LTFU

Long-Term Follow-Up Study

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In this issue

Biologic samples (body fluids, cells, and tissues) are among the most valuable contributions from LTFU Study participants. Survivors who develop a second cancer are asked to provide a small blood sample. And all survivors and siblings in the study are asked to send in a saliva sample for research purposes. The Oragene kits we use to collect saliva make it very easy for our participants to provide these samples. The kits also make it easy to process and store the DNA that we take from the samples. These biologic samples have already been used in many research studies. We will continue to use them in the future to increase our knowledge about the genetics of cancer and survivorship.

The tests we do for research don't have much potential for risk. The samples we work with in the LTFU Study are not linked to individuals and we don't provide individual test results. An example of the kind of research we do is the study reported on page 2 of this newsletter. Dr. Smita Bhatia and her team looked at biologic samples from hundreds of participants to discover links between certain genes and the chances of developing heart problems after being treated with common chemotherapy drugs.

Genetic tests in health care. Sometimes genetic tests are done for individual health care use. A test might be needed to confirm a diagnosis of a genetic disorder such as cystic fibrosis or sickle cell disease or for many other reasons. Unlike research tests, these tests reveal specific information about an individual. They may have portential risks as well as benefits. For example, a person might suffer painful emotions if they learn that they have a serious health problem or that their children are at risk. Some people might worry that test results could be used to deny them employment or insurance coverage.

If a genetic test is recommended for you, please share any concerns you have with your doctor. Most medical centers have genetic counselors available who can also answer your questions about testing. There are also legal protections in the U.S. that ban discrimination based on genetic information.

Research on DNA, genes, and drug interactions is a field that is developing very fast. Please see the story on page 3 about a St. Jude study that is bridging the gap between genetic testing done for research and for patient care.

Notes from Participants. Erika Smith, of Newbury Park, California, was diagnosed with acute lymphoblastic leukemia when she was 8 years old. She was treated at the City of Hope, in Duarte, California. Today, she is 22 years old and in excellent health. She attends California Lutheran University, studying to become an elementary school teacher. She loves volleyball and hopes to coach as well as teach when she graduates from college.

Erika is an enthusiastic participant in the LTFU Study. "Any time I get an opportunity to be in some research I take it," she says. She understands that research helped cure her and she wants to do her part to help others. "I'll do anything I can to help," she says. And when asked to provide a saliva sample for genetic research Erika said, "Of course!" Thank you, Erika. And thanks to everyone who has contributed a biologic sample!

Study Update

Gene Tests Offer Hope for Future Survivors

It's well known that some survivors of childhood cancer and similar serious illnesses develop health problems after treatment, often many years later. Sometimes these "late effects" of treatment are severe, disabling or even life-threatening. Dr. Smita Bhatia, an LTFU Study investigator at the City of Hope in Duarte, California, is leading a research study to identify which patients are likely to develop such late effects based on their treatment history and unique characteristics, including their genetic make-up. These individuals could then be followed more closely in order to prevent the problem from occurring or find it early when it may be successfully treated.

Are genetic variations involved in the risk of late effects? Dr. Bhatia's team wanted to find out if natural differences in certain genes among individuals are related to a person's chance of developing a particular late treatment effect. These natural differences are called variations. There are millions of gene variations in the human population. Variation is normal and most variations don't cause any problems.

As part of their study, Dr. Bhatia's team looked at a set of genes known as CBR's, which process anthracycline chemotherapy drugs. Anthracyclines, such as doxorubicin and daunorubicin, are used to treat many cancers because they are very effective. Unfortunately, they are known to be toxic to the heart.

Dr. Bhatia

The research team wanted to learn if differences in the CBR genes were linked to cardiomyopathy, weakening of the heart muscle that can lead to heart failure.

How did the team study this question? The research team compared two groups of survivors:

- *170 survivors with cardiomyopathy*
- *317 survivors without cardiomyopathy*

Participants in both groups provided either a blood or a saliva sample. DNA was removed from the samples and analyzed to detect known differences in the CBR genes.

The team found that . . .

- People with a particular gene variation (known as CBR3:GG) were more likely to develop problems with the heart muscle after exposure to low-to-moderate anthracycline doses, compared to those with other CBR gene variations.
- Those exposed to high doses of anthracyclines (more than 250 mg/m^2) were at risk of heart muscle problems no matter what gene variation they had.

