Pharmacogenomics

Using our Genetic Information to Personalize our Medical Needs

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Contents

Personalized Medicine using Pharmacogenomics

Author's Note

This curriculum unit was created with the purpose of teaching 9th grade biology honors students the importance of research in the area of pharmacogenomics. The focus in current research is the application of science through the utilization of the genetic information that we have obtained since the genome project was completed in 2001. The unit was prepared with the level of understanding that my students have about DNA technology and genetics. The intention is to start at the students' level and move up to a higher level of understanding with critical thinking. The activities included are strategically prepared to take the students from no understanding to a high cognitive and intellectual understanding of DNA technology, genomics and its application in pharmacogenetics.

As a science teacher, you must be able to understand the current advances in the area of personalized medicine to correctly transmit the information to the students with enthusiasm and an application to pharmacogenetics. That is why this curriculum provides all the background information for a greater understanding of the science and technology involved in pharmacogenetics.

The lab activities included in the lessons could easily be used to teach the applications of DNA sequencing and gene expression with the utilization of genomics for personalized medicine. As you will notice the lessons have a topic but they are part of the overall theme of personalized medicine use in pharmacogenetics. Due to the large amount of prescribed medicine today, researchers have found a need to personalize the dose concentration or type of prescribed medication to fit the individual's genetic uniqueness. The "fits all" is no longer applicable in medicine.

Introduction

Today, we live in a world full of health problems and disease. Most people argue that we have less disease than in the 1800's plus we live longer due to the advances in technology and science. The truth is that as the population increases along with technology we have a growing number of people suffering from obesity, cardiovascular disease and diabetes among other health issues. The Centers for Disease Control (CDC) stated that the leading cause of death in the United States is heart disease with 597,689 deaths in 2011. Diabetes claimed 69,071 lives in 2011. These previous diseases can be triggered by our all-time high obesity rate in the United States. According to the CDC, more than one-third of U.S. adults (35.7%) are obese.

Science has contributed to knowledge and new technology that has allowed our population longer lives while treating disease. The drugs we have been able to develop have been successful in treating disease while not providing a cure. "Nearly 70 percent of Americans are on at least one prescription drug, and more than half take two, Mayo Clinic and Olmsted Medical Center researchers say". Over the years, we have all witnessed an increase in pharmaceutical products that are currently prescribed to our general population without any personalization besides the routine questions of allergy or known complications to a particular drug. This trend of prescribed drugs will continue to increase without the necessary understanding of potential cure of benefits to the patient. If you do some research you will find that prescription drugs are actually killing people. According to the CDC deaths by overdose or misuse of prescribed medications has increased from 46, 523 in 1999 to 72, 080 in 2003, also a 55% increase.

The University of Florida and Shands Hospital launched a human genetics medicine program in 2011 to implement pharmacogenetics called the Personalized Medicine Program. The implementation of the program was on the gene CYP2C19 to determine the efficiency and metabolic susceptibility of the drug Clopidogrel. The objective of Personalized Medicine is to establish a genetic-guided care by genotyping patients on broad panel (256 SNPs) to model pre-emptive genomic data approach to develop informatics systems to handle large scale genomic data linked to EMR and to evaluate the impact on patient drug safety, outcomes and costs of care. Pharmacogenomics functions under the umbrella of personalized medicine. The ultimate goal is to use genetic information to individualize drug therapy to improve treatment outcomes, improve drug safety and potentially reduce costs of medical care.

This curriculum unit is a compilation of information gathered from the generosity of the Clinical and Translational Science Institute (CTSI) program at the University of Florida with the collaboration of the CPEP program. This revolutionary way of treating patients is part of the move of implementation Science in Personalized Medicine. Pharmacogenetics is a science that examines the inherited variations in genes that dictate drug response and explores the ways these variations can be used to predict whether a patient will have a good response to a drug, a bad response to a drug, or no response at all. Finally, this could be the answer to solve our problems of drug overdose, metabolic problem reduction and adverse allergic reactions.

Personalized Medicine using Pharmacogenetics (Curriculum Unit)

KEY QUESTION(S): How can the knowledge we obtain from sequencing our DNA help in the control of disease? What hypothesis can you come up with in applying the data obtained from sequencing our DNA? How can Pharmacogenetics help in personalized medicine? Explain the relationship between pharmacogenetics and microarray technology. How can we prevent the use of ineffective prescribed medications? What facts would you select to support personalized medicine using pharmacogenetics? What variants in a gene does this patient have? What is this patient's phenotype high/normal/low metabolizer? What dose of a drug, if any, or of another drug, will work best for a patient? What steps are needed to implement pharmacogenetics as part of personalized medicine?

***SCIENCE SUBJECT:** Biology. This is a unit on DNA and genetics leading to personalized medicine in pharmacogenetics.

***GRADE AND ABILITY LEVEL:** Ninth Grade, Honors

SCIENCE CONCEPTS: Genetic correlation to disease, DNA gene sequencing, pharmacogenetics, personalized medicine, gene expression, diagnosing disease and microarray lab applications.

OVERALL TIME ESTIMATE: The unit will take six school periods of 50 minutes each.

LEARNING STYLES: The students will learn using visual, auditory, and kinesthetic.

LESSON SUMMARIES:

Lesson # 1: This lesson is on the introduction and understanding of Pharmacogenetics by using a **Jigsaw Model** to break the students in groups and share information learned from a scientific journal. On the second day, the lesson will be based on a **Pharmacogenetics Virtual Lab**. The lab is a series of activities provided by the University of Utah.

Lesson # 2: The lesson is on **Gene Expression and Microarray Virtual Lab**. Using resources from the University of Utah. During the second day of the lesson, students will conduct a **DNA Microarray Simulation Wet Lab** provided by CPET that will afford students the opportunity of a hands on lab and critical thinking.

Lesson # 3: The lesson is based on six different **case studies** related to pharmacogenetics, diagnosis and treatment of disease.

LESSON SEQUENCING GUIDE:

All lessons are based on a 50 minute class period.

	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5
WEEK # 1	LESSON 1 Pharmacogenetics Article Jigsaw	LESSON 1 Pharmacogenetics Article Jigsaw Group Presentations	LESSON 1 Pharmacogenetics Virtual Lab	LESSON 2 Gene Expression And Microarray Virtual Lab	LESSON 2 DNA Microarray Simulation Wet Lab
WEEK # 2	LESSON 3 Pharmacogenetics Case Studies				

VOCABULARY: The vocabulary of the unit will be all related to DNA, Protein Synthesis, Cell Structure, Laboratory Techniques, Genetics and Pharmacogenetics. Each individual lesson will have a list of all the vocabulary it will cover.

Amino Acids: An organic molecule containing an amino group (-NH2), a carboxyl (-COOH) group, and a variable side chain (R group) that distinguishes the amino acid. Proteins are synthesized from amino acids.

Amplification: An increase in the number of copies of a gene in a cell, resulting in an elevation in the level of the RNA or protein encoded for by the gene and a corresponding amplification of the phenotype that the gene confers on the cell. Drug resistance in cancer cells is linked to amplification of the gene that prevents absorption of the chemotherapeutical agent by the cell.

Anticodon: a triplet of nucleotide bases in transfer RNA that identifies the amino acid carried and binds to a complementary codon in messenger RNA during protein synthesis at a ribosome.

Asthma: A respiratory condition marked by spasms in the bronchi of the lungs, causing difficulty in breathing. It usually results from an allergic reaction or other forms of hypersensitivity.

Cardiovascular disease: refers to any disease that affects the cardiovascular system, principally cardiac disease, vascular diseases of the brain and kidney, and peripheral arterial disease.

Chemotherapy: is a type of cancer treatment that uses drugs to destroy cancer cells.

Codon: a triplet sequence of nucleotides that directs the tRNA's "anticodon" to acquire select amino acids for protein production.

Denaturation: A process in which the structure of nucleic acid is disrupted, such as the dissociation of a double stranded DNA into a single stranded state by heating.

Diabetes: often referred to by doctors as **diabetes mellitus**, describes a group of metabolic diseases in which the person has high blood glucose (blood sugar), either because insulin production is inadequate, or because the body's cells do not respond properly to insulin, or both.

DNA Microarray: A small solid support, usually a membrane or glass slide, on which sequences of DNA are fixed in an orderly arrangement. DNA microarrays are used for rapid surveys of the expression of many genes simultaneously, as the sequences contained on a single microarray can number in the thousands. Also called *DNA chip*.

Enzymes: Any of numerous proteins produced in living cells that accelerate or catalyze chemical reactions.

Gel – electrophoresis: method used to separate DNA fragments by size. It is a common diagnostic procedure used in molecular biological labs.

Gene: Chemical factor that determines traits.

Gene Expression: is the process by which information from a gene is used in the synthesis of a functional gene product. These products are often proteins, but in non-protein coding genes such as rRNA genes or tRNA genes, the product is a functional RNA.

Genetics: is the study of heredity. Heredity is a biological process where a parent passes certain genes onto their children or offspring.

Genomics: is the study of the genomes of organisms. The field includes intensive efforts to determine the entire DNA sequence of organisms and fine-scale genetic mapping efforts.

Haplotype: is a group of genes, which is inherited together by an organism from a single parent.

Helicase: The enzyme responsible for "unzipping" DNA during replication and RNA formation.

Leukemia: is cancer of the blood cells. It starts in the bone marrow, the soft tissue inside most bones. Bone marrow is where blood cells are made.

mRNA: An abbreviated expression for Messenger Ribonucleic Acid. This genetic sequence is responsible for "coding" a gene within the DNA for the instruction of constructing proteins within the cell's cytoplasm at a ribosome.

Meningitis: is a serious inflammation of the **meninges**, the thin, membranous covering of the brain and the spinal cord.

Microcentrifuge: An apparatus consisting essentially of a compartment spun about a central axis to separate contained materials of different densities, or to separate colloidal particles suspended in a liquid.

Mutation: is a change of the nucleotide sequence of the genome of an organism, virus, or extra chromosomal genetic element.

NCBI: National **C**enter for **B**iotechnology **I**nformation – advances science and health by providing genomic information. http://www.ncbi.nlm.nih.gov/

Nucleotide: a phosphoric ester of a nucleoside.

Obesity: is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life.

PCR: is polymerase chain reaction: a technique for rapidly producing many copies of a fragment of DNA for diagnostic or research purposes.

Personalized Medicine: an approach to the practice of medicine that uses information about a patient's unique genetic makeup and environment to customize the patient's medical care to fit his or her individual requirements.

Pharmacogenetics: is a science that examines the inherited variations in genes that dictate drug response and explores the ways these variations can be used to predict whether a patient will have a good response to a drug, a bad response to a drug, or no response at all.

Pharmacogenomics: Uses large groups of patients to evaluate how candidate drugs interact with a range of genes and their protein products.

Pharmacokinetics: the action of drugs in the body over a period of time, including the processes of absorption, distribution, localization in tissues, biotransformation, and excretion.

Polymerase: The enzyme responsible for DNA replication and RNA formations.

Polymorphism: is a DNA sequence variation that is common in the population. In this case no single allele is regarded as the standard sequence.

Polypeptide: are chains of amino acids. Proteins are made up of one or more **polypeptide** molecules.

Proteins: A linear polymer built from approximately 20 different amino acid types. The type and sequence of these amino acids are specified by the DNA, this sequence also determines shape and function of the protein.

Protein Synthesis: is accomplished through a process called translation. In translation, RNA and ribosomes work together to produce proteins

SNP: A Single Nucleotide Polymorphism. They are single-nucleotide substitutions of one base for another.

Substrate: The molecule that the enzyme acts upon.

tRNA: An abbreviated expression for Transfer Ribonucleic Acid. This genetic sequence is responsible for the "gathering" of amino acids within the cell's cytoplasm.

Transcription: The process of RNA production within the nucleus using DNA as a "template" to copy a specific location within the DNA (typically a gene). The DNA is "transcribed" from the 5'to the 3' using nucleotides

Translation: A "decoding" of the mRNA (created in transcription) at a ribosome within the extranuclear space. The process produces primary structure proteins that can be later modified to perform an assortment of structural/physiological functions.

NEXT GENERATION SUNSHINE STATE STANDARDS (NGSSS)

(http://www.nextgenscience.org/next-generation-science-standards)

BENCHMARK			
	1	2	3
SC.912.L.14.6 Explain the significance of genetic factors, environmental factors, and pathogenic agents to health from the perspectives of both individual and public health.	X	X	X
SC.912.L.15.15 Describe how mutation and genetic recombination increase genetic variation.	X	X	X
SC.912.L.16.2 Discuss observed inheritance patterns caused by various modes of inheritance, including dominant, recessive, codominant, sex-linked, polygenic, and multiple alleles.	X	X	X
SC.912.L.16.3 Describe the basic process of DNA replication and how it relates to the transmission and conservation of the genetic information.		X	X
SC.912.L.16.4 Explain how mutations in the DNA sequence may or may not result in phenotypic change. Explain how mutations in gametes may result in phenotypic changes in offspring.	X	X	X
SC.912.L.16.5 Explain the basic processes of transcription and translation, and how they result in the expression of genes.		X	X
SC.912.L.16.6 Discuss the mechanisms for regulation of gene expression in prokaryotes and eukaryotes at transcription and translation level.	X	X	X
SC.912.L.16.8 Explain the relationship between mutation, cell cycle, and uncontrolled cell growth potentially resulting in cancer.		X	X
SC.912.L.16.9 Explain how and why the genetic code is universal and is common to almost all organisms.	X	X	X
SC.912.L.16.10 Evaluate the impact of biotechnology on the individual, society and the environment, including medical and ethical issues.		X	X
SC.912.L.16.11 Discuss the technologies associated with forensic medicine and DNA identification, including restriction fragment length polymorphism (RFLP) analysis.	X	X	X
SC.912.L.16.12 Describe how basic DNA technology (restriction digestion by endonucleases, gel electrophoresis, polymerase chain reaction, ligation, and transformation) is used to construct recombinant DNA molecules (DNA cloning).	X	X	X
SC.912.L.18.1 Describe the basic molecular structures and primary functions of the four major categories of biological macromolecules.	X	X	X
SC.912.L.18.4 Describe the structures of proteins and amino acids. Explain the functions of proteins in living organisms. Identify some reactions that amino acids undergo. Relate the structure and function of enzymes.	X	X	X
SC.912.L.18.11 Explain the role of enzymes as catalysts that lower the activation energy of biochemical reactions. Identify factors, such as pH and temperature, and their effect on enzyme activity.	X	X	X
SC.912.N.1.1 Define a problem based on a specific body of knowledge, for example: biology, chemistry, physics, and earth/space science, and do the following: 1. pose questions about the natural world, 2. conduct systematic observations, 3. examine books and other sources of information to see what is already known, 4. review what is known in light of empirical evidence, 5. plan investigations, 6. use tools to gather, analyze, and interpret data, 7. pose answers, explanations, or descriptions of events, 8. generate explanations that explicate or describe natural phenomena (inferences), 9. use appropriate evidence and reasoning to justify these explanations to others, 10. communicate results of scientific investigations, and	X	X	X

