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WILL THE FDA'S 2010 WARFARIN LABEL CHANGES FINALLY PROVIDE THE LEGAL IMPETUS FOR WARFARIN PHARMACOGENETIC TESTING?

Susan A. Fuchs*

Due to newer clinical utility study results and the recent availability of warfarin pharmacogenetic testing, the Food and Drug Administration ("FDA") has modified warfarin's prescription labeling twice in the past three years. Yet, despite numerous warfarin dosing adverse events resulting from trial and error dosing, many clinicians have been reluctant to prescribe warfarin pharmacogenetic testing to increase dosing accuracy. This disparity stems from conflicts over the interpretations and results of warfarin pharmacogenetic clinical utility studies. Until the federal government implements independent clinical effectiveness testing authorized by the 2010 Patient Protection and Affordable Care Act, manufacturers, health care institutions, and health care clinicians have the unenviable task of sorting through this morass. This article examines the clinical utility of warfarin pharmacogenetic tests, the FDA's role, and other contributing factors that have an impact on the liability and practice of those responsible for the tests' implementation.

I. INTRODUCTION

In a 2006 national pharmaceutical survey, 74% of consumers admitted that they had not followed their prescribers' directions for taking their prescription medications, including 31% who had not

* 2010 LL.M., Biotechnology and Genomics summa cum laude, Sandra Day O'Connor College of Law; 1980 J.D., Cleveland-Marshall College of Law; 1976 B.A. magna cum laude, University of Cincinnati. Ms. Fuchs would like to thank Professor Gary Marchant, Executive Director of the Center for the Study of Law, Science and Innovation, Sandra Day O'Connor College of Law, for his guidance and technical assistance.
gotten a prescription filled. This prescription noncompliance may be related to the fact that 25% to 50% of medications are ineffective in a given patient, necessitating costly and inefficient trial and error prescribing.

In contrast to this scatter-shot, trial and error approach, the goal of personalized medicine is to more accurately predict an individual’s response to therapy based on unique individual characteristics, such as the patient’s genetic makeup. Accurate, clinically useful, pharmacogenetic tests allow a health care clinician to individually target patient medication and dosages. Such targeted therapy may improve patient medication adherence because the medication and dosage are more likely to be effective and less likely to have adverse effects.

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4 Pharmacogenetic tests test for genetic mutations (polymorphisms). U.S. DEP'T OF HEALTH AND HUMAN SERVS.: FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY AND FDA STAFF: PHARMACOGENETIC TESTS AND GENETIC TESTS FOR HERITABLE MARKERS 3 (June 19, 2007) [hereinafter FDA, GUIDANCE FOR PHARMACOGENETIC TESTS], available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071075.pdf. The purpose of pharmacogenetic tests in clinical settings is to delineate whether a particular therapy (medication in the case of warfarin) or dosage is appropriate for a patient given the patient’s genetic mutations and pharmacogenetic polymorphisms in conjunction with the patient’s other clinical information. Id. In contrast, a clinician seeks a genetic test in order to determine a patient’s risk of acquiring a disease or condition. Id. Pharmacogenetics is the same as pharmacogenomics; the author uses both terms interchangeably in this paper.
5 Medco, supra note 3, at 90.
Due to increasing evidentiary support for warfarin pharmacogenetic testing, the Food and Drug Administration ("FDA") has modified warfarin prescription labeling twice in the past three years. Yet, despite numerous warfarin dosing adverse events resulting from the trial and error approach, many clinicians have been reluctant to prescribe warfarin pharmacogenetic testing to increase dosing accuracy. Few question the analytical validity of FDA approved warfarin pharmacogenetic tests, but there is considerable disagreement over whether the tests offer any real clinical usefulness or utility for the medical practitioner. Numerous concerns have hampered widespread adoption of pharmacogenetic testing by clinicians: high costs, health insurance coverage issues, slow test result turnaround times, time constraints for clinician office visits, lack of informed consent, availability of genetic resources, and insufficient patient and clinician education. Independent clinical effectiveness testing, authorized by the 2010 Patient Protection and Affordable Care Act ("PPACA"), might help to clarify the above concerns, but the Act’s measures will not be implemented for several years. Meanwhile, pharmaceutical manufacturers, pharmacists, health care institutions, and health care clinicians have the unenviable task of sorting through warfarin pharmacogenetic testing concerns without the benefit of PPACA’s independent clinical effectiveness testing. This article focuses on warfarin pharmacogenetic testing as an example of both the promises and the limitations of genetic personalized medicine.

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7 BRISTOL-MYERS SQUIBB CO., COUMADIN TABLETS (WARFARIN SODIUM TABLETS, USP) CRYSTALLINE, COUMADIN FOR INJECTION (WARFARIN SODIUM FOR INJECTION, USP) 25 (Supp. No. 105, 2007) [hereinafter BRISTOL-MYERS SQUIBB Co. (2007)].

8 See infra Parts II.A.3.


examines the clinical utility of warfarin pharmacogenetic tests and the consequences that the FDA's and health insurers' actions have on the liability and practice of those responsible for implementation of the tests.

II. WARFARIN AND PHARMACOGENETIC TESTING

Warfarin is a prescription medication within the class of anticoagulant drugs.\(^{11}\) Without sufficient anticoagulation in a patient susceptible to blood clots, the patient risks death or tissue damage, depending upon where in the body the blood clot blocks or ruptures a blood vessel.\(^{12}\) A drug in this class can prevent a stroke from a coagulation that restricts blood flow in the brain,\(^{13}\) limits lung damage that would have resulted from a clot induced pulmonary embolism,\(^{14}\) and discourages other blood starved tissue injuries from clots that migrate and block blood vessels elsewhere in the body.\(^{15}\) Anticoagulants are often prescribed when blood pools in a patient's heart, a byproduct of ineffective heartbeats from atrial fibrillation. Avoidance of clotting in the pooled blood

\(^{11}\) BRISTOL-MYERS SQUIBB CO. (2010), supra note 6 at 1. Anticoagulants inhibit the blood's ability to coagulate or clot. Anticoagulant Drugs, AM. HEART ASS'N, http://www.americanheart.org/presenter.jhtml?identifier=155 (last visited Nov. 10, 2010); Arixtra, Fragmin, Innohep, and Lovenox Injection, FOOD & DRUG ADMIN. (Jan. 10, 2010), http://www.fda.gov/Safety/MedWatch/Safetylnformation/ucm196983.htm [hereinafter FDA, Arixtra]. They do not dissolve existing blood clots or reverse any tissue damage caused by those clots. Id; BRISTOL-MYERS SQUIBB CO. (2010), supra note 6, at 3. They are used preventively to limit clots from developing, lessen the growth of existing clots, and minimize resulting tissue damage. Other anticoagulant prescription drugs include fondaparinux, dalteparin, danaparoid, enoxaparin, heparin, and tinzaparin. Anticoagulant Drugs, AM. HEART ASS'N, http://www.americanheart.org/presenter.jhtml?identifier=155 (last visited Nov. 10, 2010).

\(^{12}\) BRISTOL-MYERS SQUIBB CO. (2010), supra note 6, at 3.


\(^{15}\) BRISTOL-MYERS SQUIBB CO. (2010), supra note 6, at 3.
helps to protect the patient from a myocardial infarction or stroke. Anticoagulants are also indicated to prevent the clotting process ("thrombosis") in patients with a history of thrombosis, or in patients who are more likely to have increased clotting due to cardiac valve and joint replacements.

