

Orentreich  
Foundation for the  
Advancement of  
Science, Inc.

# Vital Longevity™

Logo: Life's blood flows through the hourglass; the stopcock represents the alteration of aging and disease as biomedical research progresses.

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www.orentreich.org

## Pharmacogenomics

Over the past 50 years, physicians have learned that one size doesn't fit all. Of two persons taking the same medicine, one might have life-threatening side effects, while the other has only benefit. Or an anti-cancer drug might shrink a tumor in one patient but not in another. One major reason for this difference is genetic variation, even slight variations. Pharmacogenomics, which popular media often term "personalized medicine", is the science that studies, among other things, how genes modify pharmaceutical actions and reactions.

Many of us don't realize that we already know something about pharmacogenomics, for example, the prevalent, genetically-based inability of Native Americans to convert alcohol to its less-intoxicating metabolites. Further, many might have heard that research has suggested that alcohol metabolism with subsequent alcoholism is due to mutations in alcohol metabolizing enzymes that are genetically passed on to offspring. What might not be adequately appreciated are the molecular mechanisms of alcohol-mediated carcinogenesis from DNA mutations such as aldehyde dehydrogenase 2\*2, the same mutations associated with alcoholism.

And if you're a dog owner, you might know that not only humans are subject to pharmacogenomics; for example, Collies and other susceptible, related breeds of dog have DNA mutations that affect the transport of ivermectin, a medication commonly used against worms. Researchers found that with the Multi-Drug Resistant 1 gene, ivermectin accumulates in the brain, leading to severe neurological events and even death. Fortunately, veterinarians are aware of breed susceptibility and that there are DNA tests for this potential problem using cheek-gum brushings from the dog's mouth.

And if you're a gardener, you know that the genetics of species of plants determine whether a species will be sun- or shade-loving or need acid or alkaline soil to thrive. Others might have read our September 2006 issue about aspirin resistance and learned that, in some cases, one of several candidate genes might be the cause of such resistance.

## History

In 1959 German researcher Freidrich Vogel coined the term pharmacogenetics. It is an old (but not well recognized) area in medicine dealing with clinically significant drug responses under hereditary control. This definition covers two broad topics: 1) genetic conditions that alter the ways the body acts on drugs and 2) genetic conditions that alter the ways in which drugs act on the body. Pharmacogenetics seeks to identify precisely those differences in drug effects that have a genetic basis and to develop simple methods by which susceptible individuals can be recognized prior to drug administration.

J.H. Edwards proposed the theory of the Genetic Background of Therapy at the 1969 International

Symposium on Pharmacogenetics. In his concept, the basis of rational medical therapy is the metabolic map, consisting of a drug, its metabolites, and metabolic pathways, all under the control of enzymes that are under genetic control. Variations in the metabolic map are passed down through generations. His theory was later proven: genetically controlled variations in enzymes culminate in variations in drug metabolism. Figure 1 illustrates how blood levels of coumadin, a regularly used blood thinner, can be influenced by mutations in specific metabolic enzymes. In many cases, variations in drug metabolism lead to variations in drug response, for the most part detrimental. Edwards expected that before long these genetic variations would be identified in various segments of the population.

Differences in Time to Reach Steady-State Blood Concentration of Coumadin by CYP2C9 Genotype Variants

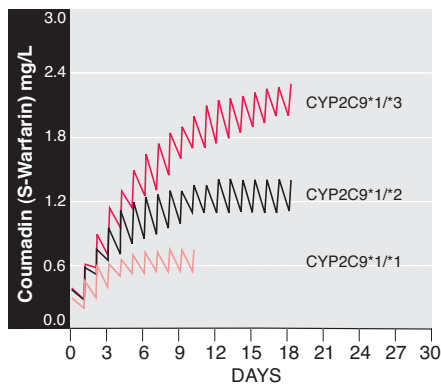


Figure 1

Source: Genetex Corp.

## Human Genome Project

In the 1990s, work on the Human Genome Project (HGP) moved what was known as pharmacogenetics forward into the science of pharmacogenomics. The HGP was an international research project designed to map and identify the approximately 20,000-25,000 human genes from both physical and functional standpoints. Most mapping was complete by the end of 2003, though there are still a number of unfinished regions. The end result of utility to the pharmaceutical industry is that specific drug metabolizing enzymes have been assigned to specific genes. Now, enzymes that contribute to therapeutic successes or failures can be established—providing, of course, the proper DNA test is available.

