FACULTY RESOURCE CASE GUIDE

CASE: JENNIFER

CASE DESCRIPTION:

Jennifer is an otherwise healthy 27-year old flight attendant of Italian descent who presents to the local women's health clinic with a one month history of increasing right leg pain, cramping, and ankle swelling, which has become worse in the past few days, causing her to stop her usual routine of running 2 miles, 4 times a week. Vital signs (TPR/BP) are normal and she denies shortness of breath (SOB), chest pain/pressure, or coughing up blood (Pulmonary Embolism symptoms). Jennifer has taken an estrogen-containing oral contraceptive for nearly 7 years, reports smoking a few cigarettes weekly for the past 6 years, and recently began drinking 8 oz. of cranberry juice daily after having had two bladder infections last year. She does not take any other medications, has been healthy throughout her life, has never had any surgery or hospitalizations including any recent trauma/injury, and has no known drug or other allergies. She has no children, but expects to after she marries the man she has been dating for the past two years. She is from Washington D.C. and now lives in Los Angeles. Jennifer's family history is notable in that her 62-year old father had a blood clot a year ago and her 58-year old mother has hypertension, as does two of her three siblings, who are all males ages 60 to 64. Jennifer has one sibling, a brother age 24, who has always been healthy. Their father has three siblings, sisters ages 60, 63, and 65; all are healthy. Their paternal grandmother died of a stroke in her 70's and their paternal grandfather died of "heart or lung problems." The maternal grandparents are also deceased of "heart or lung problems." These relatives all lived into their 80's. There are no known health conditions in the many cousins on both sides of her family. Both sides of her family are Italian.

CASE OBJECTIVES:

- Identify 2 potential benefits of genetic testing related to VTE.
- Explain the Cytochrome P450 enzyme CYP2C9 and the enzyme VKORC1 in relation to warfarin metabolism and dosing.
- Discuss the evidence and professional guidelines for pharmacogenomic testing for CYP2C9 and VKORC1.
- Summarize the warfarin drug label warning regarding genetic variation in VKORC1 and CYP2C9.
- Describe factor V Leiden and other thrombophilias as a risk factor for VTE.
- Explain inheritance for factor V Leiden and how this influences thrombosis risk.
- State when you would suspect factor V Leiden.
- Identify evidence-based and other applicable guidelines related to factor V Leiden or other genetic/genomic testing for the case scenario described.
- Identify ethical, legal, and psychosocial implications (ELSI) associated with thrombophilia pharmacogenomics testing.

SUGGESTIONS FOR HOW TO USE G3C:

This is a clinical encounter of Jennifer, a 27-year old Italian female flight attendant who presents to the women's health clinic for evaluation of pain and cramping in her right leg and edema in her right ankle. She is concerned because her symptoms, which began about a month ago, have increased such that it is too painful to continue her usual routine of running four times a week for exercise.

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 Jennifer using My Family Health Portrait.
- Report if and why you think that one lineage (maternal or paternal side of the family) is more likely to increase Jennifer's risk for cardiovascular disease than the other lineage.
- Draw your own family history using standard pedigree nomenclature. Explain why it is important to use standard nomenclature and a systematic approach to obtaining family history information.

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.

Venous Thromboembolism

- Describe the two types of VTE: DVT and PE.
- What are the differences in assessing and diagnosing DVT vs. PE?
- What are the differences in health implications of DVT vs. PE?
- How is pregnancy related to VTE?
- How are unexplained recurrent pregnancy losses related to VTE?
- Watch the video introduced by the former U.S. Surgeon General Dr. Richard Carmona in the "This is Serious" website below and summarize what you have learned.