The results of this study may be helpful in guiding treatment for individuals with cancer. Study participants can take satisfaction in knowing that their contributions may help other cancer patients. They have "paid it forward."

Future directions. Dr. Bhatia and her team are also investigating other combinations of gene variations, treatment exposures and late effects. In the future they plan to publish their findings on second cancers and strokes.

Additionally, they will soon be releasing results of a separate study about another gene that's related to the development of cardiomyopathy in survivors who received anthracyclines.

Smita Bhatia, MD, MPH, is Professor and Chair of the Division of Population Sciences at City of Hope, Duarte, California. The above results were published in the ***Journal of Clinical Oncology*** 2011: 30:1415-1421.

GINA: The Genetic Information Non-Discrimination Act

GINA was passed by the US Congress in 2008 to prohibit discrimination in insurance or employment based on genetic information. GINA put the following safeguards in place:

- Health insurance companies and group health plans may not request your “research only” gene test results.
- Health insurance companies and group health plans may not use your genetic information from your medical record when making decisions about your eligibility or premiums.
- Employers with 15 or more employees may not use your gene test results to decide to hire, promote, or fire you or when setting the terms of your employment.

Additional information about GINA is available at:

www.ginahelp.org

www.ginahelp.org/GINA_you.pdf

Pharmacogenetics and the Promise of "Personalized" Treatment

Pharmacogenetics is the study of how a person responds, based on their unique genetic make-up, to different medicines. Understanding individual differences in the genes involved in processing medications can help doctors decide the type and dose of drug to prescribe to be effective and prevent serious side effects.

Beginnings. Pharmacogenetics combines the fields of pharmacology and genetics. It got started in the 1950s when doctors noticed that people from some ethnic groups were more likely than others to have side effects from certain drugs. They also saw that the likelihood of getting a side effect from a certain drug seemed to be passed down in families. Starting from these insights, scientists have found links between many gene variations and medication effects.

Some of these links are well-known and routine testing for them is now standard practice. For example, a gene named TPMT is involved in processing chemotherapy drugs known as thiopurines that are used to treat leukemia.

About 9 out of 10 people have a version of this gene that allows their bodies to break down these drugs successfully. However, about 1 in 10 people may need lower doses of thiopurine medicines because they have versions of the TPMT gene that make it harder for them to break down these drugs. And about 1 in 400 people have a version of the gene that makes their bodies unable to process thiopurines at all. These people can develop very serious side effects (infection, anemia, and bleeding) if they receive usual doses of these medicines. So, doctors routinely test patients to find out what TPMT variation they have before making decisions about dosage of these drugs.

Today there are about 12 genes with many variations that are known to affect medication safety and effectiveness.

New techniques are enabling scientists to rapidly test increasing numbers of gene-medication interactions. However, there is a lag between the knowledge gained through research and the doctors' ability to use this knowledge to make decisions in treating patients. The use of genetic testing to guide therapy also causes concern for some parents and patients because of fears about the tests.

From the genetics lab to the clinic

At St. Jude Children's Research Hospital, Dr. Mary Relling is leading an effort to make genetic test results more readily available to doctors and patients. Dr. Relling and her colleagues are doing tests to identify variations in genes that are known to have a definite impact on medication safety or effectiveness. The results of tests that are strongly linked to drug effectiveness or side effects are placed in the medical record of patients who are enrolled in Dr. Relling's study. Doctors get computerized alerts about these test results so they can use them to guide their treatment decisions.

Dr. Mary Relling

An important feature of Dr. Relling's program is that parents of patients are involved throughout the process of deciding what test results will be included in the medical record. Parents of enrolled patients also have the option to receive test results directly once they are added to the medical record.

So far, just four genes have made their way into patients' medical records. (Results for the other tests are stored in a research database, and will be placed in the medical record as new evidence becomes available and as the research team creates tools to help doctors use the tests.) Dr. Relling's group at St. Jude together with researchers around the country are continuing to identify new gene variations that play a role in drug response. It's a big job: the human population carries an estimated 18 million gene variations, though only a few of these are likely to be important for processing medications! The hope is to provide a bridge between research and clinical care so that in the future each patient receives the best possible therapy, personalized for his or her unique genetic profile.

