FACULTY RESOURCE CASE GUIDE

CASE: STEPHANIE

CASE DESCRIPTION:

Stephanie is a 25-year old divorced African American mother of two girls who presents to the otolaryngologist with her boyfriend and her two children for discussion about the upcoming tonsillectomy for Queisha, her 6-year old daughter. Stephanie is very concerned about post-op pain management for Queisha given that her 8-year old daughter, Kiona, had a severe adverse reaction to codeine when she had her tonsils out two years ago. Stephanie is learning about pharmacogenomics in nursing school and feels that Queisha should have pharmacogenomic testing for codeine response prior to her tonsillectomy. Stephanie believes that this testing will help inform Queisha's post-operative pain management.

CASE OBJECTIVES:

- Identify the ethical, legal and psychosocial issues associated with using a pharmacogenomic test.
- Identify the ethical, legal and psychosocial issues associated with genetic testing in children.
- Identify applicable guidelines to provide recommended best care options related to pharmacogenomic testing.
- Explain cytochrome P450 enzyme nomenclature.
- Describe the various polymorphism types and impact on pharmacokinetics (PK) and pharmacodynamics (PD)
- Define the following pharmacogenomic codeine phenotypes based on CYP genotype: ultrarapid metabolizers, extensive metabolizer, intermediate metabolizer, poor metabolizer.
- Explain the ethnic variation of CYP2D6 ultrarapid metabolizers.
- Explain the value of interdisciplinary team consultation related to pharmacogenomic testing.
- Describe the current evidence regarding using genetic information for determining codeine drug dosage.
- Explain how to identify a laboratory that offers pharmacogenomic tests.
- Describe the Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for codeine use based on CYP2D6 genotype.
- Formulate a plan for post tonsillectomy and adenoidectomy pain management.
- Identify resources that support educational content on pediatric pain control.

SUGGESTIONS FOR HOW TO USE G3C:

This is a clinical encounter of Stephanie, a 25-year old African American nursing student who presents to the otolaryngologist with concerns about post-op pain management for her 6-year old daughter Queisha, because her 8-year old daughter, Kiona, had a severe adverse reaction to codeine post-tonsillectomy two years ago. Stephanie is also inquiring about pharmacogenomic testing for codeine response as a means to help guide Queisha's post-operative pain management.

The learner should be instructed to enter the virtual clinic and begin by reviewing the case materials located in the client's folder. When ready, the learner progresses to the client encounter and begins by selecting a question to ask the client from the list provided. Additional learner activities associated with the learner-selected questions are located below the client video. Supplementary case materials including those that the healthcare provider gathers during the encounter are identified by icons in the box to the right and can be viewed at any time during the case review. To gain further perspective on the case topic, the learner should also view the video commentary provided by an expert in the topic presented.

SUGGESTED SUPPLEMENTAL STUDENT ACTIVITIES:

Pedigree Construction

- Construct a three generation pedigree for Queisha using My Family Health Portrait. Since you only were provided with minimal information about the family, use your imagination to add in appropriate ages for Queisha's parents (Stephanie and her ex-husband) and to add in her maternal and paternal grandparents, and any aunts and uncles and cousins you choose to give her for relatives. Include any information provided in the case regarding response/reaction to codeine or other drugs.
- Report if and why you think that one lineage (maternal or paternal side of the family) is more likely to increase Queisha's risk for an adverse reaction to codeine than the other lineage.
- Draw your own family history using standard pedigree nomenclature.

References:

Bennett, R. et al. (2008). Standardized Human Pedigree Nomenclature: Update and Assessment of the Recommendations of the National Society of Genetic Counselors. Journal of Genetic Counseling, 17, 424–433.
http://www.ncbi.nlm.nih.gov/pubmed/18792771

Surgeon General's Family History Tool
http://www.hhs.gov/familyhistory/

Although this tool can be used by health care providers, the primary purpose is for an individual to create a family history diagram based on their own family history. The health information and family history questions use lay language and are asked in the format one asks of an individual. For example, "How many sisters do you have?" The learner should answer the questions from the perspective of the person in the case study. For "Date of Birth" on the initial screen, subtract the age of the individual in the case study from the current year to determine the year of birth and use 01/01 for the day and month of the individual's birth. Unless stated otherwise, assume that all ages are in years, all relatives are full blood relatives (e.g., no half-siblings), and that no one is adopted, has a biological twin, or

has parents who are related to each other than by marriage.

