
Anti-depressants	20-50%	
Cholesterol drugs Statins	30-70%	
Asthma Drugs Beta-2-agonists	40-70%	

**Table 1.** Patients can response differently to the same medication<sup>4</sup>

Therapeutic area	Efficacy rate (%)
Alzheimer’s	30
Analgesics (Cox-2)	80
Asthma	60
Cardiac Arrythmias	60
Depression	62
Diabetes	57
HCV	47
Incontinence	40
Migraine (acute)	52
Migraine (prophylaxis)	50
Oncology	25
Osteoporosis	48
Rheumatoid arthritis	50
Schizophrenia	60

**Table 2.** Response rates of patients to a major drug for a selected group of therapeutic areas<sup>5</sup>

About 30 percent of the breast cancer patients are characterized by over-expression of human epidermal growth factor receptor 2 (HER2) - a cell surface protein. Women with HER2-positive breast cancer don’t respond effectively to standard therapy. An antibody drug – Herceptin® (trastuzumab) that specifically inhibits the HER2 receptor has greatly improved the survival rate of women with this sub-form of cancer. Molecular diagnostic tests (HercepTest™ and PathVysion™) have been developed that measure either HER2 protein levels or gene copy numbers to identify patients who can benefit from receiving Herceptin.

Another successful example of personalized medicine is Gleevec® (imatinib) that is used to treat patients with chronic myelogenous leukemia (CML) and malignant gastrointestinal stromal tumors. CML is caused by a chromosomal rearrangement that creates a fusion between two normal proteins, producing one abnormal protein called BCR-ABL. BCR-ABL promotes an increase in the number of white blood cells. Gleevec

binds specifically to BCR-ABL and inhibits its action. Appropriate prescription of the drug can be confirmed by a diagnostics test (BCR-ABL test) that detects the presence the BCR-ABL gene. CML patients receiving Gleevec have significantly improved response rates and lower toxicity compared with patients receiving standard chemotherapy. Over 90 percent of patients receiving Gleevec respond positively to initial treatment, and many experience complete remission. Recently, Genzyme introduced a genetic test to monitor the emergence of Gleevec resistance that occurs in about 4-5 percent of CML cases<sup>6</sup>. This new test could provide an additional tool for personalized treatment.

Personalized medicine is also revolutionizing the treatment of acute lymphoblastic leukemia (ALL), the most common cancer among children. In the 60s, less than 5 percent of sick children survived 10 years after diagnosis. Today, the cure rate is increased to over 80 percent, while the five-year survival rate is approaching 90 percent. These improved clinical outcomes are benefited from the application of genetic screening technologies and improvements in treatments. Using genetic analysis to determine ALL subtypes allows clinicians to choose the optimal drug and dosage for each patient and reduce the chances of toxicity and relapse.

### Reduce adverse drug reactions

It is estimated that over 2 million serious adverse drug reactions (ADRs) occur annually in the United States, causing as many as 137,000 deaths<sup>7</sup>. Some of these deaths could be prevented by testing individuals for genetic variations that indicate their susceptibility to toxic reactions.

Many ADRs are caused by variations in genes coding for drug metabolizing enzymes. About half of all drugs are metabolized by the cytochrome P450 family of enzymes present mainly in the liver. There are over 30 different forms of these enzymes, each coded by a different gene. Variations in these genes can lead to decreased or increased metabolism of certain drugs. As a result, some individuals may have trouble inactivating a drug and eliminating it from their body, while others eliminate the drug before it has a chance to work. Individuals with low activities in drug metabolizing enzymes are called “low metabolizers”. There is an increased risk for these patients to be “overdosed” when given a typical dose, possibly resulting in serious toxicity.

The drug warfarin is used to prevent blood clots and is complicated by genetic variations in drug metabolizing enzyme (CYP2C9) and a vitamin K metabolizing enzyme (VKORC1). Dosing is typically adjusted for the individual patient through multiple rounds of trial and error, during which the patient may be at risk of excessive bleeding or further blood clots.

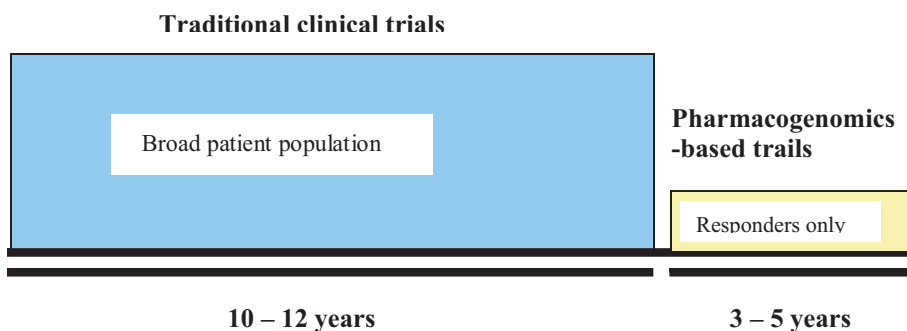
The need to get warfarin dosing right the first time to avoid adverse effects led an FDA advisor committee to recommend genotyping for all patients receiving warfarin.