A. Advantages and Disadvantages of Available Anticoagulants

1. Warfarin
   a. Warfarin’s Moldy Origins

   Scientist Karl Paul Link and his colleagues fractionated a concentrate of the active hemorrhagic ingredient in spoiled hay that was responsible for killing cattle. After testing the concentrate on laboratory rabbits, they discovered that it increased the rabbits’ blood clotting time ("prothrombin time"), resulting in hemorrhages. Link realized that vitamin K-deficient animals


18 Antithrombotic drugs consist of anticoagulant, thrombolytic and antiplatelet drug classes. Pharma Companies in R&D Battle as Warfarin Goes on, Datamonitor Researchstore (Oct. 25, 2005), http://www.datamonitor.com/store/News/pharma_companies_in_rd_battle_as_warfarin_goes_on?productid=9B9CC5A1-5984-4DD5-A227-EB5552E37A21. This scope of this paper is not broad enough to include a discussion of all antithrombotic medications.

19 The impetus for Karl Paul Link’s warfarin research began in 1933 when a frustrated Wisconsin farmer drove his truck loaded with a heifer that had bled to death; a milk can full of uncoagulated cattle blood; and a mound of moldy, spoiled, sweet clover hay to Link’s laboratory at the University of Wisconsin.

and dicumarol-fed laboratory rabbits had similar hemorrhages, noting that vitamin K has a similar structure to dicumarol. This led to Link’s use of vitamin K to reverse dicumarol’s anticoagulation properties.\textsuperscript{21}

b. Warfarin’s Mechanism of Action as an Anticoagulant

Warfarin is the only vitamin K antagonist available in the United States.\textsuperscript{22} Vitamin K is a cofactor that activates several of

\textit{CHEMISTRY} 47, 50–54 (1940). This is a modification of a naturally occurring plant chemical, coumarin. ROBERT H. BURRIS, KARL PAUL LINK: 1901–1978 186–187 (1994). They named the compound that they isolated “dicumarol.” Kresge et al., \textit{supra} note 19, at e6. The compound, C\textsubscript{19}H\textsubscript{12}O\textsubscript{6}, has the formula 3,3'-methylenebis (4-hydroxycoumarin). Mark Arnold Stahmann et al., \textit{Studies on the Hemorrhagic Sweet Clover Disease: V. Identification and Synthesis of the Hemorrhagic Agent}, 138 \textit{J. BIOLOGICAL CHEMISTRY} 513, 513 (1941). See Charles Ferdinand Huebner & Karl Paul Link, \textit{Studies on the Hemorrhagic Sweet Clover Disease: VI. The Synthesis of the δ-Diketone Derived from the Hemorrhagic Agent through Alkaline Degradation}, 138 \textit{J. BIOLOGICAL CHEMISTRY} 529, 531 (1941) (discussing the scientists’ synthetically derived dicumarol).

\textsuperscript{21}Kresge et al., \textit{supra} note 19, at e6. In 1941, after a brief period of clinical testing, dicumarol began to be used as a human anticoagulant. \textit{Id.} Link and his colleagues synthesized more than 100 dicumarol analogues including the rodenticide, warfarin. \textit{Id.} One of Link’s students and coauthors, Mark Stahmann, saw the potential of this analogue that Link had abandoned because of its toxicity; Stahmann patented warfarin as a rodenticide. \textit{Id.} Warfarin is named after the Wisconsin Alumni Research Foundation or WARI that funded the patent process. DAVID NELSON & ROBERT BURRIS, \textit{MEMORIAL RESOLUTION OF THE FACULTY OF THE UNIVERSITY OF WISCONSIN-MADISON: ON THE DEATH OF PROFESSOR EMERITUS MARK ARNOLD STAHMANN} 1 (Faculty Document 1617, Mar. 2002). Link’s colleagues later developed a more soluble warfarin derivative for human use, warfarin sodium, which replaced the less potent dicumarol. \textit{Id.} at 18.; Jerold A. Last, \textit{Profiles in Toxicology—The Missing Link: The Story of Karl Paul Link}, 66 \textit{TOXICOLOGICAL SCI.} 4, 4 (2002). The warfarin patented as a rodenticide is a different warfarin compound from warfarin sodium, the generic of Coumadin. Last \textit{supra} at 4. DuPont Pharmaceuticals was the first manufacturer to own the rights to warfarin sodium. \textit{History, BRISTOL-MYERS SQUIBB CO.}, http://www.bms.com/ourcompany/Pages/history.aspx (last visited Apr. 2, 2010). They sold it under the brand name Coumadin until 2001, when Bristol-Meyers Squibb purchased DuPont Pharmaceuticals, along with the rights to Coumadin. \textit{Id.}

\textsuperscript{22}A vitamin K antagonist is a chemical that counteracts or neutralizes the affects of vitamin K. \textit{Antagonist}, MERRIAM WEBSTER’S MED. DICTIONARY,
the proteins that cause blood to coagulate ("clotting factors"). The body has limited stores of vitamin K, so the body cyclically regenerates existing vitamin K for reuse. During this regeneration process, the enzyme vitamin K epoxide reductase ("VKOR") converts the inactive form of vitamin K ("vitamin K epoxide") into the active form of vitamin K. Warfarin inhibits the VKOR enzyme’s ability to change vitamin K epoxide back into vitamin K. This results in less vitamin K available to facilitate the activation of clotting factors such as Factor II ("prothrombin"). Ultimately, this creates an increase in prothrombin time: less prothrombin activation slows the conversion of prothrombin into thrombin, making less thrombin available to alter fibrinogen into fibrin to form blood clots.

2. Heparin and Low Molecular Weight Heparin Mechanisms of Action

http://www2.merriam-webster.com/cgi-bin/mwmedsamp (last visited Nov. 30, 2010). Warfarin is a synthetic dicumarol which is a hydroxycoumarin derivative. Coumarin is a natural plant chemical. Although warfarin is the only synthetically created dicumarol/coumarin derivative in the U.S., two other derivatives, phenprocoumon and acenocoumarol, are sold in some European countries. All three dicumarol/coumarin derivatives are vitamin K antagonists. Vitamin K Antagonist, Warfarin, Warfarin Therapy, THROMBOSIS ADVISER, http://www.thrombosisadviser.com/scripts/pages/en_thrombosis/warfarin.php (last visited Apr. 3, 2010).


26 Hidgon, supra note 24. Coumarin based anticoagulants also depress Factors VII, IX, and X as well as Proteins C and S. BRISTOL-MYERS SQUIBB Co. (2010), supra note 6, at 2–3. In the 1940s, Karl Paul Link first realized that this increase in prothrombin time is the same in subjects who had taken warfarin’s precursor as in subjects who had vitamin K deficiencies. See supra notes 20–21 and accompanying text.

27 Last, supra note 21, at 4.
Heparin ("heparin" or "unfractionated heparin") and low-
molecular-weight heparin ("LMW heparin" or "fractionated
heparin") enhance the effect of antithrombin to inhibit factors Xa
and IIa ("thrombin"). When antithrombin inactivates these
factors, it prevents fibrinogen from clotting. Both heparin and
LMW heparins are associated with increased risks of heparin-
induced thrombocytopenia ("HIT") syndrome, which can be fatal,
and osteoporosis.