References:

Nutescu EA. Assessing, preventing, and treating venous thromboembolism: evidence-based approaches. Am J Health Syst Pharm. 2007 Jun 1;64(11 Suppl 7):S5-13. http://www.ncbi.nlm.nih.gov/pubmed/17519445

This is Serious is a national campaign developed by the Vascular Disease Foundation and the hospital network Spirit of Women, in partnership with the Centers for Disease Control and Prevention (CDC) and the Venous Disease Coalition (VDC).
www.thisisserious.org

Thrombophilias/Genetics

- Describe factor V Leiden, how it is inherited, and what it means in terms of risk for thrombosis.
- Now that you have learned about factor V Leiden and factor II (prothrombin), describe other inherited thrombophilias.
- Explain what is meant by heterozygous, homozygous, mutation, and wild type.
- For learners with at least basic genetic knowledge: Explain what is meant by being a double heterozygote for factor V Leiden and prothrombin 20210G>A.
- Discuss how genetic admixture might influence risk for factor V Leiden.

References:

Genetics Home Reference. http://ghr.nlm.nih.gov/condition/factor-v-leiden-thrombophilia

Genetics Talking Glossary. http://www.genome.gov/glossary/

Kujovich JL. Factor V Leiden Thrombophilia.In: Pagon RA, Adam MP, Bird TD, Dolan CR, Fong CT, Stephens K, editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2013. 1999 May 14 [updated 2010 Mar 9]. http://www.ncbi.nlm.nih.gov/pubmed/20301542; http://www.ncbi.nlm.nih.gov/books/NBK1368/

The U.S. National Cancer Institute (NCI) Dictionary of Genetic Terms.
http://www.cancer.gov/geneticsdictionary

Varga EA, Kujovich JL. Management of inherited thrombophilia: guide for genetics professionals. Clin Genet. 2012 Jan;81(1):7-17. doi: 10.1111/j.1399-0004.2011.01746.x. Epub 2011 Jul 25. http://www.ncbi.nlm.nih.gov/pubmed/21707594

Varga E. Inherited thrombophilia: key points for genetic counseling. J Genet Couns. 2007

Jun;16(3):261-77. Epub 2007 May 1
http://www.ncbi.nlm.nih.gov/pubmed/17473965

Warfarin Dosing

- Explain what is meant by warfarin INR values and how this affects clinical care.

Reference:
Coumadin® Tablets label
http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/009218s108lbl.pdf

Ethical, Legal and Social Implications (ELSI)

- What is the difference between clinical validity and clinical utility?
- What might be some ELSI concerns when considering genetic testing for inherited thromboses?

Reference:
Segal et al. Outcomes of Genetic Testing in Adults with a History of Venous Thromboembolism. Evidence Report/Technology Assessment No. 180. (Prepared by Johns Hopkins University Evidence-based Practice Center under contract no. HHSA 290-2007-10061-I). AHRQ Publication No. 09-E011. Rockville, MD. Agency for Healthcare Research and Quality.2009.
http://www.ahrq.gov/research/findings/evidence-based-reports/fvl-evidence-report.pdf

SUGGESTED CLASSROOM DISCUSSION POINTS:

1. Venous thromboembolism (VTE) encompasses: 1) deep venous thrombosis (DVT), a blood clot in a deep vein, typically the legs, and 2) pulmonary embolism (PE), a blood clot that travels through the bloodstream to the lungs (a travelling blood clot is termed an embolus).
2. Scope of the problem: VTE is a major morbidity and mortality health issue in the U.S. and other developed countries, where it is a leading cause of pregnancy-related deaths. VTEs affect more than 900,000 persons in the U.S. yearly. VTE recurrence risk is about 30%. At least 50% of VTEs are asymptomatic. Death can occur if not treated quickly. About 25% of sudden deaths are due to PE.
3. Non-hereditary (circumstantial) risk factors for VTE include: major surgery, trauma, immobilization including during long ($\geq$ 4 hours) flights, pregnancy, estrogen therapy and oral contraceptive use [higher risk in smokers], central venous catheters, cancer, older age, obesity, infection, HIV.
4. Inherited risk factors for VTE include: thrombophilias such as factor V Leiden (the most common thrombophilia [the R506Q mutation]); factor II (Prothrombin; the second most common thrombophilia [the G20210A mutation]); protein C and protein S deficiencies; antithrombin deficiency; and dysfibrinogenemia. The effect is additive; persons with more than one of these risk factors have a much higher risk for thrombosis.
5. Acquired or inherited risk factors for VTE include: Activated protein C (APC) resistance (identified in up to 21% of initial, and 60% of recurrent, VTE cases), high levels of factor VIII, IX or XI, hyperhomocysteinemia (primarily due to altered MTHFR enzyme metabolism),

and low free protein S.