Pharmacogenomics

- Name three other pain control drugs in addition to codeine whose efficacy may be affected by one's CYP2D6 genotype.
- Discuss the FDA warning on codeine associated with breastfeeding by an ultra-metabolizer mother, including what you would tell a nursing mother about signs of morphine overdose.
- What precautions should be taken for pain control in children with obstructive sleep apnea?
- Explain how being an ultra-rapid metabolizer affects the blood level of morphine after taking a typical dose of codeine.
- What ethnic group has the highest prevalence of ultra-rapid metabolizers?
- If Queisha and her sister were Asian instead of African American, how might this influence the likelihood of an adverse drug reaction due to CYP2D6 metabolism?

References:

Sadhasivam S, Chidambaran V. Pharmacogenomics of opioids and perioperative pain management. Pharmacogenomics. 2012 Nov;13(15):1719-40. Review. http://www.ncbi.nlm.nih.gov/pubmed/23171337 (Comment: Although a difficult read for non-genetics professionals, this article is recommended because it also contains more easily understood information about pharmacogenomics and opioid pain management, particularly if the following two FDA references are read first.)

U.S . FDA Warning on Codeine Use by Nursing Mothers. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108968.htm

U.S. FDA Drug Safety Communication: codeine use in certain children after tonsillectomy and/or adenoidectomy may lead to rare, but life threatening adverse events or death. www.fda.gov/drugs/drugsafety/ucm313631.htm

- For a fun, fast, and informative exercise, choose a CYP2D6 genotype for yourself from *1 through *21 (e.g., *1/*2, *19/*1, *8/*14). Use your chosen genotype in the Clinical Pharmacogenetics Implementation Consortium (CPIC) reference below. What does tell you about your chosen genotype and phenotype, response to codeine, and care recommendations? What is the strength of the recommendation? Do you agree? Why or why not? Try this exercise with other genotypes to see how the information changes. Continue until you find at least one ultrarapid, extensive, intermediate, and poor metabolizer combination.

Reference:

CPIC Dosing Guideline for codeine and CYP2D6 http://www.pharmgkb.org/drug/PA449088

SUGGESTED CLASSROOM DISCUSSION POINTS:

1. Codeine is a commonly used opioid analgesic to manage postoperative pain, given as a single medication or in combination with acetaminophen (Tylenol with codeine).
2. Codeine is frequently used for post-operatively pain control in children older than 2 years of age, however genetic and non-genetic factors and the narrow therapeutic range of codeine and other opioids contribute to the problem of inadequate pain control.
3. Codeine is a prodrug: it must be converted to its active metabolite, morphine, to enable pain control. This conversion occurs primarily through the cytochrome P450 (CYP450) enzyme CYP2C6.
4. CYP450 is a complex of more than 40 liver enzyme families (e.g., CYP2D6, CYP3A4, CYP2C9): the CYP1, CYP2, and CYP3 families are important in the metabolism of many drugs. The terms 'enzyme' and 'gene' are often used interchangeably when referring to CYP450.
5. The nomenclature of cytochrome P450 enzymes (e.g., CYP2D6*1) is:
    a. First set of letters and numbers identify the specific gene family (CYP2), subfamily (D), and polypeptide (6).
    b. followed by a number represents variations in the gene that may influence enzyme activity and thus drug metabolism (e.g., *2; pronounced "star 2").
    c. Metabolic function varies based on the specific variation (*2, *3, etc.).
    d. The function of a specific variation is enzyme specific, i.e., the CYP2D6 *2 variant confers
6. An individual's ability to convert codeine to morphine depends on his/her CYP2D6 metabolic status (*genotype*; e.g., *1/*1 or *1/*2 confer the *phenotype* of extensive [normal] metabolism). This conversion does not occur in poor metabolizers (PMs), thus PMs will not get pain relief but may still experience an adverse drug reaction (ADR) from taking codeine. As much as 10% of children prescribed codeine in the U.S. are predicted to have a PM phenotype.
7. Ultra-rapid metabolizers (UMs) convert codeine to morphine too quickly resulting in toxic levels of morphine even at low doses of codeine and risk for a severe or fatal ADR. The actual risk of having an ADR for UMs is not known.
8. ADRs are defined as any untoward medical occurrence associated with a medication prescribed at the recommended dose.
9. Deaths have been reported in UMs given codeine for pain management post-tonsillectomy and/or adenoidectomy for obstructive sleep apnea. As such, on 8/15/2012, the U.S. Food and Drug Administration (FDA) published a safety communication titled: Codeine use in certain children after tonsillectomy and/or adenoidectomy may lead to rare, but life-threatening adverse events or death.
10. On 2/20/13, the FDA updated the safety communication to a new Black Box Warning and Contraindications related to codeine use, noting that codeine is no longer recommended for pain control in children undergoing a tonsillectomy and/or adenoidectomy.
11. The prevalence of impaired CYP2D6 metabolic genotypes varies by race and ethnicity and is estimated to be <1 in 100 individuals to as much as 28 in 100 individuals. However, genetic admixture, - the increasing mixing of different races/ethnicities, particularly in the U.S., has changed the genetic make-up of various populations (e.g., African Americans may have 20-25% European ancestry), which influences how a person responds to codeine and other drugs. Greater genetic variation is found among U.S. Hispanics, dependent upon the country of