11. evaluate the merits of the explanations produced by others.			
SC.912.N.1.3 Recognize that the strength or usefulness of a scientific claim is evaluated through scientific argumentation, which depends on critical and logical thinking, and the active consideration of alternative scientific explanations to explain the data presented.	**X**	**X**	**X**
SC.912.N.1.4 Identify sources of information and assess their reliability according to the strict standards of scientific investigation.	**X**	**X**	**X**
SC.912.N.1.5 Describe and provide examples of how similar investigations conducted in many parts of the world result in the same outcome.	**X**	**X**	**X**
SC.912.N.1.6 Describe how scientific inferences are drawn from scientific observations and provide examples from the content being studied.	**X**	**X**	**X**
SC.912.N.1.7 Recognize the role of creativity in constructing scientific questions, methods and explanations.	**X**	**X**	**X**
SC.912.N.2.4 Explain that scientific knowledge is both durable and robust and open to change. Scientific knowledge can change because it is often examined and re-examined by new investigations and scientific argumentation. Because of these frequent examinations, scientific knowledge becomes stronger, leading to its durability.	**X**	**X**	**X**
SC.912.N.4.1 Explain how scientific knowledge and reasoning provide an empirically-based perspective to inform society's decision making.	**X**	**X**	**X**
SC.912.N.4.2 Weigh the merits of alternative strategies for solving a specific societal problem by comparing a number of different costs and benefits, such as human, economic, and environmental.	**X**	**X**	**X**
HE.912.C.1.3 Evaluate how environment and personal health are interrelated.	**X**	**X**	**X**
HE.912.C.1.5 Analyze strategies for prevention, detection, and treatment of communicable and chronic diseases.	**X**	**X**	**X**
HE.912.C.1.7 Analyze how heredity and family history can impact personal health.	**X**	**X**	**X**

COMMON CORE STANDARDS (http://www.corestandards.org/)

COMMON CORE STANDARDS			
	1	**2**	**3**
LACC.910.RST.1.1 Cite specific textual evidence to support analysis of science and technical texts, attending to the precise details of explanations or descriptions.	**X**		
LACC.910.RST.1.2 Determine the central ideas or conclusions of a text; trace the text's explanation or depiction of a complex process, phenomenon, or concept; provide an accurate summary of the text.	**X**		
LACC.910.RST.1.3 Follow precisely a complex multistep procedure when carrying out experiments, taking measurements, or performing technical tasks attending to special cases or exceptions defined in the text.	**X**	**X**	**X**
LACC.910.RST.2.4 Determine the meaning of symbols, key terms, and other domain-specific words and phrases as they are used in a specific scientific or technical context relevant to grades 9–10 texts and topics.	**X**	**X**	**X**
LACC.910.RST.3.8 Assess the extent to which the reasoning and evidence in a text support the author's claim or a recommendation for solving a scientific or technical problem.	**X**	**X**	**X**
LACC.910.WHST.1.1e Provide a concluding statement or section that follows from or supports the argument presented.	**X**	**X**	**X**
LACC.910.WHST.2.6 Use technology, including the Internet, to produce, publish, and update individual or shared writing products, taking advantage of technology's capacity to link to other information and to display information flexibly and dynamically.	**X**	**X**	

LACC.910.WHST.3.7 Conduct short as well as more sustained research projects to answer a question (including a self-generated question) or solve a problem; narrow or broaden the inquiry when appropriate; synthesize multiple sources on the subject, demonstrating understanding of the subject under investigation.	**X**		
LACC.910.WHST.3.9 Draw evidence from informational texts to support analysis, reflection, and research.	**X**	**X**	**X**
LACC.910.SL.1.a Come to discussions prepared, having read and researched material under study; explicitly draw on that preparation by referring to evidence from texts and other research on the topic or issue to stimulate a thoughtful, well-reasoned exchange of ideas.	**X**		
LACC.910.SL.1.1b Work with peers to set rules for collegial discussions and decision-making (e.g., informal consensus, taking votes on key issues, presentation of alternate views), clear goals and deadlines, and individual roles as needed.	**X**	**X**	**X**
LACC.910.SL.2.4 Present information, findings, and supporting evidence clearly, concisely, and logically such that listeners can follow the line of reasoning and the organization, development, substance, and style are appropriate to purpose, audience, and task.	**X**	**X**	**X**
LACC.910.SL.2.5 Make strategic use of digital media (e.g., textual, graphical, audio, visual, and interactive elements) in presentations to enhance understanding of findings, reasoning, and evidence and to add interest.	**X**	**X**	
MACC.912.N-Q.1.1 Use units as a way to understand problems and to guide the solution of multi-step problems; choose and interpret units consistently in formulas; choose and interpret the scale and the origin in graphs and data displays.	**X**	**X**	

LITERATURE:

See attached documents for more reference and resources used to modify the unit

RESOURCES/REFERENCES:

CDC – Leading Cause of Death in the U.S.
http://www.cdc.gov/nchs/fastats/lcod.htm

CDC - Obesity
http://www.cdc.gov/obesity/data/adult.html

Pharmacogenetics Article
http://www.medscape.com/viewarticle/590270_print

Prescribed Drugs
http://www.cdc.gov/obesity/data/adult.html
http://www.mayoclinic.org/news2013-rst/7543.html
http://www.ncbi.nlm.nih.gov/pubmed/17536879

Pharmacogenetics
https://ufhealth.org/news/2011/personalized-medicine
http://ptr.pharmacy.ufl.edu/training/seminars/
http://www.phgfoundation.org/tutorials/pharmacogenomics/

Microarray Virtual Lab
http://learn.genetics.utah.edu/content/labs/microarray/
http://www.carolina.com/teacher-resources/Interactive/dna-microarray-simulation/tr10710.tr

Gene Expression
http://learn.genetics.utah.edu/content/labs/microarray/expression/

Resources from the University of Utah
http://teach.genetics.utah.edu/content/
http://learn.genetics.utah.edu/content/health/pharma/

Case Study using Pharmacogenetics
http://sciencecases.lib.buffalo.edu/cs/collection/detail.asp?case_id=247&id=247
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2656342/

Pharmacogenomics - Lesson # 1

TITLE: The understanding of our genetic code and its relationship to drug efficacy

KEY QUESTION(S): Explain the discovery of pharmacogenetics and its application to patient care. What hypothesis can you come up with in the application of genetic data obtained from sequencing our DNA? How can pharmacogenetics help in personalized medicine?

SCIENCE CONCEPTS: The application of the understanding of the human genetic code and the role of pharmacogenetics in personalized medicine. In simple terms Pharmacogenomics; drug response; genetic variation; disease risk; drug development.

OVERALL TIME ESTIMATE: This lesson requires three class periods of 50 minutes each.

LEARNING STYLES: Visual, auditory, and kinesthetic.

VOCABULARY:

Chemotherapy: is a type of cancer treatment that uses drugs to destroy cancer cells.

Enzymes: Any of numerous proteins produced in living cells that accelerate or catalyze chemical reactions.

Gene: Chemical factor that determines traits.

Gene Expression: is the process by which information from a gene is used in the synthesis of a functional gene product. These products are often proteins, but in non-protein coding genes such as rRNA genes or tRNA genes, the product is a functional RNA.

Genetics: is the study of heredity. Heredity is a biological process where a parent passes certain genes onto their children or offspring.

Genomics: is the study of the genomes of organisms. The field includes intensive efforts to determine the entire DNA sequence of organisms and fine-scale genetic mapping efforts.

Haplotype: is a group of genes, which is inherited together by an organism from a single parent.

Helicase: The enzyme responsible for "unzipping" DNA during replication and RNA formation.

Leukemia: is cancer of the blood cells. It starts in the bone marrow, the soft tissue inside most bones. Bone marrow is where blood cells are made.

mRNA: An abbreviated expression for Messenger Ribonucleic Acid. This genetic sequence is responsible for "coding" a gene within the DNA for the instruction of constructing proteins within the cell's cytoplasm at a ribosome.

Mutation: is a change of the nucleotide sequence of the genome of an organism, virus, or extra chromosomal genetic element.

NCBI: National **C**enter for **B**iotechnology **I**nformation – advances science and health by providing genomic information. http://www.ncbi.nlm.nih.gov/

Nucleotide: a phosphoric ester of a nucleoside.

PCR: is polymerase chain reaction: a technique for rapidly producing many copies of a fragment of DNA for diagnostic or research purposes.

Personalized Medicine: an approach to the practice of medicine that uses information about a patient's unique genetic makeup and environment to customize the patient's medical care to fit his or her individual requirements.

Pharmacogenetics: is a science that examines the inherited variations in genes that dictate drug response and explores the ways these variations can be used to predict whether a patient will have a good response to a drug, a bad response to a drug, or no response at all.

Pharmacogenomics: Uses large groups of patients to evaluate how candidate drugs interact with a range of genes and their protein products.

Pharmacokinetics: the action of drugs in the body over a period of time, including the processes of absorption, distribution, localization in tissues, biotransformation, and excretion.

Polymorphism: is a DNA sequence variation that is common in the population. In this case no single allele is regarded as the standard sequence.

Polypeptide: are chains of amino acids. Proteins are made up of one or more **polypeptide** molecules.

Proteins: A linear polymer built from approximately 20 different amino acid types. The type and sequence of these amino acids are specified by the DNA, this sequence also determines shape and function of the protein.

Protein Synthesis: is accomplished through a process called translation. In translation, RNA and ribosomes work together to produce proteins.

SNP: A Single Nucleotide Polymorphism. They are single-nucleotide substitutions of one base for another.

Substrate: The molecule that the enzyme acts upon.

tRNA: An abbreviated expression for Transfer Ribonucleic Acid. This genetic sequence is responsible for the "gathering" of amino acids within the cell's cytoplasm.

Transcription: The process of RNA production within the nucleus using DNA as a "template" to copy a specific location within the DNA (typically a gene). The DNA is "transcribed" from the 5 to the 3' using nucleotides.

Translation: A "decoding" of the mRNA (created in transcription) at a ribosome within the extra nuclear space. The process produces primary structure proteins that can be later modified to perform an assortment of structural/physiological functions.

LESSON SUMMARY:

On the first day, the lesson is on Pharmacogenetics by using a **Jigsaw Model** to break the students in groups and share information learned from a scientific journal. The class of twenty five students will be divided into groups of eight. Each group will have a part of the article to read, answer two basic questions, formulate their own question, and write their group answers on a poster paper and on the second day students will present their findings to the class.

On the third day, the lesson will be based on a **Pharmacogenetics Virtual Lab**. The lab is a series of activities provided by the University of Utah's Genetic Science Learning Center. Students will be divided in pairs to work on a computer to go through the three virtual activities on understanding pharmacogenomics. The three activities were modified from the University of Utah. The labs are the following: Your doctor's new genetic tools, Making SNPs make sense and Pus-Poppin' Frogs.

STUDENT LEARNING OBJECTIVES WITH NEXT GENERATION SUNSHINE STATE STANDARDS:

1. Students will be able to practice reading, interpreting scientific information and discover the role of pharmacogenomics.
2. Students will be able to learn how information about genetic variation may be used to predict differences in drug response and assess disease risk.

NEXT GENERATION SUNSHINE STATE STANDARDS (NGSSS)
(http://www.nextgenscience.org/next-generation-science-standards)

SC.912.L - 14.6, 15.15, 16.2, 16.4, 16.6, 16.9, 16.11, 16.12, 18.1, 18.4, 18.11
SC.912.N - 1.1, 1.3, 1.4, 1.5, 1.6, 1.7, 2.4
HE.912.C – 1.3, 1.5, 1.7

COMMON CORE STANDARDS (http://www.corestandards.org/)

LACC.910.RST – 1.1, 1.2, 1.3, 2.4, 3.8
LACC.901.WHST – 1.1e, 2.6, 3.7, 3.9
LACC.910.SL – 1.a, 1.1b, 2.4, 2.5
MACC.912.N.Q.1.1

MATERIALS and ESSENTIAL:

- 25 copies of the Pre-test/post-test multiple choice questions with answer sheets
- 15 Laptops
- 2 essay questions as an exit slip after the jigsaw activity
- 25 copies of the Pharmacogenetics Article (8 Groups of 3 students)
- 25 Pharmacogenetics Web Quest Virtual Lab write-ups (Complete one per pair)

BACKGROUND INFORMATION:

Personalized medicine Use of information about an individual, including their family history, diseases, environmental factors, and genetic information to personalize or individualize care.

- Disease risk prediction
- Disease prevention strategies
- Defining disease phenotype
- Treatment decisions

Pharmacogenomics functions under the umbrella of personalized medicine. The ultimate goal is to use genetic information to individualize drug therapy to:

- Improve treatment outcomes
- Improve safety
- Potentially reduce costs of medical care

The objective of Personalized Medicine is to establish a genetic-guided care by genotyping patients on broad panels (256 SNPs) to model pre-emptive genomic data approaches to develop informatics systems to handle large scale genomic data linked to EMR and to evaluate the impact on patient drug safety, outcomes and costs of care.

ADVANCE PREPARATION:

The teacher needs to read all the provided resources on pharmacogenetics and understand the scientific journal used in the jigsaw activity. Copies of the journal and lab write-ups need to be obtained class. Depending on class size the teacher may need extra copies of the write-ups.

PROCEDURE AND DISCUSSION QUESTIONS WITH TIME ESTIMATES:

Day #: 1 – Scientific Journal Jigsaw Analysis

1. (10 min) The teacher should start by providing each student a pre-test on Pharmacogenomics.

2. (1 min) Without explaining the topic the teacher will hand out to each corresponding group their portion of the journal article **Pharmacogenetics: From Discovery to Patient Care** by Jaekyu Shin, Steven R. Kayser, Taimour Y. Langaee.

3. (1 min) Students will be divided in eight groups of three.

4. (1 min) Explain that each group will have a different section of the article to read, comprehend, answer two questions, formulate one question and present their findings to the class (jigsaw model).

5. (15 min) Students will read with their group and answer the following: **What is the main purpose of this section of the article? How can we apply what we have learned to science?** Each group should also formulate one question of their own about the portion of their article.

6. Each group should be provided a large poster paper to write their answers and hang on the wall in the order of the group assignment. This will allow for class discussion and a greater understanding of the big picture of the role of Pharmacogenomics in Personalized Medicine. Hang each group's completed poster paper on the wall for presentations the next day.

Day #: 2 – Scientific Journal Jigsaw Group Presentations

1. The teacher will start the class by having the students sit back in their groups.

2. (5 min) Students will be allowed five minutes to prepare for their group presentations. With no teacher explanation the students should present in the order of the article 1-8.

3. (30 min) Allow each group at least three to four minutes to present.

4. (5 min) Once all groups have presented the teacher should wrap up the discussion and administer a formative assessment in form of an exit slip.

5. (5 min) The following two **exit questions** should be answered by each student in form of an essay on a small paper to turn in to the teacher. Using your projector display the following: **What hypothesis can you come up with in the application of genetic data obtained from sequencing our DNA? How can Pharmacogenetics help in personalized medicine?**

Day #: 3 – Pharmacogenomics Virtual Lab

1. Before students show up to class distribute and make sure all computers are online.

2. (2 min) Assign two students per computer with a handout each. The handout has two pre-lab questions.

3. (5 min) Have students answer the pre-lab questions before they log in to the computers.

4. (5 min) Once they have answered the two questions, they can log on to http://learn.genetics.utah.edu/content/pharma

5. (15 min) Instruct the students to use this module to answer the questions on the *What is Pharmacogenomics?* handout. They should answer one handout per pair. All three virtual labs should be completed by the end of class and turned in to the teacher.

6. (15 min) At the end of the fifteen minutes administer the pre/post test given on day one of the lesson to grade, access progress and provide remediation.