3. Differences between Warfarin and Heparin/LMW Heparin

Although the anticoagulation result is the same using warfarin
as it is with fractionated or unfractionated heparin, warfarin and
heparins make thrombin unavailable to fibrinogen through
different pathways. Since heparins are not vitamin K antagonists,
clinicians can prescribe warfarin and heparin concurrently. A
clinician may start a patient on one of the heparins because their
anticoagulant affects are quite rapid, often occurring within 24
hours. It can take four to five days to get a warfarin international
normalized ratio ("INR") response within the therapeutic range.

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28 Umesh R. Desai, *Heparins*, VCU SCHOOL OF PHARMACY,
Xa and IIa are the two main procoagulant proteases. *Id.*

29 *Id.*

30 There is some controversy over whether there is less of a risk of HIT with
LMW heparin than with heparin. Theodore E. Warkentin & Andreas
Greinacher, *So, Does Low-Molecular-Weight Heparin Cause Less Heparin-
Induced Thrombocytopenia Than Unfractionated Heparin or Not?*, 132 CHEST J.
1108, 1109 (2007).

31 BRISTOL-MYERS SQUIBB CO. (2010), *supra* note 6, at 29.; David A. Garcia
et al., *Delivery of Optimized Anticoagulant Therapy: Consensus Statement from
the Anticoagulation Forum*, 42 THE ANNALS OF PHARMACOTHERAPY 979, 985
(2008).

32 In one study, patients achieved activated partial thromboplastin time
("APTT") ratios and heparin therapeutic blood levels in 24 hours, 71% of the
time, when they received continuous intravenous heparin, versus 37% of the
time when they received heparin subcutaneously. Jack Hirsh et al., *Heparin and
Low-Molecular-Weight Heparin Mechanisms of Action, Pharmacokinetics,

33 The INR is a standardized method of rating an oral anticoagulant (such as
warfarin) patient's prothrombin time ("PT") blood test results into a ratio using
an international sensitivity index reference. This PT ratio is used internationally
The advantage of warfarin over heparins is that warfarin is available orally as a pill, while the others are only available as injectables. The warfarin pill allows a patient to easily self-administer the medication as an outpatient. LMW heparin is not as convenient as warfarin, but usually more so than unfractionated heparin. A patient can self-administer most LMW heparins subcutaneously instead of requiring a hospital stay for intravenous heparin.

The issue of hospitalization is important for managing the cost of anticoagulation therapy. Though heparin and some LMW heparins are off-patent, hospital stays for intravenous anticoagulation therapy are costly. In data collected from

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34 BRISTOL-MYERS SQUIBB CO. (2010), supra note 6, at 1.
36 However, other oral anticoagulants may soon be available. Rivaroxaban, a pill that reportedly inhibits the Xa clotting factor, is in phase III testing. Steven Reinberg, New Anticoagulant Pill Works Well in Trial, HEALTHDAY NEWS (June 17, 2009). Apizaban is another proposed Xa inhibitor undergoing phase II and III trials. The thrombin inhibitor dabigatran looks promising in phase III trials; although AstraZeneca withdrew another thrombin inhibitor, ximelagatran, because of liver toxicity. Dave Levitan, New Drugs and Targets Promise Change in Oral Anticoagulation, HEMONC TODAY (Mar. 25, 2008), available at http://www.hemonctoday.com/article.aspx?rl=27221. A potential factor 1Xa inhibitor, TTP889, is in phase II trials. Id.
December 2006 through June 2008, an average hospital stay to obtain a therapeutic INR range or to treat a bleeding episode is 4.8 days. The median 4.8 day hospital cost is $10,419; patient costs are higher. In contrast, warfarin is available generically and is 1,000 times less costly, at $10.83 for 100 7.5 milligram tablets of warfarin. Warfarin’s ease of self-administration and cost savings have contributed to clinicians writing more than 30 million warfarin prescriptions in 2004 alone.

B. Genetic Factors Affecting Warfarin Dosing

All anticoagulants have bleeding risks if a patient receives too much, and clotting risks if a patient receives too little. Warfarin has a narrow therapeutic range (a target INR of 2.5 with a range of 2.0–3.0). A number of risk factors, including age, weight, sex, drug and food interactions, and genetic factors, affect achieving

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39 Id.
40 Pricing & Ordering Comparisons, All Prices for: Warfarin—Generic Version, PHARMACYCHECKER, http://www.pharmacychecker.com/Pricing.asp?DrugName=Warfarin&DrugId=19462&DrugStrengthId=33097 (last visited Apr. 4, 2010). Even though warfarin is cheaper and easier to administer, researchers in one study estimate that warfarin had the second highest level of emergency department adverse drug events (“ADEs”) in 2004 to 2005. Daniel S. Budnitz et al., National Surveillance of Emergency Department Visits for Outpatient Adverse Drug Events, 296 J. AM. MED. ASS’N 1858, 1864 (2006). Heparin and LMW Heparins were not on the study’s list of medications that have 1% or more emergency department ADEs. Id.
41 The International Warfarin Pharmacogenetics Consortium, Estimation of the Warfarin Dose with Clinical and Pharmacogenetic Data, 360 NEW ENG. J. MED. 753, 753 (2009). Warfarin is the highest selling anticoagulant and one of the top two selling antithrombotics. Heart & Vascular Center: Atrial Fibrillation, BARNES JEWISH HOSP., http://www.barnesjewish.org/heart-vascular/atrial-fibrillation-treatment (last visited Nov. 30, 2010). Sanofi-Aventis’ antiplatelet drug, Plavix (generic drug is “clopidogrel”), is the other highest selling antithrombotic. Id.
42 E.g., BRISTOL-MYERS SQUIBB CO. (2010), supra note 6.
43 BRISTOL-MYERS SQUIBB CO. (2010), supra note 6, at 20, 24.
that narrow therapeutic range. Several known genetic factors that affect warfarin dosage are in the CYP2C9 and VKORC1 genes.

1. **CYP2C9 DNA Sequence Variants**

The Cytochrome P450 enzyme, in subfamily IIC, polypeptide 9, is also known as CYP2C9. It is the body’s main metabolizing enzyme for warfarin. Two frequent polymorphisms in the genes that encode the enzyme, CYP2C9*2 and CYP2C9*3, are found primarily in Caucasians. These polymorphisms are known to affect how a person’s body metabolizes warfarin.