Thiopurine methyltransferase (TPMT) is another enzyme that has been studied from personalized medicine perspective. TPMT is responsible for inactivating purine drugs used for treating ALL and other diseases. TPMT gene variations can cause variations in enzymatic activity and thus drug metabolism. One in 300 patients has both copies of TPMT genes coding for an inactive form of the enzyme, a condition known as TPMT deficiency. In these patients, the normal dose of purine drugs results in an accumulation of active compound, which may cause a potentially fatal bone marrow reaction that results in abnormal lowering of the white blood cell count. After a few cases of fatal toxicity in TPMT-deficient ALL children treated with a purine drug, physicians started screening for variations in the TPMT gene before administering the drug. When a TPMT deficiency is detected, the dose is lowered to 10-15 percent of the standard dose. The adjustment ensures that systemic levels of the drugs are comparable to those found in patients with normal TPMT who have been given a standard dose.

The Amplichip cytochrome P450 test approved by the FDA can detect variations in two important cytochrome P450 genes. The information provided by Amplichip and similar tests will help physicians make better decisions about drug treatments and dosages. The UGT1A1 assay was also approved by the FDA to predict patients’ safety-related response to irinotecan. The test allows physicians to adjust the irinotecan dosage for approximately 10 percent of the patients who metabolize the active drug form too slowly.

### Reduce time, cost, and failure rate of clinical trials

New drug discovery and development is a very costly and lengthy process. Theoretically, using pharmacogenomic data, or information about how patients’ genetic makeup affect their drug responses, could reduce the time and cost of drug development. By analyzing and evaluating data from molecular or genetic tests, researchers could pre-select patients for clinical studies. Using those most likely to respond positively or least likely to suffer side effects to enrich the clinical trial pool could reduce the size, time, and expense of clinical trials (Figure 3). Moreover, using pharmacogenomic data in the early stage of drug development process could reduce product failures by focusing resources on drug candidates most likely to be safe and effective. According to a report by the Boston Consulting Group<sup>8</sup>, pharmaceutical companies could save as much as \$335 million per drug by incorporating this type of data into certain drug development programs.



**Figure 3.** *How Pharmacogenomics can streamline clinical trials.*  
 Source: *Quintiles Transnational, 2004*

Anecdotal evidence suggests that pharmacogenomics can cut the length of clinical trials as well. A very recent example involves patients taking the highly touted drug Tykerb (lapatinib), an oral medication for breast cancer that could compete with Herceptin. Fifteen percent of patients reported unpleasant side effects, including diarrhea and rash. An analysis of densely mapped SNPs in cytochrome P450 metabolizing genes revealed a strong association between the side effects and variants in CYP2C19. Only patients homozygous for the \*2 allele experienced side effects. This phase III clinical trial was completed early due to the drug's remarkable success in treating a genetically defined subset of patients with breast cancer<sup>9</sup>.

### Reduce drugs that are failing in clinical trials

The Herceptin story is an excellent example of adapting clinical trials to alter the fate of a new drug. Clinical data from Phase III trials in 1997 showed the drug to be ineffective in the overall population tested. However, subsequent evaluation of trial results revealed that women tested positive for HER2 over-expression had a significantly better response to the drug suggesting that the HER2-positive subset, defined by a diagnostic test, would benefit from the drug<sup>10</sup>. The FDA approved the drug/diagnostic combination in 1998.

So far, no examples have been reported that a drug returns to market based on genetic or molecular diagnostics after having been withdrawn for serious adverse events.

### Prevention medicine

Personalized medicine introduces the ability to use molecular markers that signal a risk of disease or its presence before clin-

ical signs and symptoms appear. This information underlies a healthcare strategy focused on prevention and early intervention, rather than reaction to advanced stages of disease. Such a strategy can delay disease onset or minimize symptom severity. Examples of prognostic molecular markers now being used in clinical practice include C reactive protein, indicating risk of cardiovascular diseases,

and LDL and HDL cholesterol indicating risk of atherosclerosis. Detecting abnormal levels of these molecular markers may trigger steps aimed at preventing future diseases.