ASSESSMENT SUGGESTIONS:

1. Students will practice reading, interpreting scientific information and discover the role of pharmacogenomics.
    - **This objective will be assessed by using class presentations, essay exit slip questions and the lesson multiple choice post-test.**
2. Students will learn how information about genetic variation may be used to predict differences in drug response and assess disease risk.
    - **This objective will be assessed by using pre-lab questions, the lab write-up questions package and the lesson multiple choice post-test.**

EXTENSIONS:

The teacher can extend an invitation to have Betsy Shenkman, Ph.D. Director, Institute for Child Health Policy at the UF College of Medicine present during our school teach-in week. Dr. Shenkman has offered her help in providing her services as a school wide speaker on the subject of Personalized Medicine using Pharmacogenomics.

ACTIVITIES:

Drug Development Today and Tomorrow
http://learn.genetics.utah.edu/content/pharma/development/

Challenges and Issues in Personalized Medicine
http://learn.genetics.utah.edu/content/pharma/

LITERATURE:

Personalized Medicine
http://www.ctsi.ufl.edu/about/ctsi-programs/personalized-medicine/

https://ufhealth.org/personalized-medicine

One size does not fit all: The promise of Pharmacogenomics
http://www.ncbi.nlm.nih.gov/About/primer/pharm.html

RESOURCES/REFERENCES:

Pharmacogenetics Article for the Jigsaw
http://www.medscape.com/viewarticle/590270_print
NCBI
http://www.ncbi.nlm.nih.gov/About/primer/pharm.html

University of Utah – Exploring Pharmacogenomics Web Quest
http://gslc.genetics.utah.edu/units/pharma

Modified Teacher Resources from the University of Utah
http://learn.genetics.utah.edu/

Pharmacogenomics Test (Pre/Post Test)

1. The first Pharmacogenetics discovery was:
a. last year by a scientist investigating the human body.
b. more than five decades ago in patients deficient in an enzyme to metabolize a drug for treatment.
c. years ago by a student of Harvard University.
d. two years ago by accident investigating the digestion of pigs.

2. The study of the time course of drug absorption, distribution, metabolism, and excretion is called:
a. pharmacodynamics.
b. drug concentration.
c. pharmacokinetics.
d. kinetic homogeneity.

3. The application of pharmacokinetic principles to the safe and effective therapeutic management of drugs in an individual patient is known as:
a. pharmacodynamics.
b. clinical pharmacokinetics.

4. Since we cannot practically measure drug concentration in specific tissues, we measure it in the plasma and assume that this concentration is the same as that in tissue.
a. False
b. True

5. *Pharmacodynamics* refers to the relationship of drug:
a. dose to drug concentration in plasma.
b. dose to drug concentration at the receptor site.
c. concentrations to drug effect.
d. dose to drug effect.

6. What is the difference between pharmacogenomics and pharmacogenetics?
a. pharmacogenetics focuses on the effect of a single gene on drug response and pharmacogenomics deals with the effects of multiple genes on drug response
b. They are both the same, they deal with the metabolism of the body
c. Pharmacogenetics focuses on the effects of multiple genes on drug response and pharmacogenomics deals with a single gene.
d. none of the above

7. What made the understanding of pharmacogenomics possible?
a. the discovery of genetics
b. the sequencing of the human genome in 2001
c. new drugs for treatment
d. mutations in the human genome

8. Which gene is involved in the effectiveness of the drug Clopidogrel?
a. CYP2C06 b. CYP2C19
c. CYP2C9 d. CYP1B1

9. Currently the University of Florida is the only one in the State using the application of Pharmacogenomics. For which treatment is personalized medicine currently used at UF clinics?
a. Foot bleeding b. Kidney failure
c. Cardiovascular disease d. Anemia

10. Provide a good reason for the use of Personalized Medicine through Pharmacogenomics.

a. To create new and improved drugs
b. To save health insurance money
c. To eliminate medical drugs completely
d. To improve treatment outcome and disease prevention

Answer Key:

1. **B**
2. **C**
3. **B**
4. **A**
5. **C**
6. **A**
7. **B**
8. **B**
9. **C**
10. **D**

Pharmacogenetics: From Discovery to Patient Care

Jaekyu Shin, Steven R. Kayser, Taimour Y. Langaee
Am J Health Syst Pharm. 2009;66(7):625-637.

Pharmacogenetics: From Discovery to Patient Care Jigsaw Activity

Students will be divided in eight groups of three to read a portion of the article. The groups will be given fifteen minutes to read and discuss to answer two basic questions. Each group will come up with the following answers**: What is the main purpose of this section of the article? How can we apply what we have learned to science? Come up with one questions you want answers about the literature.** At the end of the given time, students will have written down their answers on a poster paper and will send a student up from each group to present their answer in the order of the article.

Group Assignments

Group #: 1

Introduction

The first pharmacogenetic discovery was made more than five decades ago in patients deficient in glucose-6-phosphate dehydrogenase who developed hemolysis after treatment with primaquine.[1] The term pharmacogenetics was coined by Vogel in 1959.[2] Although pharmacogenetics focuses on the effect of a single gene on drug response and pharmacogenomics deals with the effects of multiple genes on drug response, both terms are used interchangeably in this review to simplify the discussion (see the appendix for a glossary and resources).[3-6] Despite almost 50 years of history, most of the progress in pharmacogenetics has been made in recent years, and the number of publications associated with pharmacogenetics has dramatically increased. The completion of the Human Genome Project[7] and the International HapMap Project,[8] along with the rapid development of advanced genetic technologies, has greatly affected pharmacogenetic discoveries and may increase the number of publications containing new pharmacogenetic discoveries.

Currently, there are over 120 drugs whose labeling includes pharmacogenetic discoveries,[9] and that number is likely to increase in the future. These drugs encompass a variety of therapeutic areas including infectious diseases (voriconazole), cardiology and hematology (warfarin), neurology (carbamazepine), psychiatry (atomoxetine), and oncology (azathioprine, irinotecan, trastuzumab, and cetuximab). In a white paper, the Food and Drug Administration (FDA) recognized pharmacogenomics as an opportunity to identify new biomarkers that may expedite the drug development process.[10] The agency also published a guidance document to facilitate the use of pharmacogenomic discoveries in drug development and has taken a leading role in evaluating a genomic marker as a new biomarker by forming various consortiums including the government, industry, and academia.[11] Thus, many future pharmacogenetic discoveries are expected to be used in both drug development and clinical practice.

Compared with the rapid progress being made in the field of pharmacogenetics, knowledge of and experience with pharmacogenetics among pharmacists are rather limited.[12-14] Most practicing pharmacists have not received any formal education and training in pharmacogenetics, and the Accreditation Council for Pharmacy Education has only recently required pharmacogenetics to be included in the curriculum of all accredited doctor of pharmacy programs.[14,15] In addition, it is not easy for most practicing pharmacists to keep up with the rapid developments in

pharmacogenetics. This article reviews the basic concepts of pharmacogenetics to help pharmacists interpret different approaches to pharmacogenetic studies and pharmacogenetic discoveries recognized by FDA. To make the discussion more practical, examples of genes and drugs that are included in FDA-approved package inserts are presented. Finally, future directions and the potential roles for pharmacists in applying pharmacogenetic discoveries to patient care are also discussed.

Group #: 2

Basic Concepts

The human genome consists of approximately 3 billion base pairs, and the sequence of these varies among individuals. These variations include single nucleotide polymorphisms (SNPs), base insertions or deletions, copy-number variations, and variable numbers of tandem repeats.[4-6] Because these variations can change the function of proteins that interact with a drug, the response to a drug may differ among individuals. Understanding how these variations influence drug response could help in tailoring drug therapy based on an individual's genetic makeup.

The study of pharmacogenetics can arbitrarily be divided into drug disposition and drug targets. Sequence variations in drug-disposition genes can alter the pharmacokinetics of a drug, while those in drug-target genes can change the pharmacodynamics of a drug. Because it may be easier to understand the basic concepts with this classification, the following section is divided into drug-disposition pharmacogenetics and drug-target pharmacogenetics.

Drug-disposition Pharmacogenetics

The disposition of a drug includes its absorption, metabolism, distribution, and excretion. If a genetic polymorphism alters the function of a protein that is involved in the disposition of a drug, then concentrations of the parent drug or its active metabolites at the site of drug action may also be affected. For example, if a genetic polymorphism leads to lower activity of a metabolizing enzyme, the plasma concentrations of the parent drug may increase and plasma concentrations of metabolites may decrease. If only the parent drug exhibits pharmacologic activity, the genetic polymorphism will potentiate the drug response, including adverse drug reactions. If only the metabolites have pharmacologic activity, then the genetic polymorphism may reduce the drug response. Examples of genetic variability impairing the function of metabolizing enzymes and altering drug responses include warfarin and the cytochrome P-450 (CYP) isoenzyme 2C9 (*CYP2C9* polymorphisms, tamoxifen and *CYP2D6* polymorphisms, and thiopurine drugs and thiopurine *S*-methyltransferase (*TPMT*) polymorphisms.

Group #: 3

Warfarin. Warfarin, an oral anticoagulant, is a racemic drug. *S*-warfarin, which is three to five times more potent than *R*-warfarin, is primarily metabolized by CYP2C9.[16] The *CYP2C9* gene is highly polymorphic.[17] Most polymorphisms are located in noncoding regions, and many of them are in strong linkage disequilibrium with SNPs in the coding regions. Thus, studies of SNPs located in the coding regions would also cover the genetic variations in the noncoding regions. Two polymorphisms in the coding region that are relatively common (6-10% frequency) in Caucasians and rare in African Americans and Asians have been extensively studied for their influence on the variability in stable warfarin dose requirements.[18] One is *CYP2C9*2* (a cytosine to thymine [C to T] change at nucleotide position 430, abbreviated 430C> T), which encodes an amino acid substitution (arginine to cysteine change at codon 144 [Arg144Cys]) that results in a 30-40% reduction in enzymatic activity for *S*-warfarin metabolism.[19] The other is *CYP2C9*3* (1075A> C), which encodes an Ile359Leu change that causes an almost

complete loss of *S*-warfarin metabolism.[20] Thus, one would expect that patients carrying either one or both of these two alleles would have higher serum concentrations of *S*-warfarin at a given dosage and require smaller dosages of warfarin to maintain a therapeutic International Normalized Ratio (INR) compared with patients who do not have a variant allele. A study in Caucasians found that patients carrying either *CYP2C9*2* or *CYP2C9*3* required significantly lower daily dosages of warfarin to maintain a therapeutic INR compared with patients carrying *CYP2C9*1/*1,* abbreviated **1/*1* here ($p < 0.001$).[21] The mean ± S.D. daily warfarin sodium dose was 5.63 ± 2.56 mg with **1/*1,* 4.88 ± 2.57 mg in patients with **1/*2,* 3.32 ± 0.94 mg in patients with **1/*3,* 4.07 ± 1.48 mg in patients with **2/*2,* 2.34 ± 0.35 mg in patients with **2/*3,* and 1.60 ± 0.81 mg in patients with **3/*3.*[21]

Tamoxifen. The study of tamoxifen pharmacogenetics demonstrates how serum concentrations of an active metabolite are influenced by genetic variations in the tamoxifen-metabolizing enzyme. Tamoxifen is commonly used for breast cancer treatment. Endoxifen, a metabolite of tamoxifen, is 100 times more potent than the parent drug as a selective estrogen receptor modulator and exhibits about 7 times higher plasma concentrations than the other active metabolites at steady state.[22-24] CYP2D6 is involved in generating endoxifen from tamoxifen, and its genotype and phenotype have been associated with variability in plasma concentrations of endoxifen among individuals.[25] The CYP2D6 phenotype -- traditionally classified as an ultraextensive metabolizer, an extensive metabolizer, an intermediate metabolizer, or a poor metabolizer -- is determined by the urinary metabolic ratio of a probe drug such as sparteine or debrisoquine.[26] The CYP2D6 phenotype may also be determined using the *CYP2D6* genotype. The *CYP2D6* gene, which has over 70 alleles, contains a variety of genetic polymorphisms, such as SNPs, gene deletions, and gene duplications.[27] Because CYP2D6 activity differs by *CYP2D6* allele ( ), the CYP2D6 phenotype may be determined by the number of functional, nonfunctional, and reduced-functional alleles a person carries.[28,29]

Table 1. Frequency of Important *CYP2D6* Alleles[28]a

Classification	Alleles	Frequency of Alleles by Race (%)		
		Caucasian	African American	Asian
Normal	**1, *2, *39*	70	50	50
Reduced	**10, *17, *29, *41*	5	35	45
Nonfunctional	**3, *4, *5, *6*	25	15	5

[a]CYP2D6 = gene cytochrome P-450 isoenzyme 2D6.

In general, the ultraextensive metabolizer phenotype may be present in people who carry multiple copies of a functional *CYP2D6* allele, the extensive metabolizer phenotype may be present in people who carry a functional *CYP2D6* allele, the intermediate metabolizer phenotype in individuals who are heterozygous for a reduced-functional allele and a nonfunctional allele, and the poor metabolizer phenotype in those who carry neither a functional nor a reduced-functional allele.[30] For example, *CYP2D6*1/*1* denotes an extensive metabolizer, *CYP2D6*3/*17* an intermediate metabolizer, *CYP2D6*3/*3* a poor metabolizer, and *CYP2D6*1/*1XN* (gene duplication) an ultraextensive metabolizer.

Since higher-metabolizing- enzyme activity results in higher blood concentrations of an active metabolite of a drug that is metabolized by the enzyme, extensive or ultraextensive metabolizers would have significantly higher serum concentrations of endoxifen compared with intermediate and poor metabolizers. Jin et al.,[31] in fact, showed that serum concentrations of endoxifen in ultraextensive and extensive metabolizers were about two and four times higher than in intermediate and poor metabolizers, respectively. Though not confirmed, one study suggested that breast cancer patients with intermediate- or poor-metabolizer phenotypes had significantly lower relapse-free survival rates compared with extensive or ultraextensive metabolizers.[32]

Group #: 4

Thiopurines. The pharmacogenetics of thiopurines provides a classic example of how alleles that produce defective drug-metabolizing enzymes increase the risk of adverse drug events. TPMT metabolizes cytotoxic and immunosuppressant thiopurine drugs such as mercaptopurine and azathioprine, a prodrug of mercaptopurine. TPMT activity is highly variable among individuals, and reduced TPMT activity is associated with a higher frequency of mercaptopurine-associated adverse events, such as neutropenia.[33] Genetic polymorphisms of *TPMT* have been associated with variability in TPMT activity. Of the more than 20 *TPMT* alleles that have been linked with variable TPMT activity, 3 alleles are common ( ) and account for over 95% of TPMT inherited deficiency.[34,35] *TPMT*2* (238G> C) encodes an amino acid change (Ala80Pro).[36] Allele **3A* (460G> A and 719A> G) causes two amino acid changes (Ala154Thr and Tyr240Cys), and **3C* (719A> G) changes one amino acid (Tyr240Cys).[37,38] The resultant proteins are nonfunctional because these alleles produce an enzyme more susceptible than normal to cellular degradation.[39,40] Patients who do not carry a wild type *TPMT* allele (*TPMT*1*) have extremely low TPMT enzyme activity and almost always develop neutropenia compared with patients with *TPMT*1/*1*.[35,41] Based on these data, FDA has recommended that clinicians consider a reduction in the dosage of a thiopurine in patients carrying a nonfunctional *TPMT* allele and suggested alternative therapies in patients with homozygous nonfunctional *TPMT* alleles.[42]

Table 2. Frequency of *TPMT*2, TPMT*3A,* and *TPMT*3C* Alleles[34]a

Allele	Frequency of Alleles by Race (%)		
	Caucasian	African American	Asian
*TPMT*2*	0.2	0.4	0
*TPMT*3A*	3-5	0.4-0.8	0
*TPMT*3C*	0.2	2-7	2-5

[a]TPMT = thiopurine *S*-methyltransferase.