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44 Id. at 5–6, 26–27.
45 Id. at 5. The FDA has classified the CYP2C9*2, CYP2C9*3, and VKORC1-1639G>A alleles as valid biomarkers. Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels, FOOD & DRUG ADMIN. (Feb. 17, 2010), http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm.
47 Id.
48 A human polymorphism is a genetic mutation that occurs in 1% or more of people. What is a gene mutation and how do mutations occur?, GENETICS HOME REFERENCE (Nov. 22, 2010), http://ghr.nlm.nih.gov/handbook/mutationsanddisorders/genemutation. Polymorphisms are responsible for normal human variations. Id. Some of these polymorphism variations are easily perceived, such as blue eye color. Id. Others are invisible to the naked eye, requiring genetic test results to reveal their genetic variations, such as the CYP2C9*2 and CYP2C9*3 gene alleles. Id. In the CYP2C9*2 allele polymorphism, 8–13% of the time, the cysteine amino acid substitutes for the arginine amino acid. Robert D. McBane et al., Warfarin Sensitivity Genotyping: Why? When? How to Use It to Best Advantage (Mar. 2010), http://www.mayomedicallaboratories.com/tests/warfarin/warfarinvideo.html; Yuan et al., supra note 46 at 1749. This polymorphism occurs much more frequently in some racial groups than others. See infra notes 60-64, and accompanying text. For Caucasians, the FDA estimates that CYP2C9*2 occurs in 11%, while CYP2C9*3 occurs in 7%. BRISTOL-MYERS SQUIBB CO. (2010), supra note 6, at 4.
49 In the CYP2C9*3 polymorphism, 6–10% of the time, the leucine amino acid substitutes for the isoleucine amino acid. McBane et al., supra note 48; Yuan et al., supra note 46, at 1749.
50 Yuan et al., supra note 46, at 1747–48. People with African ancestry have infrequent CYP2C9 enzyme activity in *5, *6, and *11 regions; Caucasians have infrequent CYP2C9 enzyme activity in *5, *9, and *11 regions. BRISTOL-
CYP2C9*1 is the unmodified allele that does not contain a polymorphism. The enzyme encoded by this allele metabolizes warfarin more rapidly than the enzymes from CYP2C9*2 and CYP2C9*3 alleles, so a patient having the *1 allele will need a higher dose of warfarin than those with the *2 and *3 polymorphisms. The *3 polymorphism slows warfarin metabolism more severely than a *2 polymorphism. Thus, this slowed metabolic effect is compounded in a warfarin patient with homozygous *3 alleles.

CYP2C9 polymorphisms do not have a direct impact on the vitamin K cycle. Because the presence of CYP2C9*2 and CYP2C9*3 alleles slow the metabolism of warfarin, more warfarin is absorbed through smaller doses than from the presence of the CYP2C9*1 allele. A patient with CYP2C9*1/*1 generally requires the highest warfarin dose, while a patient with CYP2C9*3/*3 generally requires the lowest dose, with the other combinations in between. If both the CYP2C9*1/*1 patient and the CYP2C9*3/*3 receive the same initial average dose, the latter slow metabolizer has a greater hemorrhage risk.

2. VKORCl Gene

The VKORCI gene encodes the proteins responsible for the vitamin K regeneration cycle. The identified polymorphism in the VKORCI gene is not in the coding regions of the gene like it is with CYP2C9 polymorphisms. Instead, the VKORCI gene has

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McBane et al., supra note 48.

55 The VKORCI gene encodes one subunit in the VKOR enzyme complex ("VKORC"). Robertson, supra note 23, at 1077.

56 McBane et al., supra note 48. See supra notes 22–27 and accompanying text.

57 McBane et al., supra note 48.
single nucleotide polymorphisms ("SNPs") in the promoter area of the gene, particularly in the -1639 promoter site.58

A patient who has a VKORC1-1639 G>A adenine nucleotide ("A") allele requires less warfarin than average to achieve the target INR coagulation level; whereas, a patient who has a VKORC1-1639 G guanine nucleotide ("G") allele requires a higher dose of warfarin than average to achieve the target INR coagulation level.59 Patients who receive average initial warfarin dosing that have VKORC1-1639 GG alleles are likely to have problems associated with blood clot formation (venous thromboembolisms, strokes, heart attacks), while patients at the other end of the spectrum with VKORC1-1639 AA alleles are at risk for excessive bleeding. Either extreme can be deadly.

3. CYP2C9 and VKORC1 Polymorphism Combinations

The CYP2C9 and VKORC1 polymorphisms need to be evaluated together because even though some alleles indicate that a patient most likely requires a lower warfarin dose (CYP2C9*2, CYP2C9*3, and VKORC1-1639 A), the VKORC1-1639 G and CYP2C9*1 alleles indicate the opposite.60 As shown in the chart below, a patient can have homozygous CYP2C9 and VKORC1 alleles from either extreme, heterozygous alleles, or a combination of both.61

Although some CYP2C9 and VKORC1 alleles may occur more frequently in patients who have the same racial ancestry, CYP2C9

58 BRISTOL-MYERS SQUIBB Co. (2010), supra note 6, at 5; Yuan et al., supra note 46, at 1746. The VKORC1 gene makes messenger ribonucleic acid ("mRNA") in the promoter area which regulates how the protein becomes synthesized, ultimately leading to encoding of the VKORC1 proteins. VKORC1-1639 represents 1,639 base pairs before the VKORC1 starting codon. McBane et al., supra note 48.

59 Yuan et al., supra note 46, at 1746. Thus, a patient with a VKORC-1639 GG base pair requires significantly more warfarin, while one with a VKORC1-1639 AA base pair requires significantly less warfarin, and a heterozygous patient with a VKORC1-1639 AG base pair is in-between. McBane et al., supra note 48.

60 Yuan et al, supra note 46.

61 Per allele: *1=high dose, less sensitive; G=high dose, less sensitive; *2 and *3=low dose, more sensitive; and A=low dose, more sensitive.
and VKORC1 warfarin pharmacogenetic testing is more accurate than racial self-identification for predicting these warfarin genetic sensitivities. Thus, clinicians do not need to risk incorrectly evaluating a patient’s racial ancestry as a factor separate from the patient’s CYP2C9 and VKORC1 genetic factors. For example, in the Medco-Mayo Clinic Warfarin Effectiveness Study (“Medco-Mayo study”), researchers used the same pharmacogenetic dosage recommendations as in the 2010 Coumadin label. Even though the study findings charted below indicated a prevalence of some allele combinations in patients based on a patient’s racial ancestry, it omitted contradictory 2010 label suggestions about separate dosage adjustments for self-identified racial ancestry.

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62 BRISTOL-MYERS SQUIBB CO. (2010), supra note 6, at 27.
63 See infra notes 111–20 and accompanying text.
64 See infra notes 183–85 and accompanying text.
**Table 1: Medco-Mayo Study Warfarin Dosing**

<table>
<thead>
<tr>
<th>Warfarin sensitivity</th>
<th>CYP2C9</th>
<th>VKORC1</th>
<th>C = Caucasian AF = African AS = Asian[^65]</th>
<th>Incidence</th>
<th>+ or – to Base Dosage</th>
<th>Coumadin 2010 dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low sensitivity</td>
<td>*1/*1</td>
<td>GG</td>
<td>AF mostly</td>
<td>25.4%</td>
<td>Dose + 20% = 6 mg</td>
<td>5–7 mg</td>
</tr>
<tr>
<td>Normal sensitivity</td>
<td>*1/*1</td>
<td>GA</td>
<td>C mostly</td>
<td>29.2%</td>
<td>Dose = 5 mg</td>
<td>5–7 mg</td>
</tr>
<tr>
<td>Mild sensitivity</td>
<td>*1/*2</td>
<td>GG</td>
<td>12.2%</td>
<td>Dose – 10% = 5.5 mg</td>
<td>5–7 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*1/*3</td>
<td>GA</td>
<td>26.6%</td>
<td>Dose – 30% = 3.5 mg</td>
<td>3–4 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*2/*2</td>
<td>5 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>*1/*3</td>
<td>20%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>*2/*3</td>
<td>20%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>*1/*1</td>
<td>AA</td>
<td>Almost all AS here</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High sensitivity</td>
<td>*2/*3</td>
<td>GA</td>
<td>4%</td>
<td>Dose – 5% = 2 mg</td>
<td>0.5–2 mg</td>
<td></td>
</tr>
<tr>
<td>Very high sensitivity</td>
<td>*3/*3</td>
<td>G/A</td>
<td>2.6%</td>
<td>Dose – 5% = 2 mg</td>
<td>0.5–2 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*1/*3</td>
<td>AA</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>*2/*2</td>
<td>&lt;2 mg + frequent INR</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>*2/*3</td>
<td>&lt;2 mg + frequent INR</td>
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</tr>
<tr>
<td></td>
<td>*3/*3</td>
<td>&lt;2 mg + frequent INR</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