6. Signs/symptoms of DVT include: lower leg pain, cramping (may feel like a "charley horse") or tenderness, lower leg edema, redness or other color change in leg, warmth in in area of edema or discomfort.
7. Signs/symptoms of PE include: sudden death, sudden shortness of breath, rapid pulse, rapid respirations, diaphoresis, blood in sputum, chest pain especially if sharp, stabbing, and worse on inhalation or coughing.
8. Importance of preventing VTE: in contrast to superficial thrombosis, a DVT can have serious consequences including obstruction of blood flow, causing venous stasis and ischemia; PE can result in death.
9. VTE prevention includes: VTE assessment upon hospital admission with prophylaxis initiated for those at moderate or high risk; specific recommendations vary by medical condition and include anticoagulants, graduated compression stockings (GCS), early ambulation; avoidance of behaviors increasing risk (immobilization, etc.). Avoidance of estrogen use in females at high risk including those with factor V Leiden, regardless of if *heterozygote* (having one abnormal copy of the F5 gene or *homozygote* (having 2 abnormal copies of the F5 gene). Prophylaxis for asymptomatic persons is circumstance-driven and controversial.
10. Diagnostic tests: for DVT, ultrasound (U/S), D-dimer, and if no clear diagnosis on U/S, venography for PE, MRI and CT.
11. VTE treatment includes: heparin/ fondaparinux, or rivaroxaban if acute DVT or PE, and vitamin K antagonists, primarily warfarin. Specific recommendations exist for VTE in neonates, children, pregnancy, and medical conditions such as stroke and cancer.
12. 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).
13. CYP450 is a complex of more than 40 liver enzyme families: the CYP1, CYP2, and CYP3 families are important in the metabolism of many drugs. Each CYP family has multiple subfamilies, denoted by a capital letter after the CYP family number, which is followed by another number designating the polypeptide that encodes for a specific gene, e.g., CYP2C9. The terms 'enzyme' and 'gene' are often used interchangeably when referring to CYP450.
14. The gene for the CYP2C9 enzyme (also denoted as CYP450 2C9) influences how warfarin and other drugs are metabolized: two CYP2C9 variants known as *2 (pronounced "star two") or *3 reduce warfarin activity by 30-50% and 90% respectively. Greater than 30% of Caucasians and Europeans have one or two copies of these variants, which are rare in Asians and Africans. Also involved with warfarin response is the gene necessary for vitamin K blood clotting activation. Genetic testing for variation in these genes is widely available and is typically performed on a blood sample or a buccal (cheek) swab. These inherited variants are also referred to as polymorphisms, single nucleotide polymorphisms (SNPs, pronounced "snips") or mutations.
15. Professional guidelines for pharmacogenomic testing for CYP2C9 and VKORC1 vary: it is postulated that CYP2C9 and VKORC1 testing for inherited response to warfarin can help guide dosing to achieve the optimal therapeutic effect faster while minimizing the risk of an adverse drug reaction or for consideration of an alternative therapy (e.g., clopidogrel, Aspirin), for persons with impaired metabolism. Nevertheless, warfarin dosing algorithms incorporating both genetic (CYP2C9 and VKORC1) and non-genetic factors are available at

http://www.pharmgkb.org/drug/PA451906.