Drug-target Pharmacogenetics

In general, drugs exert their pharmacologic effects by modulating activities of enzymes or receptors. Thus, genetic polymorphisms that change the activity of the drug target may also alter the drug response. For example, if a genetic polymorphism reduces the activity of a drug-target enzyme, the amount of drug required to inhibit the enzyme may be less than the amount required to inhibit the enzyme with normal activity. Also, drugs that inhibit

or antagonize an enzyme or a receptor will produce a greater response at a given dosage in patients whose genetic polymorphisms confer higher activities of the target protein. Fewer genetic polymorphisms in pharmacodynamic genes have been recognized by FDA when compared with the genetic polymorphisms of the drug-disposition genes. Two good examples that illustrate this concept include (1) vitamin K epoxide reductase complex subunit 1 gene polymorphisms (*VKORC1)* and warfarin response and (2) $ß_1$-adrenergic receptor gene polymorphisms (*ADRB1*) and ß-blocker response.

VKORC1. *VKORC1* encodes vitamin K epoxide reductase, which is inhibited by warfarin.[43,44] This inhibition interferes with carboxylation of vitamin K-dependent coagulation factors II, VII, IX, and X and anticoagulation proteins C and S.[16] Two haplotypes (A and B) formed by five noncoding *VKORC1* SNPs in strong linkage disequilibrium have been associated with differences in mean ± S.D. daily warfarin sodium dosage (2.7 ± 0.2 mg per day for patients with A/A haplotype, 4.9 ± 0.2 mg per day for patients with A/B, and 6.2 ± 0.3 mg per day for patients with B/B).[45] This finding has been replicated in other studies.[46-48] The A haplotype has been shown to be associated with lower levels of VKORC1 mRNA expression compared with B haplotype.[45,49] Thus, patients with A haplotype may produce smaller amounts of VKORC1 (the warfarin target protein) than do patients with B haplotype. Importantly, this association is independent of *CYP2C9* genotype.[45,50] This finding also explains, in part, the well-known clinical observation that Asian patients require smaller warfarin doses to maintain a therapeutic INR than other races since the majority of Asians carry *VKORC1* haplotype A ().[45]

Table 3. Frequency of *VKORC1* Haplotypes[45]a

Haplotype	Frequency of Haplotypes by Race (%)		
	Caucasian	African American	Asian
A	37	14	89
B	58	49	10
Total	96	62	99

[a]VKORC1 = vitamin k epoxide reductase complex subunit 1.

Group #: 5

The candidate-gene approach is a useful tool to study a genetic association with drug response if there is a plausible link between the gene and the drug response. Because physiological or pharmacologic effects of the genes (or genetic variations) on disease or drug response may already have been characterized, the results of a study (especially a positive association) using the candidate-gene approach are often easier to understand than GWAS results. This approach is less expensive and requires a smaller sample size than GWAS.[61,62] A major disadvantage of the candidate-gene approach is that it requires prior knowledge of the function of the gene regarding the drug response. If information on the function of the gene is limited, the selection of the gene is difficult to justify.

Genome Wide Association Study (GWAS)

The GWAS surveys the common genetic variations for a role in disease or drug response by genotyping large sets of SNPs across the genome.[58-63] The human genome is estimated to have about 12 million common SNPs. There are many small regions (10-100 kb) in the genome where SNPs are in linkage disequilibrium and form two to four common haplotypes.[64] Thus, an SNP in a region can be selected to represent its genetic variation. In other words, a tag SNP can be used as a proxy for the other SNPs in the region. This enables the genetic variations across the genome to be surveyed by genotyping tag SNPs. The number of SNPs used in a GWAS ranges from 100,000 to 1,000,000, with a higher number generally providing better coverage of the variations in the genome.[65]

Most GWASs have been conducted as a case-control, cohort, or family study.[66-70] The goal is to determine whether a particular allele or a set of alleles is more common in patients with a certain disease or a better (worse) drug response. Since a large number of SNPs are surveyed and compared, the a priori level of significance should be lowered to account for an increasing chance of a false-positive finding by multiple comparisons.[71] The strength of an association is usually assessed using an odds ratio (OR) or a relative risk and *p* value. As with the candidate-gene association study, the findings should be replicated in multiple independent populations.[60]

Since a GWAS does not hypothesize a possible role of a gene in the drug response, it is a great tool to discover new functions of a gene or to identify a new genetic biomarker that may be used as a surrogate for the drug response. For example, a GWAS that compared the allele frequencies of SNPs among patients with coronary artery disease and control groups revealed that the SNP (rs1333049) at chromosome 9q21.3 was associated with an increased risk of coronary artery disease.[68,72] This discovery has been replicated in multiple independent populations.[71] The region of chromosome 9 that harbors this SNP contains cyclin-dependent kinase inhibitor 2A (*CDKN2A*) and cyclin-dependent kinase inhibitor 2B (*CDKN2B*) genes, which encode cyclin-dependent kinase inhibitor INK4 proteins p16INK4a and p15INK4b, respectively.[68] Although both proteins are thought to play an important role in cell-cycle regulation, neither has ever been proposed as having a role in coronary artery disease.[74] This discovery may help in exploring new functions for the genes involved in the development of coronary artery disease.

Since rare but serious adverse drug reactions are not predictably associated with the known pharmacology of a drug and are not easily predicted with current biomarkers, GWASs can be used to identify new biomarkers that could explain the underlying mechanisms of adverse drug reactions. The development of ximelagatran, an oral direct thrombin inhibitor, was stopped due to its association with elevated liver enzyme levels, which was unpredictable.[75] A recent GWAS found that two major histocompatibility complex (MHC) alleles, *DRB1*07* and *DQA1*02,* were associated with elevated liver enzyme levels after ximelagatran treatment, suggesting the involvement of the immune system in the pathogenesis of the drug's hepatotoxicity.[76] If the roles of the MHC alleles in the development of liver toxicity are characterized and the findings are replicated with other hepatotoxic drugs, these two alleles could be used as biomarkers for monitoring drug-induced liver toxicity in clinical practice.

The requirement for a large clinical sample size and the high cost of whole-genome SNP panels for GWASs compared with the candidate-gene approach have been the limiting factors in using GWASs.[58,61] The coverage of genetic variations also differs among various commercial SNP panels. For example, rare SNPs and copy-number variations may not be included in a certain set of SNPs in a GWAS.[58] Despite the abovementioned limitations, the GWAS holds great potential for contributing to the understanding of complex disease development and identifying the factors that affect variable drug responses.

Group #: 6

[a]Drugs with "information only" pharmacogenetic discoveries are not comprehensively presented. FDA = Food and Drug Administration; EGFR = epidermal growth factor receptor; HER2/NEU = v-erb-b2 erythroblastic leukemia viral oncogene homolog 2; CCR-5 = chemokine C-C motif receptor; HLA = human leukocyte antigen; CYP2C9 = cytochrome P-450 isoenzyme 2C9; VKORC1 = vitamin K epoxide reductase complex subunit 1; TPMT = thiopurine *S*-methyltransferase; UGT1A1 = uridine diphosphate-glucuronosyltransferase 1A1; c-KIT = v -kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; CYP2C19 = cytochrome P-450 2C19; CYP2D6 = cytochrome P-450 isoenzyme 2D6; DPD deficiency = dihydropyrimidine dehydrogenase; G6PD = glucose -6-phosphate dehydrogenase; NAT = *N*- acetyltransferase; PML/RAR = promyelocytic leukemia/retinoic acid receptor.

In December 2007, FDA added a black-box warning on the carbamazepine label, recommending testing for the *HLA-B*1502* allele in patients with Asian ancestry before initiating carbamazepine therapy because these patients are at high risk of developing carbamazepine-induced Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).[78] Interestingly, while Asians or patients with Asian ancestry have been reported to have a strikingly high frequency (98%; OR = 1357; 95% CI, 193-8838) of carbamazepine-induced SJS or TEN if they carry an *HLA-B*1502* allele, other races carrying the allele do not seem to have the increased risk.[79-82] In addition, the frequency of *HLA-B*1502* is higher in South Asians, including Taiwanese, Hong Kong Chinese, Thai, and Indians (8-11%), than in North Asians, such as Beijing Chinese, Japanese, and Koreans (1-2%).[82,83]

Pharmacogenetic testing is recommended for patients treated with warfarin, thiopurines, valproic acid, irinotecan, abacavir, or rasburicase. Irinotecan is a prodrug used for the treatment of colorectal cancer, small-cell lung cancer, and other solid tumors. The active metabolite of irinotecan is SN-38, a topoisomerase I inhibitor, and uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) plays a critical role in inactivating SN-38.[84,85] The low activity of the UGT1A1 enzyme may increase the risk for adverse events associated with irinotecan therapy (e.g., neutropenia) by increasing serum concentrations of the active metabolite. The promoter region in *UGT1A1* contains a TATAA box, a regulatory sequence that is polymorphic, consisting of five to eight copies of TA repeats [$(TA)_nTAA$]. [86,87] The wild-type regulatory sequence has six repeats of dinucleotide TA (*UGT1A1*1*), while the common variant sequence contains seven repeats of the dinucleotide (*UGT1A1*28*).[84,86,87] The other two alleles (five and eight TA repeats) are rare. It has been found that the longer the repeat allele, the lower the promoter activity.[87] Patients homozygous for the *UGT1A1*28* allele may have lower enzyme expression and activity compared with patients with wild-type alleles and may have higher serum concentrations of SN-38 with an associated increased risk of adverse events. In clinical studies, patients homozygous for *UGT1A1*28* demonstrated a significantly higher risk of neutropenia compared with those patients carrying *UGT1A1*1.*[88-90] Based on these findings, FDA recommended reducing the irinotecan dose in patients with *UGT1A1*28/*28.*

Factors Influencing the Application of Pharmacogenetic Discoveries to Patient Care

Many factors can influence the application of pharmacogenetic discoveries to patient care. These include mechanisms to introduce a pharmacogenetic test into clinical practice, turnaround time, cost, reimbursability, and interpretation of a test.

Test Regulation

There are two mechanisms by which a pharmacogenetic test can be introduced to clinical practice. In the first mechanism, FDA regulates in vitro diagnostic devices (IVDs) or test kits, which manufacturers produce, package, and sell with all ingredients and instructions needed to perform the test.

In the second mechanism, an individual clinical laboratory develops and offers a test.[95] These so-called "home-brew" tests account for the vast majority of the more than 1300 genetic tests available for clinical use.[96] These tests do not require FDA approval. Instead, the quality of testing in the clinical laboratories is regulated under the Clinical Laboratory Improvement Amendment of 1988 (CLIA). Both the Centers for Medicare and Medicaid Services and the Centers for Disease Control and Prevention are responsible for ensuring the quality of the clinical laboratories.[95] Under CLIA, clinical laboratories performing tests that are classified as moderate to highly complex are required to be enrolled in a proficiency test program in order to maintain a high quality of testing. Although genetic testing, including pharmacogenetic testing, is classified as moderately or highly complex, laboratories performing genetic testing are not currently required to be enrolled in a proficiency test program.[97] Thus, whenever possible, it is important to have the pharmacogenetic tests performed by a reliable and experienced laboratory.

Group #: 7

Test Availability, Cost, and Reimbursement

Despite technological improvement in pharmacogenetic tests, which can genotype multiple loci in a short time, test availability limits application of pharmacogenetic discoveries to patient care. A recent survey found that only 8% of U.S. laboratories offer pharmacogenetic testing. lists some of the clinical laboratories that offer pharmacogenetic tests for clinical use.[98-107] Limited test availability also influences its turnaround time for test results. The turnaround time for the results of a pharmacogenetic test performed in an in-house laboratory may be within a day because an assay itself usually takes only about two to six hours to perform. If, however, pharmacogenetic testing must be conducted by an outside laboratory, turnaround may take several days.[99-107] The significance of the turnaround time depends on the purpose for testing. If a test is performed for a drug that should be administered immediately, such as warfarin, the turnaround time is crucial for clinical decision-making. In contrast, if the purpose of testing is to obtain genotype information for future use, a fast turnaround time is not as important.

[b]Simultaneous genotyping for multiple genes.

The price of testing ranges from $250 to $500.[108-110] The cost of pharmacogenetic testing required by FDA is generally reimbursed by most insurance plans. The cost of testing not required by FDA may be covered by an insurance plan if the test is considered medically necessary. This usually requires high-quality evidence for the clinical utility of the testing.[95] Currently, few pharmacogenetic tests have evidence to support their clinical utility because many of them have been recently introduced. Thus, most insurance plans consider a vast majority of pharmacogenetic tests "experimental."[95] This lack of high-quality study results and limited reimbursability may delay widespread adoption of pharmacogenetic testing to clinical practice. Interestingly, Medicare's "Coverage with Evidence Development" policy may cover a pharmacogenetic test if a patient has "appropriate" indications for an "experimental" test or if the patient participates in a registry to help develop evidence to support testing.[95]

Test Interpretation

Interpretation of a pharmacogenetic test result is particularly important for a test that influences a dosage of a drug in clinical practice. In its draft guidelines, National Academy of Clinical Biochemistry (NACB) recommends that

clinical laboratories should not indicate a specific dosage of a drug in the laboratory report.[111] The package insert of a drug with pharmacogenetic information on the label does not generally provide a specific dosage of the drug for patients with a particular genotype. However, in the case of atomoxetine, FDA recommends that the starting dosage should be based on the patient's phenotype. For example, the recommended starting dosage of atomoxetine hydrochloride is 0.5 mg/kg daily in poor metabolizers of CYP2D6 who weigh 70 kg or less.[112] Some experts have proposed clinical guidelines for the use of *CYP2C19/ CYP2D6* polymorphism testing, which provide dosing recommendations for antidepressants and antipsychotics according to *CYP2C19/ CYP2D6* genotype.[30]

Given the complex interplay among the many factors that influence drug dosage, determination of an appropriate dosage of a particular drug for a given patient will eventually require knowledge about genetic and non-genetic factors that affect drug disposition and pharmacodynamics. One way to determine a drug dosage with genotype information is to use a dosing algorithm that accounts for genetic and non-genetic factors that cause dose variability of the drug. Although algorithms are useful, clinicians should be aware of advantages of and limitations in using an algorithm, which has been well illustrated for warfarin dosing algorithms.

The warfarin dosing algorithms are essentially a linear regression model that predicts an individualized warfarin dosage based on genetic and non-genetic variables obtained from an individual patient.[113-115] While all warfarin dosing algorithms require genotype information from at least three loci (*CYP2C9*2, CYP2C9*3,* and *VKORC1-1639G/A* [or its equivalent]), the required non-genetic variables (e.g., age, race, interacting drugs, smoking status, target INR) for dosage calculation vary by algorithm.[48,113-115] Despite this, it appears that the predicted warfarin dosages do not statistically differ among the algorithms.[116] The R^2 value of the algorithms ranges from 0.4 to 0.7, suggesting that 40-70% of the variability in warfarin dosage is explained by the regression models.[48,113-115] When compared with models using only non-genetic variables, the models including both non-genetic and genetic variables had 20-40% higher R^2 values, indicating a substantial contribution of genetic variables to warfarin dosage variability.

Other factors should also be considered when a dosing algorithm is used. The dosing algorithms cannot predict who will be outliers from the regression line. In addition, most dosing algorithms may not be useful when adjusting the dosage after warfarin is given. Thus, an individual patient's genotype data should be obtained before warfarin is prescribed. Finally, the algorithms do not predict when a therapeutic INR is reached. Thus, it is still important to closely monitor the INR and to adjust the dosage even when a dosing algorithm is used.