[^65]: The main studies that this author found showing this genetic metabolism effect are based on studies conducted in China with ethnic Chinese subjects. See supra note 50 and infra note 93 and accompanying text. These same results should not be generalized to all of Asia because the population in the other 46 ethnically diverse Asian countries does not necessarily have the same genetic warfarin metabolism as do ethnic Chinese. See Jaekyu Shin et al., Pharmacogenetics: From Discovery to Patient Care, 66 AM. J. HEALTH-SYS. PHARMACISTS 625, 629–30 (2009) for a discussion of two genetic haplotypes that encompass this genetic metabolism effect.

[^66]: McBane et al., supra note 48; Robert S. Epstein et al., Warfarin Genotyping Reduces Hospitalization Rates: Results from the MM-WES (Medco-Mayo Warfarin Effectiveness Study), 55 J. OF THE AM. COLL. OF CARDIOLOGY, 1, 3
In 2008, Washington University’s Brian Gage and fellow researchers published a study in which they created an online algorithm for dosing warfarin. As part of the study, they evaluated the warfarin pharmacogenetic genotypes, body surface area, target INR, smoking status, amiodarone use, race, and thrombosis status in 1,015 warfarin study patients to develop the pharmacogenetic algorithm. They also evaluated an additional 292 similar patients to validate their findings. Consistent with prior studies, the results showed that clinical factors accounted for 17–21% of dosage variations. By adding VKORC1-1639 G>A and CYP2C9 genotypes, the factors accounted for 53–54% of dosing variations. The algorithm factors in clinical and/or genetic information to calculate initial and revised doses based on available patient information. Since first publishing the online warfarin algorithm calculator, the researchers have replaced it with at least 20 versions to update the site with new data gathered from the site’s participants. The result is a free, user-friendly, internet

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68 Amiodarone is a medication used to treat ventricular arrhythmias. Heart & Vascular Center: Atrial Fibrillation, BARNES JEWISH HOSP., http://www.barnesjewish.org/heart-vascular/atrial-fibrillation-treatment (last visited Nov. 30, 2010).
70 Id. at 3-4.
C. Validity of Warfarin Pharmacogenetic Tests

In order for clinicians to be able to make effective treatment decisions based on a patient’s pharmacogenetic data, several factors must be present. Tests need to be available that accurately measure those data. In addition, the pharmacogenetic test information must provide a clinical benefit that outweighs the tests’ risks. Furthermore, the clinician must be able to understand the test results and the benefits. Finally, the patient or the insurer must be willing to pay the associated costs.

1. Analytical Validity

A genetic test has analytical validity if it accurately and reliably measures the genetic information that the test is designed to measure.73 When a pharmacogenetic test manufacturer submits a Food Drug and Cosmetic Act § 501(k) application to the FDA for a pharmacogenetic test, the manufacturer must provide data to prove the pharmacogenetic test’s analytical validity.74 In September of 2007, the FDA approved the first § 501(k) premarket notification for a CYP2C9/VKORC1 genetic test system for warfarin by Nanosphere, Inc., deeming the test to have sufficient analytical validity.75 Three more warfarin pharmacogenetic test

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72 The calculator takes into account the patient’s status as a new patient: beginning warfarin dose, age, sex, ethnicity (includes “unknown”), race (includes “other”), weight, height, smoking, liver disease, reason for warfarin, baseline INR, target INR, randomize and blind INR, amiodarone dose, statin/HMG CoA reductase inhibitor, anyazole drug (e.g., Fluconazole), any sulfa drugs, VKORC1 variables, CYP2C9 *2-6 variables, CYP4F2 V433M variables (CC, CT, TT), and GGCX rs11676382 variables (CC, CG, GG). WARFARIN DOSING, http://www.warfarindosing.org/Source/ Home.aspx (last visited Apr. 3, 2010).
73 Shin et al., supra note 65, at 631.
74 FDA, GUIDANCE FOR PHARMACOGENETIC TESTS, supra note 6 at 6.
systems were approved by the FDA in 2008, and another was approved in 2009.

2. Clinical Validity and Clinical Utility

A pharmacogenetic test should also have both clinical validity and clinical utility. A test is clinically valid if it can predict a patient’s response to a drug therapy. Traditionally, a test has clinical utility when a randomized controlled trial (“RCT”) assesses the balance of the risks and benefits of pharmacogenetic testing including the risks and benefits of maintaining the status quo, exploring other alternative treatments, and evaluating cost and time efficiencies. However, FDA directors Woodcock and Lesko argue that comprehensive RCTs may not be necessary when evaluating the clinical utility of warfarin pharmacogenetic testing.

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77 TrimGen Corp., eQ-PCR Warfarin Genotyping Kit 510(k) Summary, FOOD & DRUG ADMIN. (Feb. 6, 2009), http://www.accessdata.fda.gov/cdrh_docs/pdf7/K073071.pdf [hereinafter FDA, TrimGen 510(k)]. TrimGen Corporation, AutoGenomics, Inc., and Osmetech Molecular Diagnostics demonstrated to the FDA that their pharmacogenetic test systems will accurately identify CYP2C9*2, CYP2C9*3, VKORCI-1639 A, and VKORCI-1639 G alleles. Id.; FDA, AutoGenomics 510(k), supra note 76; FDA, Osmetech 510(k), supra note 76. Nanosphere, Inc. and Paragon Dx demonstrated to the FDA that their pharmacogenetic test systems will accurately identify the same CYP2C9 alleles as the three manufacturers above, as well as VKORCI 1173 T and VKORCI 1173 C alleles. FDA, Nanosphere 510(k), supra note 75; FDA, Paragon 510(k), supra note 76.

78 Shin et al., supra note 65, at 631.

79 Id.

80 Janet Woodcock & Lawrence J. Lesko, Pharmacogenetics—Tailoring Treatment for the Outliers, 360 NEW ENG. J. MED. 811, 813 (2009). Janet Woodcock is Director of the FDA’s Center for Drug Evaluation and Research.
They point out that pharmacogenetics has the potential to benefit those statistical outliers at both ends of the spectrum who do not have average responses. Given the small numbers of these warfarin genetic outliers, it is not surprising that there is a lack of information on genetic outliers in the larger warfarin patient population and a scarcity of RCT studies. Woodcock and Lesko conclude that these circumstances suggest that “less rigorous approaches” than RCTs may be sufficient, such as studies that focus on the warfarin genetic outliers instead of those in the general warfarin population. Brian Gage concurs:

For new drugs, experts agree that randomized, controlled trials are required to demonstrate safety and effectiveness.

In contrast, diagnostic tests can be validated against a gold standard, thereby bypassing the need for [RCTs].