ancestral origin and residence area in the U.S.; this too has important implications for pharmacogenomic testing and use of opioids for post-op pain control. As such, decisions regarding pharmacogenomic testing based on ancestry information are inadequate.

12. The gene for the CYP2D6 enzyme (also denoted as CYP450 2D6) influences how codeine and other drugs are metabolized: two CYP2C6 variants known as *1 and *2 (pronounced "star one," "star two") are the most common active (functioning) variants associated with normal codeine metabolism. Dozens of other variants are partially active (e.g., *9) or inactive (e.g., *3) and thus are associated with impaired (reduced or nonfunctioning) codeine metabolism.
13. Individuals inherit various forms of genes from their parents. An individual's genotype does not change over one's lifetime, but interactions with other genes, non-genetic factors, and acquired genetic changes can influence the expression of one's genotype. For instance, CYP2D6 metabolism and elimination may be affected by drug interactions; drugs that inhibit CYP2D6 can result in extensive metabolizers functioning as intermediate metabolizers or poor metabolizers. Dosing and adherence are other key factors in drug efficacy and ADRs.
14. Because the CYP2D6 genotype for normal (extensive) metabolism overlaps with that of the ultrarapid metabolizer, it is possible for a person with normal genotype (e.g., *1/*1) to experience an ADR – this has important implications for clinical care since it should not be assumed that a person with a normal genotype is not at risk for an ADR.
15. CYP450 variants are also commonly referred to as polymorphisms, single nucleotide polymorphisms (SNPs; pronounced "snips"), mutations, or alleles (referring to a different [alternate] copy of a gene, such as the gene for type A blood vs. the gene for type B blood, or the gene for blue eyes vs. the gene for brown eyes).
16. Genetic testing to identify one's genotype is typically performed on a blood sample or a buccal (cheek) swab.
17. Purpose of the U.S. National Institutes of Health (NIH) Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Pharmacogenomics Knowledge Base (PharmGKB) websites: to provide peer-reviewed, clinically relevant information about human genetic variation influencing drug response (periodically updated literature reviews/summaries, guidelines, FDA labels, etc.; http://www.pharmgkb.org)
18. The Clinical Pharmacogenetics Implementation Consortium (CPIC) has published guidelines to assist clinicians in clinical decisions based on CYP2D6 genotype (i.e., dosing adjustments or use of another drug not affected by the CYP2D6 pathway). The goals of genotype-guided codeine use are to provide optimal pain control while minimizing the risk of severe adverse drug reactions including death.
19. Purpose of the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative: to provide evidence-based assessment of and recommendations for genomic technology including that of genetic tests, to support translation from research to clinical practice.
20. Psychological or ethical, legal, social implication (ELSI) related to pharmacogenomic testing: the potential for discrimination in health insurance or employment and other concerns such as stigmatization have been of concern tests that identify disease risk (e.g., for cancer) or unexpected or incidental findings (e.g., risk for Alzheimer's disease). In the U.S., the Genetics Information Non-Discrimination Act (GINA) of 2008 was enacted to at least partially address these concerns. GINA does not apply to persons receiving care through the military health system, the veteran's administration system or the Indian Health Service because the laws amended by GINA are not applicable to these entities. In contrast to other genetic/genomic

tests, CYP testing provides information related to drug efficacy and safety, with little, if any, implication for disease risk and the associated ethical, legal, or social concerns.