16. Warfarin Black Box Warning: the warfarin package insert contains a warning regarding pharmacogenomic testing for warfarin response, given the very narrow therapeutic index and bleeding risk with warfarin use, and that about 40% of warfarin response variance is attributed to genetic variants in VKORC1 (primarily) and CYP2C9; and age, height, weight, interacting drugs, and indication for warfarin use account for an additional 15% of response variability. Prediction algorithms based on these factors to tailor the initial warfarin dose are controversial because of contradictory data and lack sufficient evidence to support genotyping coverage costs by insurers (who may or may not cover the cost). Ongoing clinical trials are expected to provide best evidence for/against this testing.
17. The ultimate goals of genotype-guided warfarin therapy are to: 1) reduce the risk of major bleeding events by avoiding higher international normalized ratio (INR) values; and 2) provide better protection from thrombosis by reducing INR values (but not under-dosing) during warfarin initiation.
18. Factor V Leiden (FVL): FVL (discovered in 1994 by clinical scientists at the University of Leiden) is the most common inherited thrombophilia, present in 4-6% of the population in the U.S. It is characterized by poor anticoagulation response to activated protein C (APC), resulting in a blood clot at some point in about 10% of heterozygotes and 80% of homozygotes (see inheritance explanation below). A much as 30% of DVTs and PEs occur in persons who have FVL.
19. Inheritance: humans inherit one copy of the gene for FVL (the F5 gene) from each parent and pass on, at random, one or the other copy to each child. *Heterozygotes* are persons who inherit two different alleles (copies) of a gene, e.g., one normal (working; referred to as "wild type") and one mutated (non-working) copy of a gene (or two different mutations, referred to as double or compound heterozygote; see explanation below); *homozygotes* are those who inherit two alleles that are the same, e.g., two normal or two mutated copies of a gene (one allele from each parent).
20. Regarding FVL, heterozygotes (primarily whites; less often Hispanics or Africans; rare in Asians) for the F5 gene are at moderately increased risk for venous thrombosis whereas homozygotes are at very high thrombosis risk.
21. The only known variant in the F5 gene that is associated with FVL is the R506Q mutation (R is the one-letter abbreviation for the amino acid arginine; Q is the one-letter abbreviation for the amino acid glutamine; 506 represents the protein position [amino acid number] in the F5 gene). R506Q is sometimes referred to as 1691 G>A (the change of arginine to glutamine at nucleotide 1691 in the FV gene) or Arg506Gln (this uses the 3-letter abbreviation for these amino acids). R506Q, 1691Q>A, and Arg506Gln are various designations of the same F5 gene variant.
22. Expression of FVL hypercoagulability (excessive clotting) varies widely dependent upon one's genotype, co-inheritance of a prothrombin variant (most commonly the G20210A mutation) or another thrombophilia and other non-modifiable and modifiable genetic and non-genetic risk factors. Having two mutations in different genes (e.g., inheritance of the FVL R506Q mutation and the prothrombin G20210A mutation) is referred to as a *double heterozygote or compound heterozygote*.
23. Racial/ethnic ancestry and genetic admixture (genetic variants that arise in a population over time from mating between persons of different racial/ethnic ancestry) influences risk for VTE: the prevalence of inherited risk factors for VTE varies considerably by race/ethnicity. 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). Greater genetic variation is found among Hispanics in the U.S., dependent upon the country of ancestral origin and residence area in the U.S. As such, decisions regarding pharmacogenomic testing based on ancestry information are inadequate. Other important implications for pharmacogenomic testing include that FVL and prothrombin G20210A are relatively new mutations not found in Africa or Asia, but due to genetic admixture could be found in African Americans or Asian Americans. The drug label for warfarin states that Asians may need lower drug initiation and maintenance. As another example, the increased risk for VTE and early vascular disease associated with high plasma homocysteine levels due to *homozygosity* of the MTHFR enzyme, a rare event, may be reduced by dietary folate and/or pyridoxine supplements; this homozygosity is rare in persons of African descent.