Given the many factors that influence dosage variability among individuals and some limitations in the algorithms, a dosing algorithm using pharmacogenetic discoveries should be viewed as a tool to decrease uncertainty about a patient's dosage in the early phase of the drug treatment; subsequent doses should be adjusted based on the patient's clinical response.

Group #: 8

Future Directions and Roles for Pharmacists

Despite the great potential for pharmacogenetic discoveries to improve patient care, additional work is required before these discoveries find widespread application in clinical practice.

Need for Additional Research

Randomized clinical trials are needed to evaluate the clinical utility of a pharmacogenetic test. Although pharmacogenetic tests may help inform clinical decisions involving drug selection and dosing, it has not been

shown whether these tests improve clinical outcomes. Until the clinical benefit and risk of the use of a pharmacogenetic test are defined, routine use of the test is likely to be delayed. The clinical utility data may also help in estimating the cost effectiveness of a test and whether its cost should be reimbursed by insurance plans.

Need for Guidelines

The government and professional organizations need to develop more guidelines for the clinical use of various pharmacogenetic tests. A couple of guidelines address the use of a particular pharmacogenetic test and have been supported by the government or professional organizations. The National Comprehensive Cancer Network Task Force has published guidelines on *HER2* testing in breast cancer, which review important characteristics of the current *HER2* tests available and how to interpret the test results.[117] The Evaluation of Genomic Applications in Practice and Prevention Working Group supported by the Agency for Health Research and Quality has developed guidelines for the use of *CYP2C19/ CYP2D6* polymorphism testing.[118] It discourages the use of this test in nonpsychotic, depressed patients who are beginning treatment with a selective serotonin-reuptake inhibitor because of "insufficient evidence to support a recommendation for or against use of the test."

A working group of the American College of Medical Genetics reviewed warfarin pharmacogenetics and does not presently endorse routine use of warfarin pharmacogenetic testing, though the group suggests that "*CYP2C9* and *VKORC1* testing may be useful and warranted in determining the cause of unusual therapeutic responses to warfarin therapy in certain situations."[119] Because many new pharmacogenetic tests may be introduced into clinical practice in the future, it is important to develop guidelines supported by respected professional organizations and the government to guide the use of such tests.

Need for Education

Provider education on pharmacogenetics is needed. Although health care providers' knowledge of pharmacogenetics has not been well studied, many health care providers do not feel comfortable with offering and interpreting genetic tests in their clinical practice, due in part to a lack of knowledge about genetics.[120,121] In addition, a majority of community pharmacists feel their knowledge about pharmacogenetics is "less than adequate," though many community pharmacists expect advances in human genetics will influence their role and delivery of pharmaceuticals.[13] Thus, given the high likelihood that pharmacogenetics may change pharmacy practice in the future, education on pharmacogenetics should be provided to doctor of pharmacy students as well as practicing pharmacists.

Need for a Clinical Practice Model

A clinical practice model that can apply pharmacogenetic discoveries to patient care is needed. Although readouts of some pharmacogenetic tests such as AmpliChip CYP450 (Roche Diagnostics, Indianapolis, IN) report both genotype and phenotype, a majority of pharmacogenetic tests report only the genotype. Also, clinical laboratories are recommended to report only genotypes.[111] Thus, it is important for a health care institution to have a mechanism to relate a patient's genotype that is reported by a clinical laboratory to a phenotype. This may require a strong collaboration among professionals of various disciplines including pharmacists.

Role of Pharmacy

Pharmacists may play a key role in applying pharmacogenetic discoveries to patient care. Application of pharmacogenetic discoveries requires knowledge and understanding of the disposition and pharmacodynamics of

drugs. In addition, a good understanding of clinical factors that can influence pharmacokinetics and pharmacodynamics of drugs is also important in the effective application of pharmacogenetic discoveries to patient care. Because pharmacists are experts in pharmacokinetics and pharmacodynamics, they can take a lead in application of pharmacogenetics in clinical practice. For example, NACB draft guidelines suggest that pharmacists may be engaged in interpreting pharmacogenetic testing results.[111] In addition, some experts have suggested that pharmacists need access to patients' genetic information in order to provide individualized pharmaceutical care before they fill prescriptions.[122] Although such involvement would require regulations and systems that secure and maintain patient confidentiality, the application of pharmacogenetics in clinical practice presents an opportunity where pharmacists can expand their roles in the genomic era.

What is Pharmacogenomics?

Pre-Lab Questions

1. **How is pharmacogenomics an important part of personalized medicine?**

2. **Explain: How does pharmacogenetic insure that patients get the right medication?**

3. **Complete the following table:**

	Pharmacogenomics	**Pharmacogenetics**
Definition		
Goal		
Benefits		

Log on to: http://learn.genetics.utah.edu/content/pharma/intro/

Virtual Lab #:1

Go to **Your Doctor's New Genetic Tools**

1.How is pharmacogenetics shifting from science fiction to fact?

2.Latrice has been diagnosed with _____ which is …

3.What is chemotherapy?

4.Her doctor wants to prescribe Purinethol, a common chemotherapy drug that works by...

5.Some patients suffer severe side effects from Purinethol because they...

6.What percent of the children population has full enzymatic activity and can receive a full dose of Purinethol with no severe side effects?

7.How can physicians deal with the 11% of the children population and why?

8.What happens to 0.33% of the children that have TPMT with insufficient enzymatic activity?

9.What can the Doctor do to make sure Latrice gets the correct dosage of Purinethol for her treatment?

10.Explain Latrice's recommendation for treatment based on her test results.

11.How can doctors use genetic tests in the clinic?

Virtual Lab #:2

Go to **Making SNPs Make Sense**

1. What is a SNP?

2. What is a haplotype?

3. To be classified as a SNP, it must be present in at least _____ % of the population. How many SNPs occur throughout the human genome? _____

4. Draw a good example of what a SNPs look like on DNA molecules.

5. Briefly explain how physicians might *Apply SNP Profiles to Drug Choices* when designing a treatment for a patient. Use the following words: **SNP profile, known data, predict**

Virtual Lab #:3

Go to **Drug Development Today and Tomorrow**

1. How pharmacogenetic approaches might make the drug process more efficient?

2. What are drugs?

3. How can drugs interact with proteins?

4. List the names of the teams involved in the development of drugs.

5. How long it takes for a new drug to be on the pharmacist's shelf and how much money it costs for a single drug?

6. How is the drug development changing today?

7. Which problem in the United States is pharmacogenomics working on obtaining a drug?

8. How is the use of microarray technology facilitating the development of pharmacogenomics?

9. How do scientists obtain the SNP profile of patients to determine treatment?

10. How can the use of pharmacogenomics reduce spending?

What is Pharmacogenomics? (Answer Key)

Pre-Lab Questions

1. How is pharmacogenomics an important part of personalized medicine?
The pharmaceutical industry is actively developing ways to customize medical treatments to suit our unique genetic signatures.

2. Explain: How does pharmacogenetic insure that patients get the right medication?
Individuals respond to drugs for the treatment of cancer or other illnesses differs based on the activity and function of enzymes in the body. This information is now available in each individual's genetic profile. Even today, genetics is being integrated into individuals' medical treatment plans.

3. Complete the following table:

	Pharmacogenomics	Pharmacogenetics
Definition	Uses large groups of patients to evaluate how candidate drugs interact with a range of genes and their protein products.	Evaluates how an individual's genetic make-up corresponds to the response to a particular medication.
Goal	Increase the efficiency of the drug development process and develop products that will benefit the largest population.	Tailor medical treatments to the individual, increasing their effectiveness while reducing side effects.
Benefits	Reduce the time and money it takes to design superior medications that effectively treat specific patient populations.	Tests that predict patient drug response, match drugs with the patient and assess disease risk.

Log on to: http://learn.genetics.utah.edu/content/pharma/intro/

Virtual Lab #:1

Go to **Your Doctor's New Genetic Tools**

1. How is pharmacogenetics shifting from science fiction to fact?
Genetic tests to predict patient drug response are already beginning to emerge on the market and move into the clinic.

2. Latrice has been diagnosed with _____ leukemia____ which is … is cancer of the blood cells. It starts in the bone marrow, the soft tissue inside most bones. Bone marrow is where blood cells are made.

3. What is chemotherapy? is a type of cancer treatment that uses drugs to destroy cancer cells.

4. Her doctor wants to prescribe Purinethol, a common chemotherapy drug that works by...
(Answers will vary)
The drug works by incorporating itself into rapidly dividing cancer cells and killing them.

5. Some patients suffer severe side effects from Purinethol because they...
(Answers will vary)
The effects vary due to their level of TPMT, an enzyme responsible for breaking down Purinethol.

6. What percent of the children population has full enzymatic activity and can receive a full dose of Purinethol with no severe side effects? 89% of the children population

7. How can physicians deal with the 11% of the children population and why?
They can handle a reduced dose of Purinethol due to their reduced TPMT enzyme activity.

8. What happens to 0.33% of the children that have TPMT with insufficient enzymatic activity?
They suffer serious side effects from Purinethol and will be placed on an alternative treatment.

9. What can the Doctor do to make sure Latrice gets the correct dosage of Purinethol for her treatment?
(Answers will vary)
The doctor will take a blood sample and send it to a lab for SNP profiling. This will determine which TPMT variation Latrice has.

10. Explain Latrice's recommendation for treatment based on her test results.
Latrice has "partial TPMT activity" with this information the doctor will put her on a reduced Purinethol dosage.

11. How can doctors use genetic tests in the clinic?
To predict patient response to a particular drug

Virtual Lab #:2

Go to **Making SNPs Make Sense**

1. What is a SNP?
A Single Nucleotide Polymorphism. They are single-nucleotide substitutions of one base for another.

2. What is a haplotype?
Haplotype is a group of genes, which is inherited together by an organism from a single parent.

3. To be classified as a SNP, it must be present in at least ___1___ % of the population. How many SNPs occur throughout the human genome? _10 million SNPs within the 3-billion-nucleotide human genome_____

4. Draw a good example of what a SNPs look like on DNA molecules.
CTA A/G GTA - Variation is the SNP A/G.

5. Briefly explain how physicians might *Apply SNP Profiles to Drug Choices* when designing a treatment for a patient. Use the following words: **SNP profile, known data, predict**
(Answers will vary)
In the future, a physician might first determine a patient's SNP profile, compare it with known data and predict the patient's response to a medication. The physician would then prescribe medication based on what is known to work best with that patent's SNP profile.

Virtual Lab #:3
Go to **Drug Development Today and Tomorrow**

1. How pharmacogenetic approaches might make the drug process more efficient?
   By enabling researchers to:
   - Identify genes involved in disease
   - Understand how genes and the proteins they produce are affected by various drug candidates
   - Effectively choose target populations to be used in clinical trials

2. What are drugs?
Drugs are tiny molecules that interact with proteins and other cellular molecules to change the way they work in the body.

3. How can drugs interact with proteins?
Most interactions don't cure any disease, and may even make you sicker.

4. List the names of the teams involved in the development of drugs.
Team leaders; Molecular Biologists; Biochemists; Cell Biologists; Structural Biologists; Toxicologists; Chemists; Robotics Engineers and Pharmacologists.

5. How long it takes for a new drug to be on the pharmacist's shelf and how much money it costs for a single drug?
It can take from 10-15 years and a cost of about $802 million.

6. How is the drug development changing today?
It's changing by the application of pharmacogenomics

7. Which problem in the United States is pharmacogenomics working on obtaining a drug?
The problem of obesity

8. How is the use of microarray technology facilitating the development of pharmacogenomics?
Microarray technology can identify gene expression and identify a gene that is overactive in a large percentage of obese patients.

9. How do scientists obtain the SNP profile of patients to determine treatment?
Their SNP profile is obtained by taking a blood sample.

10. How can the use of pharmacogenomics reduce spending?
It will save the drug companies time and money in determining the root of the genetic problem and the right drug to treat the patient.

DNA Chips: Gene to Disease – Lesson # 2

TITLE: Using Microarrays to Study Gene Expression

KEY QUESTION(S): How can gene expression and determining which genes play a role in a particular health condition? What is the purpose of using a microarray in the application of Pharmacogenetics?

SCIENCE CONCEPTS: Gene expression, complimentary DNA sequences, and uses for microarray technology

OVERALL TIME ESTIMATE: This lesson requires two class periods of 50 minutes each.

LEARNING STYLES: Visual, auditory, and kinesthetic.

VOCABULARY:

Amino Acids: An organic molecule containing an amino group (-NH2), a carboxyl (-COOH) group, and a variable side chain (R group) that distinguishes the amino acid. Proteins are synthesized from amino acids.

Amplification: An increase in the number of copies of a gene in a cell, resulting in an elevation in the level of the RNA or protein encoded for by the gene and a corresponding amplification of the phenotype that the gene confers on the cell. Drug resistance in cancer cells is linked to amplification of the gene that prevents absorption of the chemotherapeutical agent by the cell.

Anticodon: a triplet of nucleotide bases in transfer RNA that identifies the amino acid carried and binds to a complementary codon in messenger RNA during protein synthesis at a ribosome.

Cardiovascular disease: refers to any disease that affects the cardiovascular system, principally cardiac disease, vascular diseases of the brain and kidney, and peripheral arterial disease.

Chemotherapy: is a type of cancer treatment that uses drugs to destroy cancer cells.

Codon: a triplet sequence of nucleotides that directs the tRNA's "anticodon" to acquire select amino acids for protein production.

Denaturation: A process in which the structure of nucleic acid is disrupted, such as the dissociation of a double stranded DNA into a single stranded state by heating.

Diabetes: often referred to by doctors as **diabetes mellitus**, describes a group of metabolic diseases in which the person has high blood glucose (blood sugar), either because insulin production is inadequate, or because the body's cells do not respond properly to insulin, or both.

DNA Microarray: A small solid support, usually a membrane or glass slide, on which sequences of DNA are fixed in an orderly arrangement. DNA microarrays are used for rapid surveys of the expression of many genes simultaneously, as the sequences contained on a single microarray can number in the thousands. Also called *DNA chip*.

Enzymes: Any of numerous proteins produced in living cells that accelerate or catalyze chemical reactions.

Gel – electrophoresis: method used to separate DNA fragments by size. It is a common diagnostic procedure used in molecular biological labs.

Gene: Chemical factor that determines traits.

Gene Expression: is the process by which information from a gene is used in the synthesis of a functional gene product. These products are often proteins, but in non-protein coding genes such as rRNA genes or tRNA genes, the product is a functional RNA.

Genetics: is the study of heredity. Heredity is a biological process where a parent passes certain genes onto their children or offspring.

Genomics: is the study of the genomes of organisms. The field includes intensive efforts to determine the entire DNA sequence of organisms and fine-scale genetic mapping efforts.

Haplotype: is a group of genes, which is inherited together by an organism from a single parent.

Helicase: The enzyme responsible for "unzipping" DNA during replication and RNA formation.

mRNA: An abbreviated expression for Messenger Ribonucleic Acid. This genetic sequence is responsible for "coding" a gene within the DNA for the instruction of constructing proteins within the cell's cytoplasm at a ribosome.

Mutation: is a change of the nucleotide sequence of the genome of an organism, virus, or extra chromosomal genetic element.

NCBI: National **C**enter for **B**iotechnology **I**nformation – advances science and health by providing genomic information. http://www.ncbi.nlm.nih.gov/

Nucleotide: a phosphoric ester of a nucleoside.