Two genetic tests now on the market can identify disease susceptibility and guide preventive care. One is a test for BRCA1 and BRCA2 genetic variants that show hereditary propensity for breast and ovarian cancer<sup>11</sup>. Women with BRCA1 or BRCA2 genetic risk factors have a 35 to 85 percent lifetime chance of developing breast cancer, compared with a 13 percent chance among the general female population. For ovarian cancer, women with certain BRCA1 or BRCA2 gene variants have a 15 to 60 percent chance of developing the disease, compared with a 1.7 percent chance among the general population. The BRCA1 and BRCA2 genetic test can be used to guide preventive measures, such as increased frequency of mammography, prophylactic surgery, and chemoprevention.

The second available genetic test is the p16 test for melanoma<sup>12</sup>. P16 accounts for up to 40 percent of hereditary cases of melanoma and has also been linked to pancreatic cancer. For those who test positive, several prevention options are available, including early detection, preventive surgery on suspicious lesions, and reduced sun exposure.

The treatment of early-stage breast cancer in women may be possible by scanning a panel of genes correlated with a risk of disease recurrence and response to therapy<sup>13</sup>. For example the assay Oncotype DX analyzes the expression of 21 genes<sup>13,14</sup>. The information provided by this test supports both treatment and monitoring decisions based on the foreknowledge of disease progression, time to event, and likelihood of treatment benefit<sup>15</sup>.

## The FDA regulation

The U.S. regulatory agents have been very supportive to personalized medicine, and regulators are encouraging a personalized approach to drug and diagnostic development. In recent years, the FDA has approved quite a few pharmacogenomics tests and published the guidance for genomic data submissions<sup>16-22</sup>. From 2004 to the second quarter of 2006, the number of formal requests for genomic data review and voluntary genomic data submissions to the FDA (as part of regular INDs, NDAs or BLAs) increased remarkably, from a total of 5 in 2004, to 20 in 2005, and 29 in the first half of 2006<sup>23</sup>. These actions by the FDA are helping to create a constructive regulatory environment that will foster the emergence of personalized medicine.

## Conclusions

Currently, the evidence establishing a clear-cut case for personalized medicine remains largely anecdotal rather than statistical. In oncology area, there are many proofs of principle for personalized medicine, and many more are emerging. Several examples have demonstrated the utility of personalized medicine in selecting optimal therapy, rescuing drugs from failed clinical trials, and shifting emphasis from disease treatment to disease prevention.

Many other claims still remain untested, including the ability to rescue drugs that have been withdrawn from the market or the ability to reduce the time, cost, and failure rate of clinical trials. Furthermore, little hard evidence is available on the impact of a personalized medicine approach on pharmaceutical industry productivity or healthcare economics.

Whether personalized medicine will “revolutionize” clinical care is uncertain. However, at least in some cases, a personalized medicine approach to treatment has led to cost savings in the administration of healthcare, demonstrated itself to be a viable business strategy for product development, and most importantly, proven its benefit to patients. It is therefore reasonable to expect that many more successful examples of personalized medicine will be seen in the near future.

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17. Approved the first device for rapid characterization of cytochrome P450 genes
18. Collaborated with other Federal agencies to improve cancer therapies through biomarker development and evaluation
19. Published the “Guidance for Industry: Pharmacogenomic Data Submissions,” clarifying what type of genomic data needs to be submitted to the Agency and when, and encouraging the voluntary submission of exploratory genomic data (March 2005)
20. Released its drug and diagnostic co-development concept paper (April 2005)
21. Published guidance on the incorporation of genotypic and phenotypic resistance tests into the study of anti-viral drugs (June 2006)
22. Issued “Draft Guidance for Industry, Clinical Laboratories, and FDA Staff on In Vitro Diagnostic Multivariate Index Assays” with request for public comment (September 2006)
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### Say it in Chinese

Personal Medicine : 个体化医疗  
 Microarray Chip : 微阵列芯片  
 Immunohistochemistry : 免疫组织化学技术  
 Fluorescence in situ Hybridization (FISH) : 荧光原位杂交技术  
 Germline : 种系, 先天遗传系  
 Pharmacogenomics : 药物基因组学  
 Theranostics : 治疗性诊断学  
 Single Nucleotide Polymorphism (SNP) : 单核苷酸多态性  
 Cellular Signaling Pathway : 细胞信号传递通道  
 Genetic makeup : 基因组成  
 Well-beings: 健康生活  
 Consumer Gemonics : 消费者基因组学  
 Genome-wide association studies (GWAS) : 泛基因组相关性研究  
 Molecular signatures : 分子特性谱  
 Biomarkers : 生物标记