24. Evidence-based and other applicable guidelines related to factor V Leiden or other genetic/genomic testing for the case described: women with FVL are the primary group at increased risk for VTE. Genetic testing for FVL or prothrombin variants is often used to guide choice of anticoagulant to prevent clots. The American College of Medical Genetics (ACMG) and College of American Pathologists (CAP) guidelines include offering thrombophilia testing to persons with unexplained VTE before age 50, VTE at any age if strong family history of thrombotic disease, individual with recurrent VTE, VTE occurring in conjunction with pregnancy or oral contraceptive (OC) use. VTE risk is higher in women taking OCs who have FVL. The EGAPP (Evaluation of Genomic Applications in Practice and Prevention) review recommends *against routine use* of FVL testing for adults with *idiopathic* VTE and their asymptomatic relatives *if* being done to guide preventive anticoagulant therapy, since the risk of hemorrhage is likely higher than the preventive benefit. Similar to the ACMG and CAP guidelines, *the recommendation does not extend to persons with known modifiable risk factors* such as contraceptive or estrogen replacement use, wherein risk for VTE is about 35-fold in a FVL carrier; this translates to an absolute risk of less than 1% per year (Press, 2002).
25. Psychological or ethical, legal, social implication (ELSI) related to thrombophilia pharmacogenomics testing: the CAP 2002 recommendations state that informed consent and formal genetic counseling are *not* needed for FVL testing but that it is necessary to inform patients that results could have implications for relatives. Evaluation of Genomic Applications in Practice and Prevention (EGAPP) recommends (2011) against FVL and/or prothrombin G20210A testing noting insufficient evidence that potential benefits exceed harms. Theoretical risks include insurance (life, disability, long-term care) discrimination and the potential for anxiety, misunderstanding of VTE risks and feelings of stigmatization among carriers. However, an EGAPP review (Segal et al JAMA 2009) found that among the relevant four studies identified, testing had little impact on knowledge, behavior, or distress for patients/family members, and although the evidence supports increased risk for VTE among carriers, there is no direct evidence that this testing improves outcomes compared to persons without these mutations.
26. 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. http://www.egappreviews.org/
27. Purpose of the National Institutes of Health (NIH) Clinical Pharmacogenetics Implementation Consortium (CPIC) and 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)

SUGGESTED READINGS AND RESOURCES:

Venous Thromboembolism (VTE)

VTE Overview
Deep Venous Thrombosis (DVT):
www.nlm.nih.gov/medlineplus/deepveinthrombosis.html
Pulmonary Embolism (PE): www.nlm.nih.gov/medlineplus/pulmonaryembolism.html

VTE Risk Factors
Kujovich JL. Factor V Leiden Thrombophilia.In: Pagon RA, Adam MP, Bird TD, Dolan CR, Fong CT, Stephens K, editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2013.
1999 May 14 [updated 2010 Mar 9].
http://www.ncbi.nlm.nih.gov/pubmed/20301542

Pomp ER, Rosendaal FR, Doggen CJ. Smoking increases the risk of venous thrombosis and acts synergistically with oral contraceptive use. Am J Hematol. 2008 Feb;83(2):97-102.
http://www.ncbi.nlm.nih.gov/pubmed/17726684

Schobersberger W, Toff WD, Eklöf B, Fraedrich G, Gunga HC, Haas S, Landgraf H, Lapostolle F, Partsch H, Perschler F, Schnapka J, Schobersberger B, Scurr JH, Watzke H; Hall consensus development group. Traveller's thrombosis: international consensus statement. Vasa. 2008 Nov;37(4):311-7. doi: 10.1024/0301-1526.37.4.311.
http://www.ncbi.nlm.nih.gov/pubmed/19003740

VTE and Family History
Varga EA, Kujovich JL. Management of inherited thrombophilia: guide for genetics professionals. Clin Genet. 2012 Jan;81(1):7-17. doi: 10.1111/j.1399-0004.2011.01746.x. Epub 2011 Jul 25.
http://www.ncbi.nlm.nih.gov/pubmed/21707594

VTE and Women
AHRQ: Genetic testing in adults who have had a VTE (June 2009):
http://www.ahrq.gov/research/findings/evidence-based-reports/fvltp.html

VTE Diagnostic Tests
Nutescu EA. Assessing, preventing, and treating venous thromboembolism: evidence-based approaches. Am J Health Syst Pharm. 2007 Jun 1;64(11 Suppl 7):S5-13.
http://www.ncbi.nlm.nih.gov/pubmed/17519445