One author in the pro-RCT camp criticized the clinical validity of earlier warfarin pharmacogenetic studies because they had too few subjects and none of the studies differentiated serious bleeding complications. In 2008, the American College of Medical Genetics Policy Statement concluded that there was insufficient evidence to support routine testing of CYP2C9/VKORC1 genes for warfarin dosing. However, they felt it would be reasonable to use CYP2C9/VKORC1 pharmacogenetic testing to diagnose the causes of unusually low warfarin maintenance doses or unusually high INRs. Recently, researchers have completed several large

("CDER"), and Lawrence J. Lesko is Director of FDA’s Office of Clinical Pharmacology ("OCP").

Id. at 112–113.

Id.

Id.


Id. at 150.
studies and reviews that address some of these clinical validity and clinical utility issues.

a. Centers for Medicare and Medicaid Services Decision

On August 3, 2009, the Centers for Medicare and Medicaid Services ("CMS") published a thorough analysis of the clinical utility of pharmacogenetic testing for warfarin. In the analysis, CMS looked for whether a patient's warfarin pharmacogenetic test results would cause a treating clinician to prescribe a different dose of warfarin than the clinician would have prescribed without that information and whether the different dose would improve patient health outcomes. As discussed below, the CMS analysis evaluated the 2007 Coumadin label, the positions of numerous medical, cardiac, pulmonary, and genetic organizations, public opinions, and available studies.

CMS reviewed the 2008 Tufts-New England Medical Center Evidence-based Practice Center Review ("Tufts Review"), which


89 CMS, supra note 88, at 16–17. Although Medicare does not cover preventative diagnostic screening tests for an asymptomatic patient, it does cover tests that will help the clinician to diagnose and treat a patient with an existing condition. Id. at 12. However, Medicare will begin to cover Medicare preventive services on or after January 1, 2011. See Patient Protection and Affordable Care Act, 42 U.S.C. §§ 1395y–1395z (2010).

90 CMS, supra note 88, at 4–14. The American Association for Clinical Chemistry and the College of American Pathologists believe there is sufficient clinical utility and validity evidence to warrant warfarin pharmacogenetic testing. Id. at 13. The Association for Molecular Pathology, the American Society of Hematology, the American College of Chest Physicians, and the American College of Medical Genetics hold the opposite opinion. Id. at 13–14. CMS noted that although the American Medical Association promoted using pharmacogenetic web sites, a physician would still need to monitor PT/INR, and testing has no pharmacogenetic value if the physician ignores food and more than 300 drug interactions that require warfarin dosage adjustments. Id. at 14–15.
Pharmacogenetic Testing for Warfarin

examined published studies from 1995 to 2007. CMS claimed few of the Tufts Review studies addressed the patient health benefits or harms that could be attributed to warfarin dosing guided by pharmacogenetic testing (“clinical effectiveness”). CMS also dismissed the other studies it evaluated for similar reasons.

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CMS, supra note 88, at 9–11. The 2005 meta-analysis by Sanderson concluded that the evidence of clinical effectiveness was insufficient. Id. at 9; Simon Sanderson et al., CYP2C9 Gene Variants, Drug Dose, and Bleeding Risk in Warfarin-Treated Patients: A HuGEnet™ Systematic Review and Meta-Analysis, 7 GENETICS IN MED. 97, 97-104 (2005). In 2007, Millican conducted a retrospective study finding that relying solely on INR for dosing increases the chance of too little or too much warfarin dosing. Eric A. Millican et al., Genetic-Based Dosing in Orthopedic Patients Beginning Warfarin Therapy, 110 BLOOD 1511, 1513 (2007). CMS discounted the study because all of the study participants received warfarin for the same indication. CMS, supra note 88, at 11. The 2008 McClain study found low associations between CYP2C9 pharmacogenetic testing and serious bleeding incidents, and no associations between VKORC1 and serious bleeds. Monica R. McClain et al., A Rapid-ACCE Review of CYP2C9 and VKORC1 Alleles Testing to Inform Warfarin Dosing in Adults at Elevated Risk for Thrombotic Events to Avoid Serious Bleeding, 10 GENETICS IN MED. 89, 97 (2008). A study by Schwarz in 2008 found that VKORC1 results predicted PT/INR warfarin response better than CYP2C9 but did not address health benefits. Ute I. Schwarz et al., Genetic Determinants of Response to Warfarin During Initial Anticoagulation, 358 NEW ENG. J. OF MED. 999, 1005-06 (2008). Wen’s group studied the value of pharmacogenetic testing in male Han Chinese without a comparison group. M-S Wen et al., Prospective Study of Warfarin Dosage Requirements Based on CYP2C9 and VKORC1 Genotypes, 84 Clinical Pharmacology & Therapeutics 83, 86–87 (2008). Wen’s researchers noted that CYP2C9 genotyping was less helpful since most Chinese have *1 alleles; the VKORC1 genotyping allowed the Chinese patients to reach stable INR levels sooner than in Caucasian studies because of the narrower range of Chinese variability. Id.

The 2009 studies that CMS reviewed did not fare any better. The Wadelius Scandinavian study concludes that VKORC1 and CYP2C9 pharmacogenetic testing predicts warfarin dosing sensitivity. Mia Wadelius et al., The Largest Prospective Warfarin-Treated Cohort Supports Genetic Forecasting, 113 BLOOD 784, 790–91 (2009). CMS discounted the study because it was limited to one ethnic group, and it did not consider weight and height in setting warfarin dosages. CMS, supra note 88, at 11. Kangelaris’ meta-analysis of three studies from 2005–2007 concluded that few randomized studies found that initial dosing based on pharmacogenetic test results reduced the number of major bleeds.
CMS found limitations with the most recent study in its review, the 2009 International Warfarin Pharmacogenetics Consortium ("Warfarin Consortium") study. The Warfarin Consortium compared the clinical utility of warfarin pharmacogenetic-based dosing with clinical and fixed dosing algorithms. They enrolled 5,052 warfarin patients from nine countries, each with a target INR between 2 to 3. The Warfarin Consortium developed three dosage prediction models from a random selection of 80% (4,043) of those patients: one from the patients' genetic information, one from their clinical information, and one using a fixed dose. The investigators tested the models on the remaining 20% (1,009) of the patients.

All three Warfarin Consortium study algorithms accurately predicted dosing for 54% of the patients in the middle of the dosing spectrum. The pharmacogenetic algorithm was only statistically significant for 46% of patients who were farthest from the dosing norm. The pharmacogenetic algorithm predicted accurate dosing for 54% of those patients who required 3 mg or less warfarin per day. Whereas the clinical algorithm had a 33% accuracy rate and the fixed dose model had 0% accuracy.