Obesity: is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life.

PCR: is polymerase chain reaction: a technique for rapidly producing many copies of a fragment of DNA for diagnostic or research purposes.

Personalized Medicine: an approach to the practice of medicine that uses information about a patient's unique genetic makeup and environment to customize the patient's medical care to fit his or her individual requirements.

Pharmacogenetics: is a science that examines the inherited variations in genes that dictate drug response and explores the ways these variations can be used to predict whether a patient will have a good response to a drug, a bad response to a drug, or no response at all.

Pharmacogenomics: Uses large groups of patients to evaluate how candidate drugs interact with a range of genes and their protein products.

Pharmacokinetics: the action of drugs in the body over a period of time, including the processes of absorption, distribution, localization in tissues, biotransformation, and excretion.

Polymerase: The enzyme responsible for DNA replication and RNA formations.

Polymorphism: is a DNA sequence variation that is common in the population. In this case no single allele is regarded as the standard sequence.

Polypeptide: are chains of amino acids. Proteins are made up of one or more **polypeptide** molecules.

Proteins: A linear polymer built from approximately 20 different amino acid types. The type and sequence of these amino acids are specified by the DNA, this sequence also determines shape and function of the protein.

Protein Synthesis: is accomplished through a process called translation. In translation, RNA and ribosomes work together to produce proteins.

SNP: A Single Nucleotide Polymorphism. They are single-nucleotide substitutions of one base for another.

Substrate: The molecule that the enzyme acts upon.

tRNA: An abbreviated expression for Transfer Ribonucleic Acid. This genetic sequence is responsible for the "gathering" of amino acids within the cell's cytoplasm.

Thermocycler: a laboratory apparatus used to amplify segments of DNA via the polymerase chain reaction (PCR) process.

Transcription: The process of RNA production within the nucleus using DNA as a "template" to copy a specific location within the DNA (typically a gene). The DNA is "transcribed" from the 5'→3' using nucleotides.

Translation: A "decoding" of the mRNA (created in transcription) at a ribosome within the extranuclear space. The process produces primary structure proteins that can be later modified to perform an assortment of structural/physiological functions.

LESSON SUMMARY:

Lesson # 2: The lesson is on **Gene Expression and Microarray Virtual Lab**. Using resources from the University of Utah. During the second day of the lesson, students will conduct a **DNA Microarray Simulation Wet Lab** provided by CPET that will afford students the opportunity of a hands on lab and critical thinking.

STUDENT LEARNING OBJECTIVES WITH NEXT GENERATION SUNSHINE STATE STANDARDS:

1. Students will be able to explain how small variations in our DNA (gene expression) can correlate with individual differences in response to a medication or disease risk.
2. Students will be able to conduct a DNA Microarray wet lab to investigate and interpret the differences between gene expressions.

NEXT GENERATION SUNSHINE STATE STANDARDS (NGSSS)

(http://www.nextgenscience.org/next-generation-science-standards)

SC.912.L - 14.6, 15.15, 16.2, 16.3, 16.4, 16.5, 16.6, 16.8, 16.9, 16.10, 16.11, 16.12, 18.1, 18.4, 18.11
SC.912.N - 1.1, 1.3, 1.4, 1.5, 1.6, 1.7, 2.4
HE.912.C – 1.3, 1.5, 1.7

COMMON CORE STANDARDS (http://www.corestandards.org/)

LACC.910.RST – 1.3, 2.4, 3.8
LACC.901.WHST – 1.1e, 2.6, 3.9
LACC.910.SL – 1.1b, 2.4, 2.5
MACC.912.N.Q.1.1

MATERIALS and ESSENTIALS:

- 15 Laptops
- 16 Gene Expression and Microarray Virtual Lab write-up with questions (One per pair)
- 2 Microarray Simulation Wet Lab Kits (Kit from A. Malcolm Campbell and Genisphere)
- 2 Hot water bath (for melting agarose solutions)
- 25 Microarray Simulation Web Lab protocol with questions
- scissors
- 25 gloves and goggles (for safety with hot agarose and with hybridization solution)
- camera, or colored pencils/markers (for recording results and documenting data)
- 8 float or rack (for holding dropper bottles upright while heating)
- 25 copies of the Pre-test/post-test multiple choice questions with answer sheets

BACKGROUND INFORMATION:

In order for the teacher to understand the information presented in this lesson it would be helpful to practice the activities first to understand them. This section will offer a brief understanding of the concepts addressed in the lesson.

Every cell in our bodies contains copies of each of our 20,000 or so genes. Gene products carry out cellular functions. When a gene is "on" and its protein or RNA product is being made, scientists say that the gene is being expressed. The on and off states of all of a cells genes is known as a gene expression profile. Each cell type has a unique gene expression profile.

A microarray is a solid support, roughly the size of a microscope slide that has single-stranded DNA fragments of known sequences bound to it in an ordered and known arrangement. A single microarray will have thousands of DNA sequences (fragments of genes) bound to it. Microarrays can be used to analyze targeted sequences of DNA and to measure relative levels of gene expression. Microarray analysis also plays an important role in diagnosis of disease, detection of gene variations, and drug development. Microarray technology is revolutionizing the study of genomics. The array can be either custom-designed or mass-produced. Scientists usually purchase their microarrays from biotechnology companies where they are manufactured in large quantities.

ADVANCE PREPARATION:

The teacher needs to read all the provided resources on gene expression and microarray technology. Copies of the virtual lab write-ups and microarray simulation lab protocol need to be obtained to hand out to the students. Depending on class size the teacher may need extra copies of the handed materials. Have all the computers on-line and ready for students to log on for the virtual experience part of the lab.

In order to perform the DNA Microarray Simulation Wet Lab the teacher needs to have set up two hot water baths. It is also required to have at least two kits of DNA Chips: Genes to Disease by A. Malcolm Campbell and Genisphere. These kits come with ten reusable microarrays with reagents.

http://www.carolina.com/biotechnology-dna-mircoarray/dna-chips-genes-to-disease-kit/211520.pr

PROCEDURE AND DISCUSSION QUESTIONS WITH TIME ESTIMATES:

Day #: 1 – Gene Expression and DNA Microarray Virtual Lab

1. (5 min) Without explaining the topic the teacher will sit the students in pairs with a computer.

2. (1 min) Students should log on to the website in the order below

http://highered.mcgraw-hill.com/sites/9834092339/student_view0/chapter15/simple_gene_expression.html

http://learn.genetics.utah.edu/content/labs/microarray/

3. (1 min) Instruct students working in pairs that even though they have each a copy of the virtual lab write-up only one completed paper per group will be graded.

4. (30 min) Both Gene Expression and DNA Microarray Virtual Labs should be completed.

5. (10 min) Get the attention of the class and go over the goals and objectives in form of discussion.

Day #: 2 – DNA Microarray Simulation Wet Lab

1. (10 min) Before the class begins make sure you have all reagents, microarray, hot water bath, group lab protocols and lab write-up at each table.

2. (5 min) Sit students in eight groups of three. Assign one group member to write the results and analysis for the group.

3. (20 min) Guide the students through the protocol for each group with the instructions on getting the genes on the microarray. Each group is assigned a different case with target genes to identify.

4. (10 min) Allow students to get their microarray results and answer the analysis questions provided in the lab write-up.

5. (15 min) At the end of the ten minutes administer a short essay questions test given to grade, assess progress and provide remediation.

ASSESSMENT SUGGESTIONS:

1. Students will be able to explain how small variations in our DNA (gene expression) can correlate with individual differences in response to a medication or disease risk.

This objective will be assessed by formally assessing the gene expression and Microarray Virtual lab write-up and test administered at the end of the lesson.

2. Students will be able to conduct a DNA Microarray wet lab to investigate and interpret the differences between gene expressions.

This objective will be assessed by using a visual formative assessment during the hands on lab, the information on the DNA Microarray simulation wet lab write-up and test administered at the end of the lesson.

EXTENSIONS:

ACTIVITIES:

Ghost in your Genes
http://www.pbs.org/wgbh/nova/education/activities/3413_genes.html

Macromodel of Microarray
http://learn.genetics.utah.edu/content/labs/microarray/

LITERATURE:

DNA Microarray Technology
http://www.genome.gov/10000533

DNA Microarray Wet Lab Simulation Brings Genomics into the High School Curriculum
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1681359/

HHMI Microarray Resources (BioInteractive)
www.hhmi.org/biointeractive/genomics/genechipdata/index.html

RESOURCES/REFERENCES:

DNA Chips: From Genes to Disease at GCAT
http://www.bio.davidson.edu/projects/GCAT/HSChips/Hschips.html

Microarray Virtual Lab
http://learn.genetics.utah.edu/content/labs/microarray/
http://www.carolina.com/teacher-resources/Interactive/dna-microarray-simulation/tr10710.tr

Gene Expression
http://highered.mcgraw-hill.com/sites/9834092339/student_view0/chapter15/simple_gene_expression.html

Resources from the University of Utah
http://learn.genetics.utah.edu/content/pharma/

Gene Expression and DNA Microarray Virtual Lab

Gene Expression – Genes and how they work

Go to: http://highered.mcgraw-hill.com/sites/9834092339/student_view0/chapter15/simple_gene_expression.html

1. Watch the short tutorial and place the answers to the quiz below

1. _____ 2. _____ 3. _____ 4. _____ 5. _____

2. Come up with at least two gene expressions in humans that can be life threatening.

3. How can finding the gene expression of a particular disorder or disease be valuable information?

4. Why is obesity a problem in America?

6. In which way you think we can treat or prevent obesity based on gene expression?

DNA Microarray Virtual Lab

Go to: http://learn.genetics.utah.edu/content/labs/microarray/

1. What is genomics? How does microarray technology make genomics possible?

2. What does a microarray really do?

3. List the steps involved in using microarray analysis to identify which genes are "on" in a tissue or cell sample.

4. What are DNA Microarrays made up of?

5. Why do scientists perform protein expression analysis?

6. What makes a cancer cell different from a normal cell?

7. What does reverse transcriptase do?

8. What do we call hybridization?

9. What does the computer database list when using microarray technology?

10. What do the red, yellow and green spots show on the microarray image results?

11. Which color of spots would you be interested in if you were looking for evidence of cancer genes?

12. Which gene is **"turned up"** in cancer cells?

13. How can researchers know if a gene is producing protein?

14. Explain the use of DNA microarray analysis.

Gene Expression and Microarray Virtual Lab (Answer Key)

Gene Expression

Go to: http://highered.mcgraw-hill.com/sites/9834092339/student_view0/chapter15/simple_gene_expression.html

1.Watch the short tutorial and place the answers to the quiz below

1.___B_____ 2. ___E____ 3. ____C___ 4. ___A____ 5. __A_____

2.Come up with at least two gene expressions in humans that can be life threatening.
(Answers may vary)
Heart disease and obesity

3. How can finding the gene expression of a particular disorder or disease be valuable information?
(Answers may vary)

- The researchers will use an approach called gene expression profiling to identify active and inactive genes in a cell or tissue.
- Expression profiling then tells the scientist which genes may play a role in obesity or other disease.
- Scientists run similar expression profile studies on all the family members, as well as on those of other study participants.

4. Why is obesity a problem in America?
It can lead to heart disease, high blood pressure and diabetes, especially as people age. A complex medical condition, obesity is influenced by diet, exercise, metabolism - and genetics.

5.In which way you think we can treat or prevent obesity based on gene expression?
(Answers may vary)

- Designing drugs intended to treat or prevent obesity
- Designing drugs to control expression of obesity genes.

DNA Microarray Virtual Lab

Go to: http://learn.genetics.utah.edu/content/labs/microarray/

1. What is genomics? How does microarray technology make genomics possible?
Genomics is the way to study many genes all at once. Microarray technology is the tool used to obtain the gene expression profile from DNA.

2. What does a microarray really do?
With a microarray chip scientists can pinpoint all the different types of gene expression between cells.

3. List the steps involved in using microarray analysis to identify which genes are "on" in a tissue or cell sample.

1. Collect tissue, 2. Isolate RNA, 3. Isolate mRNA, 4. Make labeled DNA copies, 5. Apply DNA,
6. Scan microarray, 7. Analyze data

4. What are DNA Microarrays made up of?
A DNA microarray is made up of thousands of spots which each spot contains multiple copies of a unique DNA sequence which corresponds to a single gene.

5. Why do scientists perform protein expression analysis?
To compare the differences in gene expression among different cells

6. What makes a cancer cell different from a normal cell?
The gene expression on or off by measuring the production of mRNA

7. What does reverse transcriptase do?
Those are enzymes that will synthesize a strand of complementary DNA (cDNA). It assembles the nucleotides to form a complementary strand of DNA.

8. What do we call hybridization?
Is when two complementary DNA strands from different sources can pair with one another

9. What does the computer database list when using microarray technology?
Our computer lists which gene is contained in each spot.

10. What do the red, yellow and green spots show on the microarray image results?
The red are cancer genes, the green are healthy genes and the green and red hybridized.

11. Which color of spots would you be interested in if you were looking for evidence of cancer genes?
The red color strands or color indicator.

12. Which gene is "**turned up"** in cancer cells?
The red spots show genes that produce more mRNA in the cancer cells than in healthy cells.

13. How can researchers know if a gene is producing protein?
Scientists rely on a technique called protein expression analysis to tell them if the mRNA is being translated into protein.

14. Explain the use of DNA microarray analysis.
DNA microarray analysis is a power tool that can identify genes that are expressed differently in two different cell types by comparing every single gene in a single experiment.

DNA Microarray Simulation – Wet Lab

DNA Microarray Technology

There is a new technology, called a **DNA microarray (chip)**, which allows scientists to efficiently measure the expression of thousands of genes at the same time by looking at the amount of RNA that is transcribed from those genes. A DNA microarray is a plastic chip or glass slide that has been "printed" (spotted at precise locations) with thousands of short, single-stranded pieces of DNA for known genes. For example, if a researcher wants to study how changes in gene expression might lead to cancer (uncontrolled cell division). DNA microarray (chip) technology compares the messenger RNA produced in cancerous colon cells with the messenger RNA produced in normal colon cells. The researcher has access to both normal cells and cancerous cells from a patient who has colon cancer.

We will use a DNA Microarray (Chip) to determine which genes might

- Prevent drug effectiveness for treatment due variation in enzyme metabolism
- Cause obesity by the gene variations being expressed
- Cause cancer by the genes associated with cancer being turned ON or expressed

1. What is the purpose of using a microarray in the application of Pharmacogenetics?

Microarray Color Spot Interpretation

GENE DESCRIPTION	COLOR OF SPOT
A gene slightly induced	Light pink
A gene with mixed expression	Purple
A gene wasn't transcribed	Blank
A gene repressed	Blue
A gene was expressed (transcribed)	Deep Pink
A gene slightly repressed	Light Blue

Lab Procedure

Part 1: Prepare the simulated microarray slide

First, you will prepare your DNA microarray by spotting each of the six different gene sequences onto a glass slide. For real microarrays, scientists actually print thousands of microscopic DNA spots onto a slide, one spot for each gene they want to examine. Your spots will be much larger than those in a regular microarray, and you will be able to view them without specialized equipment.

1. Do not touch the surface of your slide (handle it only by the edges). Make sure you have your group number on the frosted labeling are of the slide.
2. Bring your labeled slide to the waterbath area.
3. Method 1: Using the dropper bottles, a carefully spot the appropriate gene solution onto each of the labeled spots of your slide. Be sure to place the correct DNA sequence in the correct spot and place the same amount on each spot. Once the spots are hardened and dry, your microarray has been successfully "printed" with the genes you are using related to the provided patient information or protocol.

