Arnall Golden Gregory LLP

Client Alert

Contact Attorney Regarding This Matter:

William H. Kitchens
404.873.8644 - direct
404.873.8645 - fax
william.kitchens@agg.com

FDA Takes A Major Step to Advance Its Focus on Genomics and Related Fields of Science: An Update on the Current State of Personalized Medicine

Introduction

In early February 2009, the FDA created a new position in the Office of FDA's Chief Scientist dedicated to coordinating and upgrading FDA's activities involving genomics and the related fields of science that are involved in the analysis of complex DNA, protein and small molecular expression patterns. The use of genomic information, accelerated by the sequencing of the human genome and the advent of new tools and technologies, has opened new possibilities in drug discovery and development. Consequently, this step is a welcome acknowledgement by the FDA that it is serious about accepting its responsibility to advance this new era of personalized medicine and personalized health records.

To allow progress in this field of medicine, FDA must use the most advanced tools for evaluating the new and frequently highly complex products it regulates. The creation of this new scientific position signals FDA's determination that it must further integrate and coordinate the latest genomic technology into the agency's drug approval processes and decision-making to better protect and promote the public health. Such initiatives will provide FDA physicians, scientists, and drug reviewers with the necessary tools and personnel capable of high level analysis of complex genetic data. The FDA's emphasis on a coordinated genomics effort is the apparent outcome of the June 2008 FDA Symposium and Retreat on Genomics, the recommendations of FDA's advisory Science Board, and its own internal planning.

Genomics, Personalized Medicine, and Pharmacogenomics

Genomics is the study of an individual's gene structure, including how the genes interact with each other and with the environment. Experts say genomics has the potential to revolutionize the practice of medicine.

An example of a preventive approach is when a genetic test predicts which diseases an individual is likely to develop. For instance, people who have certain mutations in the BRCA1 gene have a high risk of developing breast, ovarian, and possibly prostate, and colon cancers, according to the National Cancer Institute (NCI). Alterations in the BRCA2 gene have been associated with breast, pancreatic, gallbladder, and stomach cancers. An example of a treatment approach is when a genetic test determines whether a person is among the 10 percent of those for whom a particular drug is likely to work.

Arnall Golden Gregory LLP
Attorneys at Law
171 17th Street NW
Suite 2100
Atlanta, GA 30363-1031
404.873.8500
www.agg.com

Through genomics, scientists are able to develop medical products and nutritional recommendations that are sometimes called "personalized medicine" – recommendations and therapies designed for individuals of a certain genetic makeup. The intent of "personalized medicine" is to improve the diagnosis of disease, as well as the prevention and treatment of disease. Developing products that take into account genetic make-up can increase a product's effectiveness and decrease the risk of harmful side effects. For the FDA, insights gained through genomics point a way to faster and more efficient evaluation of new medical therapies and toward enhanced food safety.

The combination of drugs (pharmacology) with genomics is known as pharmacogenomics, the science that allows researchers to predict the probability of a drug response based on a person's genetic makeup. The focus is getting the right dose of the right drug to the right patient at the right time. The main benefit of pharmacogenomics for consumers is the availability of drugs that have a greater chance of benefit in terms of treating illness. Use of pharmacogenomics can assist physicians in prescribing the right drug and the right dose. For some people who feel like they are always experiencing bad side effects from drugs, genetics plays a role. If health care professionals can identify who are the most susceptible to these risks, they can target a drug more appropriately. This may allow some drugs to be approved or to remain on the market when under normal circumstances they might otherwise face the prospect of not being approved because the risk profile in a wider population is too high

The science of pharmacogenomics has advanced significantly in recent years, but it is still in its early stages and is mostly used on a research basis. There are three main ways that pharmacogenomics is applied today. The first is to help predict the appropriate dose of a drug. The second is to target therapy to a subset of a disease. This means picking the most effective drug for the disease subset. And the third is to test viral genomics, such as in selecting treatment for HIV based on resistance.

The usual doses of drugs work well for most people. They are sometimes based on weight, age, and kidney function. But for someone who metabolizes a drug quickly, the typical dose may be ineffective and a higher dose may be needed. By contrast, someone who is a slow metabolizer may need a lower dose; the typical dose could cause toxic levels of the drug to build up in the blood.