Tidbits of this research come to the consumer through media reports on various studies. The NY Times recently related the case of a woman who took tamoxifen for years to prevent a recurrence of breast cancer. The patient underwent a new DNA test; the results indicated that, because of her genetic makeup, the drug would give her no protection: a variation in her DNA prevented an enzyme needed to metabolize tamoxifen from working correctly. Many years of wasted time, money, and false expectations were avoidably expended.

From the 1960s and through the 1990s information accumulated on genetic causes of unanticipated effects of commonly used drugs. Here are just a few examples:

- Succinyl choline (for anesthesia): malignant hyperthermia (body temperatures reaching 112°F)
- Isoniazid (for TB): hepatotoxicity
- Phenytoin (for seizures): discoordination and confusion
- Dapsone (for leprosy and dermatitis herpetiformis): imbalance of blood components
- Coumadin (for atrial fibrillation): excessive bleeding
- Phenylbutazone (for arthritis): hepatotoxicity

Without specific testing, pharmaceutical therapy might be largely trial and error. The goal of pharmacogenomics: a DNA test via blood, urine, or cheek swab to discover any genetic variation that would impact your treatment, enabling your doctor to skip some medications entirely or to customize doses.

Knowing the specific gene mutation to look for is only half the battle; reproducible, reasonably priced tests are also required. Luckily, some diagnostic testing companies have been gleaning information from the HGP to develop such tests. Pharmacogenomics is still in its infancy. It's possible that millions of genetic variations exist; identifying them all could take years—if it's even possible. In addition, drug response might be determined by two or more interacting genes. Elucidating this complicated genetic map is, of course, expensive and time consuming.

## Pharmacogenomics Today

Some types of personalized medicine based on the science of pharmacogenomics are in use today but only on a limited basis. A few tests are now available that can help predict likely responses or adverse reactions to certain medications. Some of the tests available are listed in Table 1.

Though current uses are limited, pharmacogenomics has huge potential. Some of the potential benefits include: **Better medication choices.** Each year, some 100,000 Americans die from adverse reactions to medications and more than 2 million are hospitalized. So even if a medication appears safe for most people, pharmacogenomics could preventively predict those likely to have a bad reaction. It could also predict if you can respond well to a medication—whether your breast tumor will shrink, for example. **Safer dosing options.** As it stands now, the dosage of a medication either is a standard one-size-fits-all dose or is based on factors such as your weight and age. But a standard dose might prove toxic because of genetic variations. Pharmacogenomics might predict the ideal dose, not just which medication is right. So you and your doctor can spend less time trying out various dosages to find one that works well, with the fewest side effects and most benefits for your condition.

**Improved drug development.** Pharmaceutical companies often must spend years conducting research and clinical trials for a new drug before it goes to market. They have to test a drug in many people to ensure that it's safe and effective. Pharmacogenomics can help these companies to focus their drug testing. If pharmaceutical companies know ahead of time that

a specific genetic variation will cause a bad reaction or make a drug ineffective, persons with that variation can be excluded from pre-market clinical trials. This can speed up the clinical trial process and better target persons who can be helped (or not harmed) by a new medication.

Pharmacogenomics will likely have an expanding role in the practice of medicine. Perhaps in the very near future, medicine will be truly personalized.

Supplementary reading is available at <[www.orentreich.org/vital.htm](http://www.orentreich.org/vital.htm)>, where you also can find all previous issues of VitaLongevity.

### Some Tests in Use Today

- Cytochrome P450** to determine dosing and effect of, for example, antidepressants, anticoagulants, and proton pump inhibitors.
- Thiopurine methyltransferase enzyme** to learn the body's ability to break down thiopurine, a chemotherapeutic agent to treat some leukemias and autoimmune disorders.
- UGT1A1 TA enzyme repeat genotype** to determine how the body breaks down irinotecan, a chemotherapeutic drug used to treat colorectal cancer.
- Dihydropyrimidine dehydrogenase** to detect any deficiency in this enzyme that could cause severe or even fatal reactions to 5-fluorouracil (5-FU), one of the most commonly used chemotherapeutics.
- Platelet function** to determine whether there is resistance to aspirin therapy to prevent heart attacks or strokes.

Table 1

### Information for Donors

The Orentreich Foundation for the Advancement of Science, Inc., was founded in 1961. OFAS is dedicated to biomedical research to prevent, halt, or reverse those disorders that decrease the quality or length of life. A 501(c)(3) non-profit corporation (EIN 13-6154215), OFAS is duly registered with the US Internal Revenue Service as an Operating Private Foundation under Section 4942(j)(3).

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