Kangelaris et al., supra note 17, at 662. Li's study found that pharmacogenetic testing allowed earlier predictions of INR results as its only predictive benefit. Chun Li et al., Relative Contribution of CYP2C9 and VKORC1 Genotypes and Early INR Response to the Prediction of Warfarin Sensitivity During Initiation of Therapy, 113 BLOOD 3925, 3929–30 (2009). Lindh reviewed 39 studies in a 1999–2007 meta-analysis, noting that VKORC1 data was too limited, as was homozygous CYP2C9*2 and *3 because of the latter genotypes' rarity. Jonathan D. Lindh et al., Influence of CYP2C9 Genotype on Warfarin Dose Requirements—A Systematic Review and Meta-Analysis, 65 EUROPEAN J. OF CLINICAL PHARMACOLOGY 365, 372 (2009).
Pharmacogenetic algorithm was accurate for 26% of those patients at the other end of the spectrum who needed 7 mg or more warfarin per day, versus 9% accuracy for the clinical algorithm and 0% for the fixed dose approach.\textsuperscript{102} Without the pharmacogenetic testing, clinical modeling could not as accurately predict in which dosing category a patient belonged. CMS objected to the tests because they included incomplete data on whether patients smoked, drank alcohol, or took vitamin K; limited study results to patients with INR targets of 2–3; and contained incomplete information on genotypes.\textsuperscript{103}

The studies that CMS evaluated had two to ten day time lags from when the clinician ordered the pharmacogenetic tests to when the clinician received the results.\textsuperscript{104} CMS pointed out that warfarin pharmacogenetic testing has little value for predicting outcomes after a patient has been on warfarin for five days, but noted that faster test result turnarounds would increase the tests’ clinical value.\textsuperscript{105} A Medicare Evidence Development and Coverage Advisory Committee ("MEDCAC") found that the evidence base for pharmacogenetic testing is too immature.\textsuperscript{106}

\textsuperscript{102} Id.
\textsuperscript{103} CMS, supra note 88, at 10–11.
\textsuperscript{104} Id. at 4.
\textsuperscript{105} Id. at 19.
\textsuperscript{106} MEDCAC met to decide CMS coverage recommendations using standardized genetic test evaluation tools. Id. at 12-13. The Centers for Disease Control and Prevention’s National Office of Public Health Genomics supports using the Evaluation of Genetic Applications in Practice and Prevention working group ("EGAPP"). Id. MEDCAC used an EGAPP-identified analytic and clinical validity, clinical utility, and associated ethical, legal, and social implications ("ACCE") framework to evaluate the data. Id.

MEDCAC addressed how confident they were "that methodologically rigorous evidence on the outcome is sufficient to infer whether or not diagnostic genetic testing improves [three types of] patient centered health outcomes." Id. at 12. They had high confidence for "[d]irect patient-centered healthcare outcome e.g., mortality, functional status, adverse events." Id. at 13. The voting member panelists gave an average of 4.8 out of a maximum of 5 votes. All panelists gave a slightly lower average confidence level to all three types of patient centered health outcomes. Id. They had slightly above average confidence for "[i]ndirect or intermediate healthcare outcomes e.g., changes in laboratory test results such as hemoglobin or time to achieve a target value."
CMS ultimately decided that the evidence of warfarin pharmacogenetic testing’s clinical utility for improved patient health outcomes is too insufficient to warrant Medicare coverage.\(^{107}\) Instead, Medicare patients who meet specific criteria\(^{108}\) can enroll in CMS approved prospective, randomized, controlled studies.\(^{109}\)

b. Medco-Mayo Study

The Medco-Mayo study was not concluded in time to become a part of the CMS analysis. The study examines warfarin hospitalization rates for qualifying Medco Health Solutions’ (“Medco”) pharmaceutical benefits management (“PBM”) patients.\(^{110}\) From 2007–2009, researchers contacted Medco PBM patients from forty-nine states throughout the United States who had filled new warfarin prescriptions during that time period.\(^{111}\)

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\(^{107}\) Id. The voting member panelists gave an average of 3.3 out of a maximum of 5 votes. Id. They had a little below average confidence for “’[c]hanges in physician-directed patient management.’” Id. at 12–13. The voting member panelists gave an average of 2.1 out of a maximum of 5 votes. Id. at 13. They found that a lower level of methodological rigor “would actually detract from the ethical generation of evidence for genetic testing.” Id. at 13 (emphasis removed). MEDCAC noted that when evaluating causes of death with an older Medicare population, it is difficult to distinguish genetic causes from other competing causes. MEDCAC did not explain their above findings other than making a general statement that evidence for pharmacogenomic testing is insufficient and that CMS should use its authority to gather more evidence. Id. \(^{108}\) Id. at 17–18.

\(^{108}\) Medicare patients who have not previously had CYP2C9 and VKORC1 pharmacogenetic testing, have received warfarin for less than five days, and are enrolled in a CMS approved study. Id. at 1–2.


\(^{110}\) Epstein et al., supra note 66, at 2.

\(^{111}\) Participants were restricted to outpatients who filed new prescriptions, who had not been on warfarin for the past six months, who were between ages 40–75, who provided access to complete medical records, and who had physicians willing to participate, and were followed for six months. Id.
Almost 900 patients ("pharmacogenetic patients") qualified on all criteria. Seventy-five percent of doctors agreed to participate. Three historical control groups were populated with outpatients on warfarin who had not undergone CYP2C9/VKORC1 pharmacogenetic testing.\(^{112}\)

The researchers took blood or buccal ("cheek swab") samples from each pharmacogenetic patient. Mayo Clinic analyzed the samples for CYP2C9 (combinations of *1, *2, *3 allele pairs) and VKORC1 (GG, GA, or AA allele pairs).\(^{113}\) The researchers electronically submitted each pharmacogenetic patient’s CYP2C9/VKORC1 genetic results to the patients’ physician in a report that also included one of four recommendations.\(^{114}\)

There was an 11–60 day lag time between when study patients began taking the warfarin and when their physicians received the warfarin pharmacogenetic results.\(^{115}\) The study results showed a direct correlation between progressively shorter turnaround times and less patient risk of bleeds or thromboembolisms.\(^{116}\) Despite this time lag, when compared with the control groups, the pharmacogenetic patients had 31% less hospitalization claims for all causes and 28% less hospitalization claims for bleeds or thromboembolisms.\(^{117}\) These hospitalization differences were even

\(^{112}\) Id. at 2 and 6.
\(^{113}\) Id. at 3.
\(^{114}\) 1. The patient is likely to need an increase above the usual dose to maintain a therapeutic INR.
   2. The patient is likely to respond to the usual dose to maintain a therapeutic INR.
   3. The patient is likely to need a decrease from the usual dose to maintain a therapeutic INR.
   4. The patient is likely to need a decrease from the usual dose to maintain a therapeutic INR and will need more frequent INR monitoring. If the genetic results indicated that the patient fell into this category (36 out of 896 patients), Mayo also contacted the physician by telephone with the recommendation. McBane et al., supra note 48.
\(^{115}\) This time frame included delays in patient contact until after the prescription was filled, a visit to obtain samples and informed consent, transporting samples to Mayo Clinic, and the testing-reporting process. Epstein et al., supra note 66, at 6.
\(^{116}\) Id. at 6.
\(^{117}\) Id. at 4–5.
more noteworthy when only considering hospitalizations occurring after the study’s physicians received the warfarin pharmacogenetic results: 33% and 43%, respectively.\textsuperscript{118}

Cardiologist Mandeep Mehra, speaking for the American College of Cardiology, criticized the results because they were not derived from a double blind study, and he felt that the controls were inadequate.\textsuperscript{119} However, all published reports indicate that the other cardiologists who attended the presentation did not share Dr. Mehra’s concerns.\textsuperscript{120}

3. Cost Considerations for Pharmacogenetic Testing

a. Actual Cost

FDA-approved warfarin pharmacogenetic tests have been available since 2007 and are now obtainable at numerous

\textsuperscript{118} Id.