VTE Clinical Practice Guidelines, Prevention and Treatment
Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuünemann HJ; American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed:

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):7S-47S. doi: 10.1378/chest.1412S3. http://www.ncbi.nlm.nih.gov/pubmed/22315257

Holbrook A, Schulman S, Witt DM, Vandvik PO, Fish J, Kovacs MJ, Svensson PJ, Veenstra DL, Crowther M, Guyatt GH; American College of Chest Physicians. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e152S-84S. doi: 10.1378/chest.11-2295. http://www.ncbi.nlm.nih.gov/pubmed/22315259

Nicolaides A, Hull RD, Fareed J. Prevention and treatment of venous thromboembolism: international consensus statement (guidelines according to scientific evidence). Clin Appl Thromb Hemost. 2013 Mar-Apr;19(2):116-8. doi: 10.1177/1076029612474840. http://www.ncbi.nlm.nih.gov/pubmed/23529476

Pharmacogenomics:

Holbrook A, Schulman S, Witt DM, Vandvik PO, Fish J, Kovacs MJ, Svensson PJ, Veenstra DL, Crowther M, Guyatt GH; American College of Chest Physicians. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e152S-84S. doi: 10.1378/chest.11-2295. http://www.ncbi.nlm.nih.gov/pubmed/22315259

McGlennen RC, Key NS. Clinical and laboratory management of the prothrombin G20210A mutation. Arch Pathol Lab Med. 2002 Nov;126(11):1319-25. http://www.ncbi.nlm.nih.gov/pubmed/12421139

Nutescu EA. Assessing, preventing, and treating venous thromboembolism: evidence-based approaches. Am J Health Syst Pharm. 2007 Jun 1;64(11 Suppl 7):S5-13. http://www.ncbi.nlm.nih.gov/pubmed/17519445

PharmGKB. CPIC Dosing Guideline for warfarin, CYP2C9 and VKORC1. http://www.pharmgkb.org/drug/PA451906

Sanderson S, Emery J, Higgins J. CYP2C9 gene variants, drug dose, and bleeding risk in warfarin-treated patients: A HuGEnet ™ systemic review and meta-analysis. Genet Med. 2005. www.ncbi.nlm.nih.gov/pubmed/15714076

Swen JJ, Nijenhuis M, de Boer A, Grandia L, Maitland-van der Zee AH, Mulder H, Rongen GA, van Schaik RH, Schalekamp T, Touw DJ, van der Weide J, Wilffert B, Deneer VH, Guchelaar HJ. Pharmacogenetics: from bench to byte--an update of guidelines. Clin Pharmacol Ther. 2011 May;89(5):662-73. doi: 10.1038/clpt.2011.34.

Epub 2011 Mar 16.
http://www.ncbi.nlm.nih.gov/pubmed/21412232

Factor V Leiden (FVL):

AHRQ: Genetic testing in adults who have had a VTE (June 2009):
http://www.ahrq.gov/research/findings/evidence-based-reports/fvltp.html
http://www.ahrq.gov/research/findings/evidence-based-reports/fvl-evidence-report.pdf

CPIC: http://www.pharmgkb.org/drug/PA452637

EGAPP: EGAPP Working Group Recommendation (2011; periodically updated):
http://www.ncbi.nlm.nih.gov/pubmed/21150787 (abstract only)
http://www.egappreviews.org/recommendations/FVL/htm; supplemental article
http://jama.jamanetwork.com/article.aspx?articleid=184082

Kujovich JL. Factor V Leiden Thrombophilia.In: Pagon RA, Adam MP, Bird TD, Dolan CR, Fong CT, Stephens K, editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2013.1999 May 14 [updated 2010 Mar 9].
http://www.ncbi.nlm.nih.gov/pubmed/20301542