When we take medicine, it moves through our body, gets broken down by drug-metabolizing enzymes, and interacts with countless proteins. Genes regulate drug metabolism. Differences in the sequence of a gene can cause differences in enzyme activity, which is a result of enzymes appearing in various forms in individuals. This is why different people process the same drug differently.

Targeted therapy, the second major aspect of pharmacogenomics, is also referred to as "tumor genomics." Tumors have different genomic variations, and genomic tests are helping doctors to identify cancers that are likely to respond to a particular treatment. Drugs like Gleevec (Imatinib) for chronic myeloid leukemia, Tarceva (erlotinib) for lung cancer, and Herceptin (trastuzumab) for breast cancer are examples of targeted therapy. Both Gleevec and Tarceva interact with enzymes called tyrosine kinase inhibitors. Turning off these enzymes prevents the growth of cancer cells. Herceptin targets tumors that produce excess amounts of the HER2 protein, which is produced by the HER2 gene. Overexpression of the HER2 protein causes a higher rate of cell growth. Before Herceptin is used, tumors must be tested to evaluate the amount of HER2 protein.

The third aspect of pharmacogenomics includes testing for drug resistance. For example, the HIV virus genome is always changing, and resistance testing can help doctors choose the drug that will best match the virus and suppress it. The TRUGENE HIV-1 Genotyping Kit is cleared by the FDA to detect genetic variations that make the HIV virus resistant to some anti-retroviral drugs. If drug resistance is discovered, a doctor can decide to try another treatment option.

FDA recognizes the importance of pharmacogenomics and encourages its use in drug development. This is reflected in the FDA white paper "Stagnation or Innovation? – Challenge and Opportunity on the Critical Path to New Medical Products," (http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html), which recognizes pharmacogenomics as a key opportunity for the Critical Path Initiative the agency adopted in March 2004 to stimulate and facilitate a national effort to modernize the sciences through which FDA-regulated products are developed, evaluated, and manufactured.

What Are the Potential Benefits of Personalized Medicine?

The most common approach to drug treatment today is that doctors give all patients with a given disease the same drug and an average dose, evaluate how it works, and then make adjustments as needed. But with life-threatening illnesses such as cancer and heart disease and with drugs that can have serious side effects, getting it right the first time is critical. Rather than using a trial-and-error approach, personalized medicine allows health care professionals to analyze a patient's genetic profile and prescribe the best therapy and dose from the start.

Personalized medicine tries to answer questions like: Why do some people get cancer and others don't? Why is cancer more aggressive in this person compared to that one? Why does this drug work for you and not me? Why does someone need twice the standard dose to be effective? And why do others need only half of the standard dose?

The goal of personalized medicine is to get the best medical outcomes by choosing treatments that work well with a person's genomic profile, or with certain characteristics in the person's blood proteins or cell surface proteins. Genetic information is not used alone to make treatment decisions, but rather is used with other factors such as the patient's family history, medical history, clinical exam, and other non-genomic diagnostic tests.

The hope for the future is that through personalized medicine, doctors and patients will be able to make better-informed choices about treatment. Genetic information could lead them to decide which drug to use, whether to lower a dose, or whether closer monitoring of the patient for side effects is needed.

This type of research could make drugs for many diseases more effective, including heart disease, diabetes, depression, and asthma. Many believe the field of personalized medicine will continue to grow in the interest of patient safety. Through advances in this field physicians will gain a better ability to predict adverse reactions earlier in drug development. Moreover, decreasing adverse events and increasing successful therapy could lower the cost of health care. At present medicines are normally prescribed broadly because the patients likely to benefit from a particular drug cannot be separated from the patients who would not respond well. On the other hand, personalized medicine can lead to better economic efficiencies by allowing physi-

cians to make informed prescribing decisions based on a patient's inherited characteristics compared to the variability that exists in the population.

The potential of pharmacogenomics for drug companies lies in the discovery stage--being able to create new drugs based on genetic information. A better understanding of genetics and disease helps identify new targets for drugs. This could bring drugs to the market sooner. For example, if a pharmaceutical company finds in clinical trials that 90 percent of people do not respond to a drug, it can look at groups of nonresponders that have the same genetic characteristics and conduct further research to determine the potential of the new drug. Similarly, drugs that may be harmful to only a small number of patients might be able to be used if the pharmaceutical company can find out which genes are associated with the adverse responses. The drug could then possibly be approved for people with a low risk of adverse events.