Part 2: Hybridize your microarray with labeled cDNA

In a real microarray, the principle behind the hybridization step is as follows: You cannot see the color because the cDNA is very dilute. When added to the printed microarray slide, the labeled cDNAs in the solution will base pair with complementary DNA for each gene spotted onto the microarray. As each cDNA binds to the appropriate DNA spot on the slide, the labeled cDNA becomes concentrated in that spot, allowing them to be visualized by means of a sophisticated device.

Note: You must wear gloves and goggles. The hybridization solution contains 0.4M sodium hydroxide (NaOH), which is caustic and causes burns. Do not get it in your eyes, on your skin, or on clothing. If you feel an itching sensation, wash that area of your skin in plenty of running water. Be sure to wash your hands after the lab. If you get hybridization solution in your eyes, flood them with water and seek medical attention. Also seek medical attention if you ingest any solution.

4. Carefully drop 1-2 drops of "Hybridization Solution" from the dropper bottle onto each spot. Do not allow the dropper bottle to touch the DNA spots!

Part 3: Visualize your labeled microarray results (Each group has its own protocol)

5. Record your results by writing a description of the color of each spot or drawing the results below.

Part 4: Cleanup

6. Use a paper towel to wipe off the six spots on your slide. Rinse your slide in water and dry it using a paper towel. Wear gloves and eye protection; there is NAOH on the slide.

Part 5: Analysis of Results

GENES	MICROARRY SPOT COLOR	Interpret the expression or non-expression of each gene with possible outcome to the patient involved in the study

DNA Microarray Simulation – Wet Lab (Answer Key)

DNA Microarray Technology

There is a new technology, called a **DNA microarray (chip)**, which allows scientists to efficiently measure the expression of thousands of genes at the same time by looking at the amount of RNA that is transcribed from those genes. A DNA microarray is a plastic chip or glass slide that has been "printed" (spotted at precise locations) with thousands of short, single-stranded pieces of DNA for known genes. For example, if a researcher wants to study how changes in gene expression might lead to cancer (uncontrolled cell division). DNA microarray (chip) technology compares the messenger RNA produced in cancerous colon cells with the messenger RNA produced in normal colon cells. The researcher has access to both normal cells and cancerous cells from a patient who has colon cancer.

We will use a DNA Microarray (Chip) to determine which genes might

- Prevent drug effectiveness for treatment due variation in enzyme metabolism
- Cause obesity by the gene variations being expressed
- Cause cancer by the genes associated with cancer being turned ON or expressed

1. What is the purpose of using a microarray in the application of Pharmacogenetics?
DNA microarray analysis is a power tool that can identify genes that are expressed differently in two different cell types by comparing every single gene in a single experiment. In this way Pharmacogenetics utilizes the information to come up with treatment appropriate to the patient.

Microarray Color Spot Interpretation

GENE DESCRIPTION	COLOR OF SPOT
A gene slightly induced	Light pink
A gene with mixed expression	Purple
A gene wasn't transcribed	Clear (No change)
A gene repressed	Blue
A gene was expressed (transcribed)	Deep Pink
A gene slightly repressed	Light Blue

Lab Procedure

Part 1: Prepare the simulated microarray slide

First, you will prepare your DNA microarray by spotting each of the six different gene sequences onto a glass slide. For real microarrays, scientists actually print thousands of microscopic DNA spots onto a slide, one spot for each gene they want to examine. Your spots will be much larger than those in a regular microarray, and you will be able to view them without specialized equipment.

7. Do not touch the surface of your slide (handle it only by the edges). Make sure you have your group number on the frosted labeling area of the slide.
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Note: You must wear gloves and goggles. The hybridization solution contains 0.4M sodium hydroxide (NaOH), which is caustic and causes burns. Do not get it in your eyes, on your skin, or on clothing. If you feel an itching sensation, wash that area of your skin in plenty of running water. Be sure to wash your hands after the lab. If you get hybridization solution in your eyes, flood them with water and seek medical attention. Also seek medical attention if you ingest any solution.

10. Carefully drop 1-2 drops of "Hybridization Solution" from the dropper bottle onto each spot. Do not allow the dropper bottle to touch the DNA spots!

Part 3: Visualize your labeled microarray results (Each group has its own protocol)

11. Record your results by writing a description of the color of each spot or drawing the results below.

Part 4: Cleanup

12. Use a paper towel to wipe off the six spots on your slide. Rinse your slide in water and dry it using a paper towel. Wear gloves and eye protection; there is NAOH on the slide.

Part 5: Analysis of Results (Answers will vary due to different group protocols)

GENES	MICROARRY SPOT COLOR	Interpret the expression or non-expression of each gene with possible outcome to the patient involved in the study

DNA Microarray Simulation – Wet Lab Group Protocol

Group #1 – Gene Chart –This patient had a stint placed in his heart during his visit to the catheter lab and need a drug to keep his blood thin. In order for the patient to receive Clopidogrel the doctor needs to know if his genes will produce the metabolic pathway to activated the drug for effective use of the drug.

Microarray Spot Numbers	**Gene CYP2C19: This is the gene involved in the metabolism of xenobiotics in the body. It is involved in the metabolism of server important drugs like Clopidogrel for blood thinning. This drug is usually prescribed to patients with a stent. The variations below are the polymorphisms of the gene fund as DNA SNPs.**
1	*17 – High metabolizer which means dangerous side effects
2	*2 – Splicing defect which means non-functional in metabolizing a drug
3	*1 – No allelic variant which means normal gene
4	*3 – Non-functional gene in metabolizing a drug
5	*5 - Non-functional gene in metabolizing a drug
6	*4 - Non-functional gene in metabolizing a drug

Group #2 – Gene Chart - This patient had a stroke and needs an anticoagulant medication to keep her from getting another stroke in the future. In order for this patient to receive Warfarin the doctor needs to know if her genes will produce the metabolic pathway to activated the drug for effective use of the drug.

Microarray Spot Numbers	**Gene CYP2C9: Warfarin, an oral anticoagulant, is a racemic drug. *S*-warfarin, which is Three to five times more potent than *R*-warfarin, is primarily metabolized by CYP2C9.**
1	*1 – Normal Metabolizers
2	*2 – High metabolizer which means lower dosage of drug
3	*3 - High metabolizer which means lower dosage of drug

Group #3 – Gene Chart - This patient had a stint placed in her heart during his visit to the catheter lab and need a drug to keep his blood thin. In order for the patient to receive Clopidogrel the doctor needs to know if her genes will produce the metabolic pathway to activated the drug for effective use of the drug.

Microarray Spot Numbers	**Gene CYP2C19: This is the gene involved in the metabolism of xenobiotics in the body. Involved in the metabolism of several important drugs like Clopidogrel for blood thinning. The variations below are the polymorphisms of the gene fund as DNA SNPs.**
1	*1 – No allelic variant which means normal gene
2	*2 – Splicing defect which means non-functional in metabolizing a drug
3	*17 – High metabolizer which means dangerous side effects
4	*3 – Non-functional gene in metabolizing a drug
5	*5 - Non-functional gene in metabolizing a drug
6	*4 - Non-functional gene in metabolizing a drug

Group #4 – Gene Chart - This patient will have all four wisdom tooth pulled out and will need a pain medication to control the pain. In order for this patient to receive Codeine the doctor needs to know if his genes will produce the metabolic pathway to activated the drug for effective use of the drug.

Microarray Spot Numbers	**Gene CYP2D6: is involved in the metabolism of Codeine an opioid analgesic indicated for the relief of mild to moderately severe pain. There is substantial evidence linking *CYP2D6* genotype to variability in codeine efficacy and toxicity. Increased conversion to morphine in CYP2D6 ultrarapid metabolizers can result in toxic systemic concentrations of morphine even at lo codeine doses.**
1	**1/*1xN, *1/*2xN* – Ultrarapid metabolizer
2	**1/*1, *1/*2, *2/*2,*1/*41,*1/*4,*2/*5,*10/*10* - Extensive metabolizer
3	**4/*10, *5/*41* - Intermediate metabolizer
4	**4/*4, *4/*5, *5/*5,*4/*6* - Poor metabolizer

Group #5 – Gene Chart - This patient exhibits chronic depression on his last visit to the doctor. In order for the patient to receive an antidepressant drug like tricyclics the doctor needs to know if his genes will produce the metabolic pathway to activated the drug for effective use.

Microarray Spot Numbers	**Gene CYP2D6: Polymorphisms in *CYP2D6* affect the efficacy and safety of tricyclics, with some drugs being affected by CYP2D6 only, and others by both polymorphic enzymes. The use of tricyclics to treat psychological disorders has declined in part because of the occurrence of undesirable side effects. Although tricyclics are still used to treat depression, their main therapeutic use is often for pain management.**
1	**1/*1xN, *1/*2xN* – Ultrarapid metabolizer
2	**1/*1, *1/*2, *2/*2, *1/*9,*1/*41, *41/*41, *1/*5,*1/*4* - Extensive metabolizer
3	**4/*41, *5/*9, *4/*10* - Intermediate metabolizer
4	**4/*4, *3/*4, *5/*5, *5/*6* - Poor metabolizer

Group #6 – Gene Chart - This patient has high blood pressure of 120/80 and needs a drug to keep her blood pressure low. In order for this patient to receive a Beta Blocker drug the doctor needs to know if her genes will produce the metabolic pathway to activated the drug for effective use.

Microarray Spot Numbers	**Genes and Genetic Variants LYZ, YEATS4, NPPA, RENIN, ADD1 and GNB3: These genes are involved in hypertension. Bata blockers are among the most widely prescribed of all drug classes for hypertension and various other cardiovascular diseases, blocker therapy often produces variable responses among patients due to SNPs polymorphisms. This study is still experimental. No clinical approval has been obtained to use the finding yet due to lack of substantial evidence.**
1	ADD1 – No significant difference
2	LYZ – Yes significant difference
3	YEATS4 – Yes significant difference
4	NPPA – Yes significant difference
5	RENIN – Yes significant difference
6	GNB3 – Yes significant difference

Group #7 – Gene Chart - This patient wants to know if her new born baby boy will have a high change of suffering from obesity. This type of gene analysis is used entirely for prevention and not drug interaction. The gene expression involved with obesity will show any non-functional metabolic pathways that will lead to obesity.

Microarray Spot Numbers	**Genes MC4R, LEP and LEPR: Melancortin-4 receptor (MC4R), a gene expressed in the nervous system and involved in the regulation of food intake. A large number of mutations in MC4R have shown to be associated with obesity. LEP and LEPR both these genes are candidates for obesity because of their role in the regulation of body weight and fat mass in humans.**
1	LEPR – Non-functional
2	LEPR – No allelic variant
3	MC4R – Non-functional
4	MC4R – No allelic variant
5	LEP – Non-functional
6	LEP – No allelic variant

Group #8 – Gene Chart - This patient wants to know if she has a high probability of suffering from lung cancer. This type of gene analysis is used entirely for prevention and not drug interaction. The gene expression involved with cancer detection will show any non-functional metabolic pathways that will lead to cancer.

Microarray Spot Numbers	**Genes that may express lung cancer: The six genes below may play an important role in making cancerous cells.**
1	C4BPA – is part of the immune system to kill pathogens
2	ODC1 – Enzyme to promote cell growth
3	SIAT9 – Controls cell differentiation, growth and shape
4	FGG – Encodes the protein found in the blood to form clots
5	HBG1 – Encodes to form fetal hemoglobin which is then replaced by adult hemoglobin
6	CYP24 – Controls the levels of vitamin D3 and calcium

Gene Expression and Microarray Technology Test

1. Explain: How do genes express the information encoded in DNA?

2. Once we've determined if a gene is "on" or "off", how can we use that information?

3. Using a real life example, explain the pros and cons of using our gene expression information.

4. Describe the reasons obesity is considered a major health risk.

5. How the microarray technology works in providing genetic data?

6. Explain the relationship between pharmacogenetics and microarray technology.

7. Why do individuals respond differently to medications?

8. How can Pharmacogenomics reduce side effects and improve efficacy of medications?

9. How else might Pharmacogenomics personalize medicine?

10. How will Pharmacogenomics impact the drug development process?

Gene Expression and Microarray Technology Test (Answer Key)

1. Explain: How do genes express the information encoded in DNA?
The gene expression information is obtained when a gene is "on" and its protein or RNA product is being made.

2. Once we've determined if a gene is "on" or "off", how can we use that information?
The information we gather is what they call a gene expression profile which is used to determine if a person is at high risk of disease, drug efficacy and have a high chance of adverse reaction towards a drug.

3. Using a real life example, explain the pros and cons of using our gene expression information.
(Answers will vary)
The pros are many for example being able to use an effective therapy, avoid adverse reactions from a drug and disease prevention. The con is that we may hinder our life due to knowing too much about our future disease risks.

4. Describe the reasons obesity is considered a major health risk.
It can lead to heart disease, high blood pressure and diabetes, especially as people age. A complex medical condition, obesity is influenced by diet, exercise, metabolism - and genetics.

5. How the microarray technology works in providing genetic data?
A single microarray will have thousands of DNA sequences (fragments of genes) bound to it. Microarrays can be used to analyze targeted sequences of DNA and to measure relative levels of gene expression.

6. Explain the relationship between pharmacogenetics and microarray technology.
The microarray chip technology provides the gene expression profile for scientists to collect and analyze to apply the principles of pharmacogenetics.

7. Why do individuals respond differently to medications?
Individuals respond differently to medications due to variations in genotype and environmental factors.

8. How can Pharmacogenomics reduce side effects and improve efficacy of medications?
Pharmacogenomics will lead to diagnostic genetic tests that predict a patient's response to specific drugs, and match patients with effective and safe medications based on their genotype.

9. How else might Pharmacogenomics personalize medicine?
Pharmacogenomics will lead to personalized disease prevention strategies by using genetic tests to estimate a patient's risk of getting a particular disease.

10. How will Pharmacogenomics impact the drug development process?
By adding genetic data to the drug development process, pharmacogenomics will reduce the overall cost and time it takes to develop new medications.

Case Studies – Lesson # 3

TITLE: The Application of Pharmacogenetics in Real Life Situations

KEY QUESTION(S): What variants in a gene does this patient have? What is this patient's phenotype high/normal/low metabolizer? What dose of a drug, if any, or of another drug, will work best for a patient?

SCIENCE CONCEPTS: Gene expression, genomics, drug metabolism, and microarray technology

OVERALL TIME ESTIMATE: This lesson requires one class period of 50 minutes

LEARNING STYLES: Visual, auditory, and kinesthetic.

VOCABULARY:

Asthma: A respiratory condition marked by spasms in the bronchi of the lungs, causing difficulty in breathing. It usually results from an allergic reaction or other forms of hypersensitivity.

Cardiovascular disease: refers to any disease that affects the cardiovascular system, principally cardiac disease, vascular diseases of the brain and kidney, and peripheral arterial disease.

Chemotherapy: is a type of cancer treatment that uses drugs to destroy cancer cells.

Diabetes: often referred to by doctors as **diabetes mellitus**, describes a group of metabolic diseases in which the person has high blood glucose (blood sugar), either because insulin production is inadequate, or because the body's cells do not respond properly to insulin, or both.

DNA Microarray: A small solid support, usually a membrane or glass slide, on which sequences of DNA are fixed in an orderly arrangement. DNA microarrays are used for rapid surveys of the expression of many genes simultaneously, as the sequences contained on a single microarray can number in the thousands. Also called *DNA chip*.