Press RD, Bauer KA, Kujovich JL, Heit JA. Clinical utility of factor V Leiden (R506Q) testing for the diagnosis and management of thromboembolic disorders. Arch Pathol Lab Med. 2002
http://www.ncbi.nlm.nih.gov/pubmed/12421138

VTE and FVL Reviews and Meta-analyses:

Gohil R, Peck G, Sharma P. The genetics of venous thromboembolism. Meta-analysis, primarily focused on polymorphisms related to spontaneous VTE and ethnic variation. Thromb Haemost 2009. http://www.ncbi.nlm.nih.gov/pubmed/19652888

Grody WW, Griffin JH, Taylor AK, Korf BR, Heit JA; ACMG Factor V. Leiden Working Group.American College of Medical Genetics consensus statement on factor V Leiden mutation testing. Genet Med. 2001 Mar-Apr;3(2):139-48.
http://www.ncbi.nlm.nih.gov/pubmed/11280951

Segal JB, Brotman DJ, Necochea AJ, Emadi A, Samal L, Wilson LM, Crim MT, Bass EB. Predictive value of factor V Leiden and prothrombin G20210A in adults with venous thromboembolism and in family members of those with a mutation: a systematic review. JAMA 2009. http://www.ncbi.nlm.nih.gov/pubmed/19531787

Varga EA, Kujovich JL. Management of inherited thrombophilia: guide for genetics professionals. Clin Genet. 2012 Jan;81(1):7-17. doi: 10.1111/j.1399-0004.2011.01746.x. Epub 2011 Jul 25.
http://www.ncbi.nlm.nih.gov/pubmed/21707594

Genetics of Thrombophilias and Ethical, Legal, Social Implications (ELSI):

National Institutes of Health, National Human Genome Research Institute. Genome Statute and Legislative Database.
http://www.genome.gov/PolicyEthics/LegDatabase/pubsearch.cfm

Peterson-Iyer K. Pharmacogenomics, ethics, and public policy. Kennedy Inst Ethics J. 2008 Mar;18(1):35-56.
http://www.ncbi.nlm.nih.gov/pubmed/18561577 abstract only)
http://www.scu.edu/ethics/practicing/focusareas/medical/pharmacogenomics.html (full article)

Ross LF, Saal HM, David KL, Anderson RR; American Academy of Pediatrics; American College of Medical Genetics and Genomics.Technical report: Ethical and policy issues in genetic testing and screening of children. Genet Med. 2013 Mar;15(3):234-45. doi: 10.1038/gim.2012.176. Epub 2013 Feb 21.
http://www.ncbi.nlm.nih.gov/pubmed/23429433

Varga E. Inherited Thrombophilia: Key Points for Genetic Counseling. J Genet Couns. 2007 Jun;16(3):261-77. Epub 2007 May 1.
http://www.ncbi.nlm.nih.gov/pubmed/17473965.

Varga EA, Kerlin BA, Wurster MW. Social and ethical controversies in thrombophilia testing and update on genetic risk factors for venous thromboembolism. Semin Thromb Hemost. 2008 Sep;34(6):549-61. doi: 10.1055/s-0028-1103366. Epub 2008 Nov 28.
http://www.ncbi.nlm.nih.gov/pubmed/19085654

Warfarin Resources

AMA Brochure
http://www.ama-assn.org/ama1/pub/upload/mm/464/warfarin-brochure.pdf

Blood Thinner Pills Video and booklet
http://www.ahrq.gov/consumer/btpills.htm

Discharge instructions for warfarin
http://www.nlm.nih.gov/medlineplus/ency/patientinstructions/000292.htm

Dosing and Clinical Trials information
http://www.warfarindosing.org/Source/Home.aspx

Medline Plus Warfarin (free registration required)
http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682277.html

MedScape Today: Pharmacogenomics of Warfarin: Clinical Implications
http://www.medscape.com/viewarticle/744039

Patient Education Link
http://www.warfarindosing.org/Source/PatientEducation.aspx

Additional Resources Related to Pharmacogenomics

FDA Table of Pharmacogenomic Biomarkers in Drug Labels
http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