Some pharmaceutical companies conducting human clinical trials routinely collect DNA from patients who provide informed consent for pharmacogenomic studies. This helps identify factors that may predict drug response. If only some people are experiencing adverse events and DNA is available for those patients this can provide helpful clues in determing how to lower the risk of side effects.

What Is the FDA's Role?

For now most pharmacogenomic data are of an exploratory or research nature and are not required under existing drug approval regulations. But from FDA's perspective, genomic data has the potential to help the agency understand how a drug works and for whom, which helps in assessing the risk-benefit ratio. Therefore, voluntary submissions are encouraged, and the FDA has indicated that the industry is also free to meet informally with the agency and talk freely without concern that the data will be used inappropriately for regulatory decision making. The FDA is also working on guidances on how to develop genomic tests and drugs together and on the quality of DNA analysis.

The FDA has also played a critical role in making the tools available to put the science into practice. In December 2004, the FDA cleared the AmpliChip Cytochrome P450 Genotyping Test. Doctors can order this test to gain information on whether the patient has mutations in a gene that's active in metabolizing many types of drugs, including antidepressants, antipsychotics, beta-blockers, and some chemotherapy drugs. In August 2005, the FDA cleared the Invader UGT1A1 Molecular Assay, which also detects variations in a gene that affects how certain drugs and drug metabolites are broken down and cleared by the body. Variations in the gene can influence the patient's ability to break down the major active metabolite of Campostar (irinotecan), a drug for colorectal cancer. The inability to break the metabolite down can lead to increased levels of it in the blood and a higher risk of side effects.

The FDA's role in personalized medicine should be one of bringing balance to an evolving science in a way that reaps the benefits, but also doesn't inhibit its growth. FDA's decision to establish a new position in the Office of FDA's Chief Scientist dedicated to coordinating and upgrading FDA's activities in this field is an encouraging sign that that the agency desires to engage industry in an ongoing dialogue on the significant impact pharmacogenomics can have on public health.

What Are the Challenges?

FDA's general lack of familiarity with pharmacogenomic data presents a major challenge. The science is so new and so constantly evolving that FDA must be given more resources to advance its capabilities to analyze and interpret genomic data that come into the agency and to communicate the relevant information in an understandable way in drug labels. The agency must also establish improved procedures to coordinate the efficient and timely review between FDA centers as drugs and genetic tests are co-developed.

Personalized medicine will require a new way of thinking about individualization. The hope for the future is that every patient will have a blood sample, and we can extract DNA and do a test to get a genetic profile. Then the profile along with clinical information can lead to improved care. But it is not likely going to be that simple. Some clinicians will be resistant to the routine use of pharmacogenomics in medical care, and incorporating pharmacogenomics into prescribing decisions will represent a major change for the health care community. Experts say that incorporating pharmacogenomics into everyday medicine will take time. It is currently happening mostly in academic medical institutions. Even though the Human Genome Project has sequenced a map of the body's genes, that does not mean all the targets in drug discovery have been identified. Many more studies will be needed to identify which gene variations are related to drug response and to prioritize them.

The Pharmacogenetics Research Network (PRN) of the National Institutes of Health is an example of the type collaboration that will advance personalized medicine. The PRN consists of scientists across the nation committed to studying the effects of genes in response to a variety of medicines, including antidepressants, chemotherapy, and drugs for asthma and heart disease. Even with the expansion of these type collaborations, it will likely take years before we know whether individualized doses based on genomics improves the long-term care of patients suffering from serious diseases like cancer and heart disease. Careful collection of clinical information and studies with large numbers of patients will be required.

Additionally, legal assurances will be needed so that insurance companies cannot use genetic information to discriminate against people who have a genetic risk for health problems. Then too, there may be reluctance on the part of doctors and researchers to pay for and conduct genetic tests until someone shows that these tests make a difference. Multiple genes can influence patients' response to the drug, as well as other drugs given at the same time and various environmental factors.

Perhaps the most critical challenge will be whether drug companies decide that there is enough financial benefit from therapies that help only small segments of people. Medical science will continue to make new discoveries about genes that are important in drug treatment, and we will see more diagnostic tests. The next important step for drug development based on personalized medicine will be proof of concept--proving the difference that personalized medicine makes.