Gene: Chemical factor that determines traits.

Gene Expression: is the process by which information from a gene is used in the synthesis of a functional gene product. These products are often proteins, but in non-protein coding genes such as rRNA genes or tRNA genes, the product is a functional RNA.

Genetics: is the study of heredity. Heredity is a biological process where a parent passes certain genes onto their children or offspring.

Genomics: is the study of the genomes of organisms. The field includes intensive efforts to determine the entire DNA sequence of organisms and fine-scale genetic mapping efforts.

Haplotype: is a group of genes, which is inherited together by an organism from a single parent.

Meningitis: is a serious inflammation of the **meninges**, the thin, membranous covering of the brain and the spinal cord.

Mutation: is a change of the nucleotide sequence of the genome of an organism, virus, or extra chromosomal genetic element.

NCBI: National **C**enter for **B**iotechnology **I**nformation – advances science and health by providing genomic information. http://www.ncbi.nlm.nih.gov/

Obesity: is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life.

Personalized Medicine: an approach to the practice of medicine that uses information about a patient's unique genetic makeup and environment to customize the patient's medical care to fit his or her individual requirements

Pharmacogenetics: is a science that examines the inherited variations in genes that dictate drug response and explores the ways these variations can be used to predict whether a patient will have a good response to a drug, a bad response to a drug, or no response at all.

Pharmacogenomics: Uses large groups of patients to evaluate how candidate drugs interact with a range of genes and their protein products.

Pharmacokinetics: the action of drugs in the body over a period of time, including the processes of absorption, distribution, localization in tissues, biotransformation, and excretion.

Polymorphism: is a DNA sequence variation that is common in the population. In this case no single allele is regarded as the standard sequence.

Proteins: A linear polymer built from approximately 20 different amino acid types. The type and sequence of these amino acids are specified by the DNA, this sequence also determines shape and function of the protein.

SNP: A Single Nucleotide Polymorphism. They are single-nucleotide substitutions of one base for another.

LESSON SUMMARY:

Lesson # 3: The lesson is based on six different **case studies** related to pharmacogenetics, diagnosis and treatment of disease.

STUDENT LEARNING OBJECTIVES WITH NEXT GENERATION SUNSHINE STATE STANDARDS:

1. Students will be able to understand how individual genetic variation can impact medical practice and clinical outcomes.
2. Students will be able to analyze data based on gene expression for patient drug treatment and preventive medicine.

NEXT GENERATION SUNSHINE STATE STANDARDS (NGSSS)
(http://www.nextgenscience.org/next-generation-science-standards)

SC.912.L - 14.6, 15.15, 16.2, 16.3, 16.4, 16.5, 16.6, 16.8, 16.9, 16.10, 16.11, 16.12, 18.1, 18.4, 18.11
SC.912.N - 1.1, 1.3, 1.4, 1.5, 1.6, 1.7, 2.4
HE.912.C – 1.3, 1.5, 1.7

COMMON CORE STANDARDS (http://www.corestandards.org/)

LACC.910.RST – 1.3, 2.4, 3.8
LACC.901.WHST – 1.1e, 3.9
LACC.910.SL – 1.1b, 2.4,

MATERIALS and ESSENTIALS:

- 6 Different case studies in the area of pharmacogenetics (6 Groups of 4)
- 25 copies of the UF PMP Brochure

BACKGROUND INFORMATION:

In order for the teacher to understand the information presented in this lesson it would be helpful to go over each case study to understand them. The case studies presented here are fictitious scenarios, but are based upon clinical observations. This section will offer a brief understanding of the concepts addressed in the lesson.

The eight case studies presented here investigates the applications of genetics to medicine. Specifically, the case explores one of the first examples of a pharmacogenetic test to enter mainstream clinical practice. The discipline of pharmacogenetics examines how genetic variations in an individual correlate with their responses to a specific medication. The ultimate goal of pharmacogenetics is to develop medical treatments tailored to the individual. Through a brief fictional scenario, students are introduced to the disease involved (acute lymphocytic leukemia) as well as the wide range of individual responses to the drug used to treat it. Students then interpret data similar to those initially published in scientific journals in order to construct an understanding of how genetic variation can be used to "tailor" medical care. Finally, students are asked to apply their understanding of the case material by making the appropriate medical recommendation based on a particular individual's genotype.

ADVANCE PREPARATION:

The teacher needs to read all the provided resources and have the case studies copied for each group member.

PROCEDURE AND DISCUSSION QUESTIONS WITH TIME ESTIMATES:

1. (8 min) Using the questions that follow go over with the class the goal of pharmacogenetics and the genome project. How has the genome project completion in 2001 changed our understanding about patient care? What is the major application of the knowledge we have obtained from the genome project? What do we see happening in the future in terms of patient care?

2. (15 min) Make sure all group members have a copy of their own group case study and one blank paper to place their answers. Provide each student with a PMP Brochure from the UF. Have students read the case study and answer the questions. The PMP brochure is on a PDF file.

3. (15 min) After they have written their answers, ask students to share them with the whole class as an informal presentation.

4. (10 min) Discuss the answers with the whole class.

ASSESSMENT SUGGESTIONS:

1. Students will be able to understand how individual genetic variation can impact medical practice and clinical outcomes.

This objective will be assessed informally by group engagement and discussion.

2. Students will be able to analyze data based on gene expression for patient drug treatment and preventive medicine.

This objective will be assessed by a formative assessment based on the answers to the case study assigned to each group.

EXTENSIONS:

ACTIVITIES:

Pharmacogenetics of antipsychotic adverse effects: Case studies and a literature review for clinicians
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2656342/

Pharmacogenetics Using Genetics to Treat Disease
http://sciencecases.lib.buffalo.edu/cs/collection/detail.asp?case_id=247&id=247

LITERATURE:

Bioethical Issues
http://www.nwabr.org/education/primer.html

Pharmacogenetics
http://www.aapspharmsci.org/view.asp?art=ps/2/+/8

Royal Society (2005). *Personalised medicines: hopes and realities*. Royal Society: London.

RESOURCES/REFERENCES:

Pharmacogenetics Using Genetics to Treat Disease
http://sciencecases.lib.buffalo.edu/cs/collection/detail.asp?case_id=247&id=247

Pharmacogenetics Case Studies

Each group will receive a different case study to analyze with their partners. As a group the answers will be recorded by one student from each group on a separate paper. At the end of the time allotted each group will have a reader and a presenter to share their case findings.

Group 1 – Case Study

JS is a 35 year-old man who has recently been diagnosed as HIV positive. Before initiating abacavir anti-retroviral therapy, his physician orders genetic testing to determine whether he carries the *HLA-B*5701* allele, knowing that JS would develop fever, rash, nausea and fatigue if he carried the variant allele. The test confirmed that JS carries the *HLA-B*5701* allele.

How did genetic testing help JS and his physician?

Group 2 – Case Study

DS is a 30 year-old woman who gave birth by caesarian section 10 days ago. Her physician prescribed codeine for post-caesarian pain. Despite taking no more than the prescribed dose, DS experienced nausea and dizziness while she was taking codeine. She also noticed that her breastfed infant was lethargic and feeding poorly. When DS mentioned these symptoms to her physician, he recommended that she discontinue codeine use. Within a few days, both DS's and her infant's symptoms were no longer present.

How would genetic testing help DS and her physician?

Group 3 – Case Study

JM is a 58 year-old man who recently had an acute myocardial infarction. To prevent subsequent ischemic events, JM's physician recommends antiplatelet therapy and prescribes clopidogrel. Six months later, JM suffered another acute MI, and his physician suspects that the patient has been non-adherent, or alternatively, that clopidogrel therapy may have been ineffective.

How would genetic testing help JM and his physician?

Group 4 – Case Study

ML is a 65 year-old woman who has recently been diagnosed with atrial fibrillation. To reduce the risk of stroke and other thrombotic events, ML's physician recommends warfarin therapy. To estimate the initial dose, ML's clinical characteristics (age, sex, weight, diet) were considered. However, ML will need to return to the clinic every day for INR monitoring until a stable dose is determined, and then every few weeks thereafter for maintenance monitoring.

How would genetic testing help ML and her physician?

Group 5 – Case Study

'I think I'm a bit negative there because when my daughter was doing poorly health wise, the doctor said to me, "You are just an over-reactive parent. You're being very silly. Stick to the medication and in 12 hours she'll be coming round." But 12 hours later she was in a seizure. So it was like, who do you trust? … I do trust doctors, don't get me wrong … I just think doctors need to be a bit more sympathetic where children are concerned. I mean they don't have a lot of research on meningitis. They're not that powerful where they can say, "Oh yeah, you've got meningitis." A parent has got to look for it. So the first signs has got to be from the parent, so for a doctor to tell you that you are over reacting then it's like, hang on a minute, I'm not over reacting here there's something wrong. So it was like a conflict then between the person and the doctor, which it was with me. But I have got over that because I got my daughter back. If I hadn't got my daughter back I'd been very angry'.

How would genetic testing help the patient and the physician?

Group 6 – Case Study

In general, drug and medical development was viewed as fundamentally beneficial and as having transformed society over the past century. However, there were concerns that drugs were currently dispensed far too easily in society, and social and institutional norms facilitated this process as a 'quick fix for the patient, a quick fix for the general population and a quick fix for the pharmaceutical company' (Male, 55+, White, C2DE, Oxford). The tension between systems for efficient treatment and the impact on the needs of an individual was highlighted in terms of prescription drugs. 'When you go to a doctor, you're one of 10,000 in a group practice. And those doctors have agreed what drugs they like – you know – from what is available, so they give it to you and you are a group person. So that man with asthma and that man with diabetes – we are just a group; we are not individuals, were only a group of people who need penicillin or hypertension drugs. And like with me. He didn't give me more than ten minutes – my doctor – I hadn't seen him for three years and he just said – asthma – here's your prescription, go see the nurse. He did not want to say, well do you do this, or do you do that, or let's try this'.

How would genetic testing help the patient and the physician?

Pharmacogenetics Case Studies (Answer Key)

Each group will receive a different case study to analyze with their partners. As a group the answers will be recorded by one student from each group on a separate paper. At the end of the time allotted each group will have a reader and a presenter to share their case findings.

Group 1 – Case Study

JS is a 35 year-old man who has recently been diagnosed as HIV positive. Before initiating abacavir anti-retroviral therapy, his physician orders genetic testing to determine whether he carries the *HLA-B*5701* allele, knowing that JS would develop fever, rash, nausea and fatigue if he carried the variant allele. The test confirmed that JS carries the *HLA-B*5701* allele.

How did genetic testing help JS and his physician? (Answers will vary)
Knowing that JS carried the *HLA-B*5701* variation indicated that he would likely experience a hypersensitivity reaction. JS's physician will probably not include abacavir in his antiretroviral regimen.

Group 2 – Case Study
DS is a 30 year-old woman who gave birth by caesarian section 10 days ago. Her physician prescribed codeine for post-caesarian pain. Despite taking no more than the prescribed dose, DS experienced nausea and dizziness while she was taking codeine. She also noticed that her breastfed infant was lethargic and feeding poorly. When DS mentioned these symptoms to her physician, he recommended that she discontinue codeine use. Within a few days, both DS's and her infant's symptoms were no longer present.

How would genetic testing help DS and her physician? (Answers will vary)
Genotyping of DS's *CYP2D6* gene may have revealed a duplication of *CYP2D6* genes, placing her in the ultra-rapid metabolizer category. Armed with this knowledge, DS's physician would likely have prescribed a different analgesic that would have spared DS and her infant the symptoms of opioid toxicity.

Group 3 – Case Study
JM is a 58 year-old man who recently had an acute myocardial infarction. To prevent subsequent ischemic events, JM's physician recommends antiplatelet therapy and prescribes clopidogrel. Six months later, JM suffered another acute MI, and his physician suspects that the patient has been non-adherent, or alternatively, that clopidogrel therapy may have been ineffective.

How would genetic testing help JM and his physician? (Answers will vary)
Determining JM's *CYP2C19* genotype may reveal that he carries a variant that diminishes the antiplatelet effect of clopidogrel. If this were the case, alternative anti-platelet therapies may have been considered, reducing the chance that JM would suffer a second cardiac event.

Group 4 – Case Study
ML is a 65 year-old woman who has recently been diagnosed with atrial fibrillation. To reduce the risk of stroke and other thrombotic events, ML's physician recommends warfarin therapy. To estimate the initial dose, ML's clinical characteristics (age, sex, weight, diet) were considered. However, ML will need to return to the clinic every day for INR monitoring until a stable dose is determined, and then every few weeks thereafter for maintenance monitoring.

How would genetic testing help ML and her physician? (Answers will vary)
Determination of ML's *CYP2C9* and *VKORC1* genotype would reveal whether she carries any variations that alter her ability to metabolize and respond to warfarin. Knowing about any gene variations before initiating therapy

allows for more accurate initial dosing and faster INR stabilization, and can reduce the risk for bleeding or clotting events.

Group 5 – Case Study

'I think I'm a bit negative there because when my daughter was doing poorly health wise, the doctor said to me, "You are just an over-reactive parent. You're being very silly. Stick to the medication and in 12 hours she'll be coming round." But 12 hours later she was in a seizure. So it was like, who do you trust? … I do trust doctors, don't get me wrong … I just think doctors need to be a bit more sympathetic where children are concerned. I mean they don't have a lot of research on meningitis. They're not that powerful where they can say, "Oh yeah, you've got meningitis." A parent has got to look for it. So the first signs has got to be from the parent, so for a doctor to tell you that you are over reacting then it's like, hang on a minute, I'm not over reacting here there's something wrong. So it was like a conflict then between the person and the doctor, which it was with me. But I have got over that because I got my daughter back. If I hadn't got my daughter back I'd been very angry'.

How would genetic testing help the patient and the physician? (Answers will vary)

A genetic test would make it easier for the doctor to find the cause of the abnormal symptoms displayed by the patient providing the patient with a rapid diagnosis and trust in the treatment provided. It will also provide the gene and SNP that is the variant to be able to administer the patient with the best medication appropriate to the patient's metabolic rate and efficiency. The physician will benefit by having an easy test to find out the genetic variants that would indicate disease and the type of treatment based on the patients' unique genetic make-up.

Group 6 – Case Study

In general, drug and medical development was viewed as fundamentally beneficial and as having transformed society over the past century. However, there were concerns that drugs were currently dispensed far too easily in society, and social and institutional norms facilitated this process as a 'quick fix for the patient, a quick fix for the general population and a quick fix for the pharmaceutical company' (Male, 55+, White, C2DE, Oxford). The tension between systems for efficient treatment and the impact on the needs of an individual was highlighted in terms of prescription drugs. 'When you go to a doctor, you're one of 10,000 in a group practice. And those doctors have agreed what drugs they like – you know – from what is available, so they give it to you and you are a group person. So that man with asthma and that man with diabetes – we are just a group; we are not individuals, were only a group of people who need penicillin or hypertension drugs. And like with me. He didn't give me more than ten minutes – my doctor – I hadn't seen him for three years and he just said – asthma – here's your prescription, go see the nurse. He did not want to say, well do you do this, or do you do that, or let's try this'.

How would genetic testing help the patient and the physician? (Answers will vary)

In this case the patient feels that the treatment the physician provides today is impersonal and geared to the general population without concerns of the uniqueness of a person. Pharmacogenetics under personalized medicine tailors the medication or treatment to the patient's unique genetic makeup. The physician will benefit from using pharmacogenetics by getting a better understanding of the individual patients' needs based on their genetics and metabolic pathway.