Pharmacogenomics [1]

The field of pharmacogenomics (also called pharmacogenetics) studies how our inherited genes affect the way our bodies process and respond to drugs, which can make these drugs more or less effective and safe. A drug may act differently in one person than in another person taking the same drug for the same condition. For instance, some people may experience severe side effects from a drug, while others may not, even when given comparable doses of the drug.

Pharmacogenomics is a specific kind of genetic testing. In standard genetic testing, people are tested for the presence of entire genes, such as the breast cancer genes *BRCA1* and *BRCA2,* which can tell a person if they have a higher risk of breast and ovarian cancers. The results of these genetic tests may prompt some people to have additional cancer screenings, make lifestyle changes to avoid other risk factors, and choose preventive treatment. Pharmacogenetic testing, however, tests small variations within genes to help identify differences in a person's ability to activate and deactivate drugs, which helps the doctor choose the safest and most effective dose of a drug.

Because pharmacogenomics is a relatively new field, its applications in the treatment of people with cancer are currently limited. Today, most drugs are developed to be effective for the greatest number of people possible. This is often called a ?one-size-fits-all? approach. However, researchers are working to identify additional gene variations that affect a person's response to a drug, which would enable doctors to better match patients with treatment. This is often called ? personalized medicine [2].?

How pharmacogenomics works

Many drugs that treat cancer are not fully active in the form in which they are given; these are known as prodrugs. They need to be activated (?turned on?) by enzymes (proteins that speed up chemical reactions in the body) to help treat the disease they are targeting. Each person inherits variations in these enzymes that affect how fast or efficiently these drugs are converted to their active form. If a person metabolizes (breaks down) a drug slowly, then the body doesn't make enough of the active form of the drug, and the standard doses of treatment may not work as well. Drugs also need to be deactivated (?turned off?) after the cancer is treated to limit the drug's exposure to healthy tissues. If a person has less efficient or slower enzymes that deactivate drugs, then very high levels of the unconverted drug remain in the body for a long time, and this

can increase the drug's side effects.

Although pharmacogenomics holds promise in helping to predict the results of drug therapy, it is important to note that other variables may influence how a person reacts to a drug, including age, gender, disease severity, lifestyle habits (diet, smoking, alcohol consumption), other diseases that a person has, and other medications that a person is taking.

Benefits of pharmacogenetics

Pharmacogenomics offers important benefits:

Improving patient safety. It is estimated that severe drug reactions cause more than 2 million hospitalizations each year. Pharmacogenetic testing may help identify patients who are likely to experience dangerous reactions to drugs, enabling doctors to monitor them closely and possibly adjust the dosing of the drug or choose another treatment, thereby improving patient safety and potentially saving lives.

Improving health care costs and efficiency. The time and resources that doctors and patients spend finding appropriate medications and doses through ?trial and error? is likely to decrease as pharmacogenetic tests are developed.

Challenges to pharmacogenomics

Meanwhile, there are some challenges in the development and practical use of pharmacogenomics. Pharmacogenetic testing is expensive and not widely available, and insurance plans may not cover the costs of available tests, although researchers are working to develop more efficient and less expensive testing methods. In addition, although federal legislation has been passed that makes it illegal for companies and insurers to discriminate against people based on their genetic information, some ethical, legal, and privacy issues remain unresolved, which may affect the continued development of pharmacogenomics.

Pharmacogenetic testing in practice

Despite the current barriers to widespread use, pharmacogenomic testing is now used to help guide treatment for people with certain types of cancer:

Colorectal cancer. Irinotecan (Camptosar) is a type of chemotherapy commonly used for the treatment of colorectal cancer. In some people, genetic variations cause a shortage of the UGT1A1 enzyme, which is responsible for the body's metabolism (breakdown) of irinotecan. Higher levels of irinotecan remain in the body in people with lower levels of this enzyme, which may lead to severe and potentially life-threatening side effects, especially when the drug is given at higher dose levels. Doctors may use a pharmacogenomic test called the UGT1A1 test to see which patients have this genetic variation, allowing them to prescribe a lower dose of irinotecan for those patients. Often the lower dose is just as effective but less toxic in those individuals whose bodies are programmed to make the less efficient form of UGT1A1.

Acute lymphoblastic leukemia (ALL). Doctors also use pharmacogenomic testing for children with acute lymphoblastic leukemia. Genetic variations in an enzyme called thiopurine

methyltransferase (TPMT) are found in about 10% of children. TPMT is responsible for the metabolism of chemotherapy that is used to treat ALL. To avoid severe side effects, children with lower levels of TPMT are treated with lower doses of these drugs.

Other cancer types. Fluorouracil (5-FU, Adrucil) is a type of chemotherapy that is used to treat several types of cancer, including colorectal, breast, stomach, and pancreatic cancers. A genetic variation in some people causes them to have lower levels of the enzyme called dihydropyrimidine dehydrogenase (DPD), which helps the body metabolize fluorouracil. Doctors may use a pharmacogenomic test to detect this variation in patients, allowing them to lower the dose of the drug to avoid serious side effects in these patients.

Questions to ask the doctor

Talk with your doctor to find out more about how your genetic makeup may affect your body's response to a specific drug when discussing your treatment options. Consider asking the following questions:

- Would you explain my treatment options?
- Which treatment or combination of treatments do you recommend? Why?
- What are the possible side effects of this treatment?
- Is there a method to predict how my cancer will respond to this drug or whether I might experience severe side effects?
- What are my options if the cancer does not respond to the drug or if I suffer from severe side effects?
- Whom do I call for questions or problems?

More Information

Facts About Personalized Cancer Medicine [2]

Additional Resources

American Medical Association: Pharmacogenomics [3]

National Institute of General Medical Sciences: Frequently Asked Questions About Pharmacogenetics [4]

Links:
[1] http://www.cancer.net/navigating-cancer-care/how-cancer-treated/personalized-and-targeted-therapies/pharmacogenomics
[2] http://www.cancer.net/node/24522
[3] http://www.ama-assn.org/ama/pub/physician-resources/medical-science/genetics-molecular-medicine/current-topics/pharmacogenomics.page
[4] http://www.nigms.nih.gov/Initiatives/PGRN/Background/pgrn_faq.htm