The LTFU Study Coordinating Center is located at St. Jude but Dr. Relling's research project is not being done as part of the Study. You can find additional information about her study at:

www.stjude.org/pg4kds

Mary V. Relling, PharmD, is Chair of Pharmaceutical Sciences at St. Jude Children's Research Hospital, Memphis Tennessee.

Incidental Findings

Genes that are useful for guiding medication decisions might also be linked to other health effects, such as overall risk of cancer or some other serious illness. Dr. Relling says that for the most part, "genes important for medication use don't seem to be linked to disease risk." If such a link were found, though, it would be considered an "incidental finding," that is, a condition that was accidentally discovered while looking for something else.

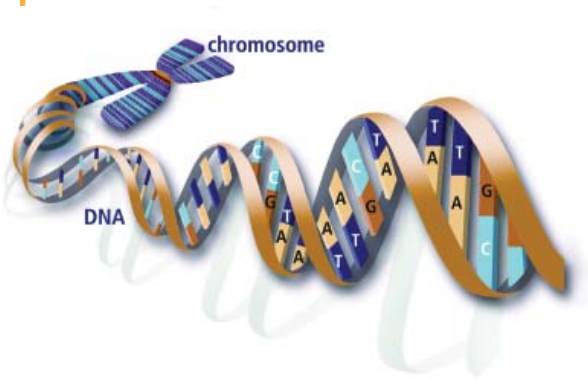
Incidental findings might not be revealed to a patient if there is no urgent need for them to take action. Adult participants in Dr. Relling's study are given the choice whether they want to be informed about incidental findings.

What is a Gene, Anyway?

DNA, genes, and genetics are common topics in the news and in many everyday conversations. Many of us, however, might not have a clear understanding of what these terms mean. Following are brief definitions of some of the most important genetic terms.

HEREDITY. Heredity is the passing of physical and mental traits from parents to children. We pass on our traits by means of an amazing molecule called DNA.

DNA. DNA is a chemical that is found in all the cells of the body. The DNA molecule is in the shape of a twisted ladder. Each rung of the ladder is made of a pair of chemical building blocks called bases, or nucleotides. There are only 4 bases in the DNA molecule. They are symbolized by the letters G, A, T, and C. The order of the base pairs is a code the body uses to make proteins .



GENES. Genes are segments of the DNA code that contain the instructions to make a particular protein. Genes are the basic units of heredity. We inherit our genes from our parents and pass them on to our children.

PROTEINS. Proteins are large biological molecules that are used in the body in many ways. Our muscles, bones, blood, and organs all contain proteins that our bodies make by using the instructions in our genes. Proteins help our lungs to breathe, our guts to digest food, and our hearts to beat.

CHROMOSOMES. In human beings the DNA is packed into 24 structures called chromosomes. Each chromosome contains many genes. Identifying genes on each chromosome is an active area of genetic research.

GENETIC VARIATION. Everyone has the same set of genes. But no peron's genes are exactly alike. Some genes come in thousands of different versions, or variations. These variations don't always produce traits that show up on the outside but they can have important health effects such as influencing the way we respond to certain medications.

SNPs. The most common type of genetic variation is known as a single nucleotide polymorphism or SNP (pronounced “snip”). Different versions of SNPs differ by just a single "letter" in their genetic code. SNPs are found normally throughout a person’s DNA. They are often found in the sections of DNA that are between genes, where they can act as biologic markers to help scientists locate genes that are linked to a disease. When SNPs are found inside a gene they may play a more direct role in causing disease by changing the gene’s function. Most SNPs have no effect on health. However, researchers have found SNPs that may help predict an individual’s response to certain drugs, susceptibility to environmental factors such as toxins, and risk of developing particular diseases.

MUTATIONS. Mutations are a kind of typographical error in a gene's DNA sequence. Mutations can cause a gene to send the wrong instructions, resulting in a protein that works incorrectly or that doesn't work at all. Not all mutations are harmful. Some have no effect, and others produce new versions of proteins that may be useful to the person who has the mutation. Mutations are rare, while SNPs are very common.

The information above is adapted from an online handbook called Help Me Understand Genetics, *a publication of the U.S. National Library of Medicine, available at:* **ghr.nlm.nih.gov/handbook**.

Addiontal information about genes and genetics can be found at **www.genome.gov/glossary.**