SUGGESTED READINGS AND RESOURCES:

Codeine Use

Clinical Practice Guidelines

Baugh, R.F. et al. and the American College of Otolaryngology and Head and Neck Surgery: Tonsillectomy in Children Guidelines (2011). Clinical practice guideline: tonsillectomy in children. Otolaryngology- Head and Neck Surgery. 144(1 Suppl):S1-30.
http://www.ncbi.nlm.nih.gov/pubmed/21493257

Crews, K.R. et al. (2012). Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Codeine Therapy in the Context of Cytochrome P450 2D6 (CYP2D6) Genotype. Clinical pharmacology & Therapeutics, 9(2), 321-326. |
http://www.ncbi.nlm.nih.gov/pubmed/22205192

FDA Guidance on Codeine Use in Children

FDA codeine information
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm118108.htm

FDA codeine 08/2012 Safety Communication
http://www.fda.gov/Drugs/DrugSafety/ucm313631.htm

FDA codeine 02/2013 Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy
http://www.fda.gov/Drugs/DrugSafety/ucm339112.htm

FDA Drug Safety Podcast: Safety review update of codeine use in children
http://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm340524.htm

Kuehn, B.B. (2013). FDA: No codeine after tonsillectomy for children. JAMA, 309(11), 1100.
http://www.ncbi.nlm.nih.gov/pubmed/23512037

Toxicities Post Tonsillectomy

Ciszkowski, C., et al. (2009). Codeine, ultrarapid-metabolism genotype, and postoperative death. New England Journal of Medicine, 361(8), 827-8.
http://www.ncbi.nlm.nih.gov/pubmed/19692698

Kelly LE, et al. (2012). More codeine fatalities after tonsillectomy in North American children. Pediatrics. 2012 May;129(5):e1343-7
http://www.ncbi.nlm.nih.gov/pubmed/22492761

Codeine Metabolism

Eissing, T., et al. (2012). Pharmacogenomics of Codeine, Morphine, and Morphine-6-Glucuronide. Molecular Diagnosis and Therapy, 16 (1), 43-53.
http://www.ncbi.nlm.nih.gov/pubmed/22352453

Drug Bank codeine
http://www.drugbank.ca/drugs/DB00318

Kirchheiner, J., et al. (2007). Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. The Pharmacogenomics Journal, 7(4), 257-65.
http://www.ncbi.nlm.nih.gov/pubmed/16819548

Madadi, P., et al. (2008). Pharmacogenetic insights into **codeine** analgesia: implications to pediatric **codeine** use. **Pharmacogenomics,** 9(9):1267-84
http://www.ncbi.nlm.nih.gov/pubmed/18781855

Pharmacogenomics:

Crews KR, Gaedigk A, Dunnenberger HM, Klein TE, Shen DD, Callaghan JT, Kharasch ED, Skaar TC; Clinical Pharmacogenetics Implementation Consortium. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for codeine therapy in the context of cytochrome P450 2D6 (CYP2D6) genotype. Clin Pharmacol Ther. 2012 Feb;91(2):321-6. doi: 10.1038/clpt.2011.287. Epub 2011 Dec 28.
http://www.ncbi.nlm.nih.gov/pubmed/22205192

Additional Suggested Reading and Resources:

Pharmacogenomics Information

CYP Allele Nomenclature Database (for genetic counselors/advanced genetic learners)
http://www.cypalleles.ki.se

FDA Codeine Drug Safety Information
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm118108.htm

FDA Table of Pharmacogenomic Biomarkers in Drug Labels
http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm236284.htm

Frequently asked questions about Pharmacogenomics
www.genome.gov/27530645

Personalized Medicine (Pharmacogenomics)
http://learn.genetics.utah.edu/content/health/pharma

Pharmacogenomics Data Base (PharmGKB)
http://www.pharmgkb.org/

PharmGenEd
http://pharmacogenomics.ucsd.edu

PharmGKB, CPIC Dosing Guideline for codeine and CYP2D6
http://www.pharmgkb.org/drug/PA449088

Ethics and Informed Consent
Peterson-Iyer, K. (2008). Pharmacogenomics, Ethics, and Public Policy
http://www.scu.edu/ethics/practicing/focusareas/medical/pharmacogenomics.html

Pain Management
American Medical Association Update June 2013
http://www.ama-cmeonline.com/pain_mgmt/printversion/ama_painmgmt_m6.pdf