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

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

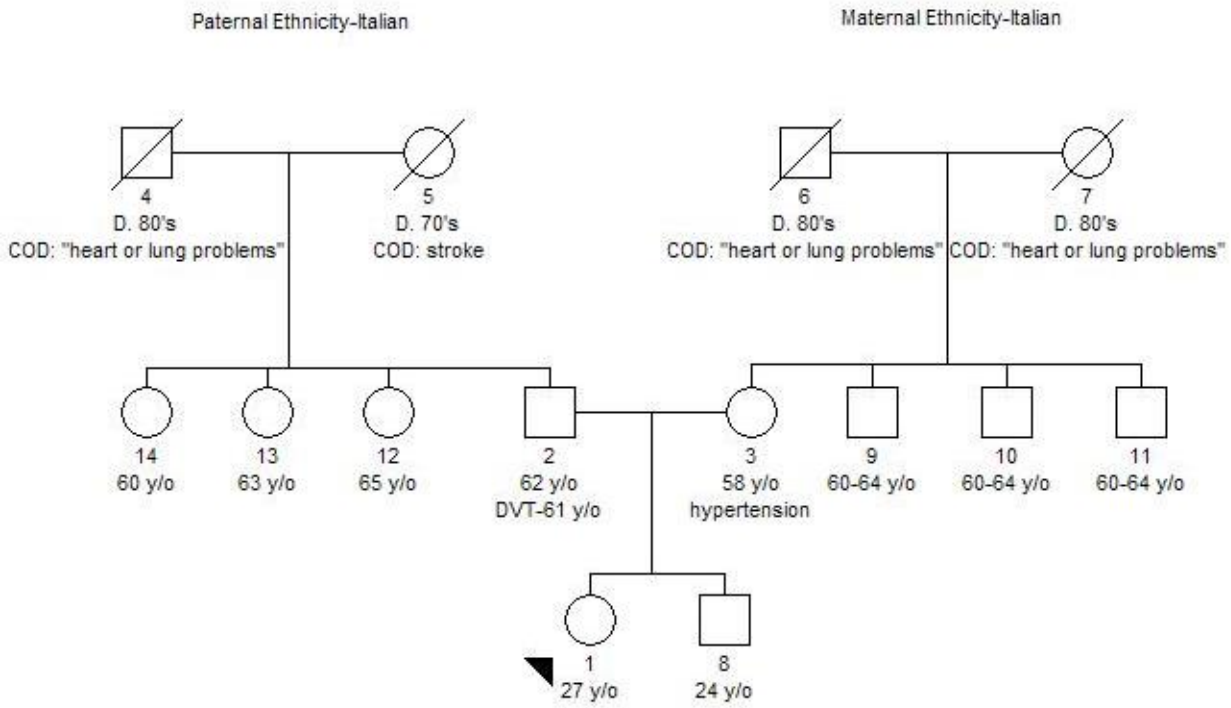
Pharmacogenomics Data Base (PharmGKB)
http://www.pharmgkb.org/

PharmGenEd
http://pharmacogenomics.ucsd.edu

Jennifer's Family History (as described in the case)

Jennifer: age 27, never married; no pregnancies; no known infertility
Mother: age 58, hypertension
Father: age 62, blood clot a year ago
Siblings: one brother, age 24, "has always been healthy"
Maternal Uncles: 3, ages 60-64, two have hypertension
Maternal Aunts: none
Maternal Grandmother: died in her 80's of "heart or lung problems"
Maternal Grandfather: died in his 80's of "heart or lung problems"
Paternal Uncles: none
Paternal Aunts: ages 60, 63, 65; all healthy
Paternal Grandmother: died in her 70's of a stroke
Paternal Grandfather: died in his 80's of "heart or lung problems"
Maternal Cousins: Many, all healthy, no other information collected
Paternal Cousins: Many, all healthy, no other information collected
Ethnicity: Italian on both sides of the family

Pedigree



Abbreviations for family history:
D. = died
COD = cause of death
y/o = years old
DVT = deep venous thrombosis