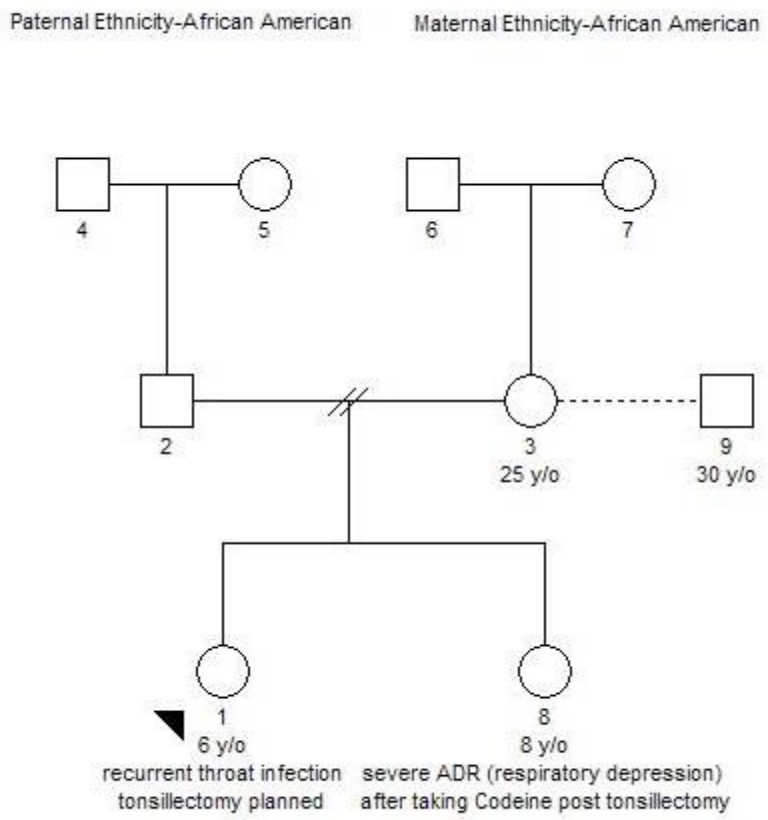
Medline Plus Codeine (free registration required)
http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682065.html

Patient Education Link
Post Surgery Codeine Puts Kids at Risk
http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm315497.htm

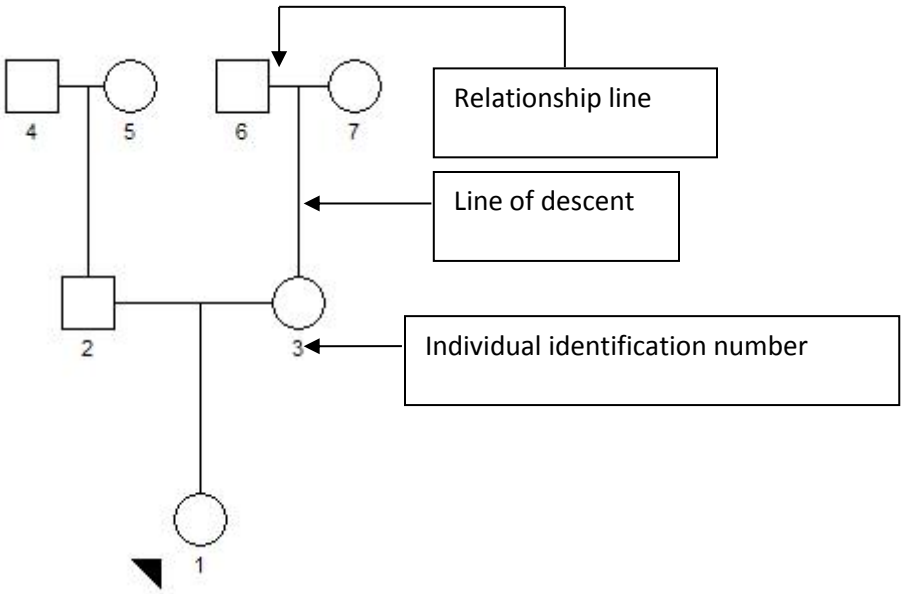
Codeine Overdose
http://www.nlm.nih.gov/medlineplus/ency/article/002613.htm

Queisha's Family History (as described in the case)
Queisha: age 6yrs, recurrent throat infections (11 this year), tonsillectomy planned. "Low pain tolerance" - given "baby Tylenol" after a fall requiring stitches in her leg last year; no ADR but ineffective pain control.
Mother: Stephanie, 25 yrs, divorced; felt "out of it" from one dose of Tylenol with codeine post-episiotomy after Kiona's birth; non-smoker, in nursing school. Baptist; active in her church, where her father (Queisha's maternal grandfather) is the Reverend and where she met her new boyfriend, Darrell, age 30, an EMT, who is present at the otolaryngologist appointment.
Father: age not provided; fractured left leg ~ 3years ago, took pain medication (NOS), pain control achieved, no ADR.
Siblings: one sister, Kiona, age 8yrs, severe ADR (respiratory depression requiring hospitalization) after taking codeine post-tonsillectomy at age 6 yrs.
Ethnicity:
Maternal: African American
Paternal: African American

Pedigree



Abbreviations for family history:
D. = died
COD = cause of death
y/o = years old
ADR = adverse drug reaction
NOS = not otherwise specified


4
5
6
7
2
3
1
Relationship line
Line of descent
Individual identification number