\textsuperscript{120} Id.; See also Sue Hughes, Thrombosis: Warfarin Genotyping Reduces Hospitalizations, THE HEART (Mar. 16, 2010), available at http://www.theheart.org/article/1058617.do. Dr. Mehra’s opposition to the study may possibly have been colored by his employer’s participation in an ongoing Genotype-Guided Dosing of Warfarin Therapy study. Dr. Mehra is a professor at the University of Maryland School of Medicine and is on staff at the University of Maryland Medical Center (“UMMC”). UMMC is a participant in the National Heart, Lung and Blood Institute, National Institutes of Health study which is expected to conclude by 2011. University of Maryland Medical Center, UMMC Has Been Selected as One of the Twelve Clinical Sites in the Nation for a Genotype-Guided Clinical Trial for Warfarin/ Coumadin Therapy (“GGDWT”), 3 MOLECULAR PROFILE 2 (2009); Genotyped Guided Dosing of Warfarin Clinical Trial Funding Opportunity—Central Laboratory RFP, UNIV. OF PA. SCH. OF MED. & NAT’L HEART LUNG AND BLOOD INST., http://rt5.cceb.med.upenn.edu/warfdcc/WARF-1_pg5.html (last visited Apr. 8, 2010). That study will be much larger than many previous studies (1,200 patients). However, since its focus is the first month of dosage initiation, there may not be much data on the prevention of serious bleeding events. Rena Conti et al., Personalized Medicine and Genomics: Challenges and Opportunities in Assessing Effectiveness, Cost-Effectiveness, and Future Research Priorities, 30 MED. DECISION MAKING 328, 333–34 (2010).
Despite the hope that pharmacogenetic testing would decrease health costs, costs for pharmacogenetic testing have escalated along with other medical costs. The actual cost of a warfarin pharmacogenetic test is much higher than the $250-$500 Genelex brand test estimate quoted in several research articles. Genelex now charges $550 plus the cost of a blood draw. The patient risks clots or hemorrhages during Genelex’s mail-order test process. After the patient receives the Genelex test kit, the patient must still go to a laboratory to have blood drawn or self-

121 Laboratories offering CYP2C9/VKORC1 warfarin pharmacogenetic testing include: Arup Laboratories (Salt Lake City, UT), Genelex (Seattle, WA), Genomas Inc. (Newington, CT), Laboratory Corporation (throughout the U.S.), Molecular Diagnostics Laboratories (Cincinnati, OH), PGXL Laboratories (Louisville, KY), Quest Diagnostics (throughout the U.S.), and Specialty Laboratories (Valencia, CA). Shin et al., supra note 65, at 633.
administers the buccal swab, mail the blood or buccal swab to Genelex, and wait for Genelex to post the results online five business days later.\textsuperscript{126}

The Mayo Clinic’s list price for its Warfarin Sensitivity Genotype test (CYO2C9*1 to CYO2C9*6 and VKORC1-1639G>A) is $439.30. This price includes DNA sequencing, rapid DNA extraction, and interpretation and review of the Warfarin Sensitivity Genotype test results. There is no mention of a blood draw cost which, presumably, would be extra.\textsuperscript{127} It is not an FDA-approved test, but rather a Clinical Laboratory Improvement Amendments (“CLIA”) approved in-house test.\textsuperscript{128} Laboratory Corporation of America (“LabCorp”) charges $622 ($588 plus $34 blood draw) for its warfarin genetic test.\textsuperscript{129} It costs a laboratory $60 for each FDA-approved TrimGen. The consumer’s cost for

\begin{footnotesize}
\begin{enumerate}
\item Mayo Clinic uses the Luminex Molecular Diagnostics’s Warfarin Tag-It PGx Mutation Detection Kit for investigational use only. \emph{Unit Code 89033: Warfarin Sensitivity, Genotype}, MAYO CLINIC, http://www.mayomedicallaboratories.com/test-catalog/Performance/89033 (last visited May 10, 2010). This is the same test that Genelex uses and that Mayo Clinic used in the Medco-Mayo study. Ray (Oct. 10, 2007), supra note 124; Epstein et al., supra note 66, at 3. CLIA gives CMS regulatory authority over laboratories that overlap with FDA’s authority. All laboratories that perform patient testing must be CLIA certified. Peter M. Kazon, \emph{Regulatory Issues Facing Genetic Testing}, 3 J. HEALTH & LIFE SCI. L. 111, 118 (2010). The FDA has recently exerted more control over this area. \emph{See Draft Guidance for Industry, Clinical Laboratories, and FDA Staff—In Vitro Diagnostic Multivariate Index Assays}, FOOD & DRUG ADMIN. (July 26, 2007), http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071455.pdf.
\item Test Menu: Warfarin (P450 2C9 and VKOEC1), LAB. CORP. OF AM., https://www.labcorp.com/wps/portal/ut/p/c1/04_SB8K8xLLM9MSSzPy8xBz9CP0os_hACzO_QCM_JwMMLxyM3AyNMyMycDU2dXQwN3M_IwkA7eKgwMlPIGOCjgb6fR35uqm6kfpR5fKirSbChp6Wxgb-ru4GBkbnj6elhb-hgZeBfoh-QXZ2moujo1AyXezw!!/ (last visited Apr. 9, 2010); Telephone Interview with Chris, Customer Service, Lab. Corp. of Am., Phoenix, AZ (Apr. 9, 2010).
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the TrimGen test is higher because the price includes the laboratory mark-up and the charge for the blood draw; whereas the price of the FDA-approved AutoGenomics test is $100 per variant for a total of $1,500.

In summary, warfarin pharmacogenetic tests cost the patient between $439 plus the price of a blood draw for the CLIA approved Mayo Clinic and $1,500 for the FDA-approved AutoGenomics tests. An insurer is more likely to cover a warfarin pharmacogenetic test within this price range if the insurer determines that the test’s price is cost effective.

b. Cost Effectiveness Analysis

A cost effectiveness analysis of a warfarin pharmacogenetic test should compare the cost and results of initiating warfarin treatment guided by a pharmacogenetic test to the cost and results of initiating warfarin treatment without a pharmacogenetic test. In 1996, the United States Public Health Service Panel on Cost-Effectiveness in Health and Medicine recommended the quality adjusted life year ("QALY") as a standardized measure for health outcomes.


131 The AutoGenomics warfarin pharmacogenomic test checks for fifteen variants which it claims is more than any other company; Biosciences and Genelex: six variants; Harvard Medical and Nanosphere: four variants; Clinical Data, Kinball Genetics, and Laboratory Corporation of America: three variants. Ray (Oct. 10, 2007), supra note 124.

132 See infra Part II.B.3.c.


134 Milton C. Weinstein et al., Recommendations of the Panel on Cost-Effectiveness in Health and Medicine, 276 J. AM. MED. ASS’N 1253, 1254 (1996). There are three parts to a QALY measurement: the cost of the health intervention, the difference between a person’s health with and without the
A QALY of below $50,000 is considered cost-effective. In order to obtain a QALY of less than $50,000, physician Mark Eckman and colleagues calculated that a warfarin pharmacogenetic test would have to cost less than $200, have a one day turnaround time, and prevent 32% of major bleeds. The twenty-four hour turnaround time is plausible with the FDA-approved tests. Even with an in-house, CLIA approved test, Mayo Clinic has established a less than twenty-four hour turnaround time from the time its clinicians order the warfarin pharmacogenetic tests to the time that the clinician receives the pharmacogenetic test results along with recommendations for increasing, maintaining, or decreasing warfarin dosages. This turnaround time goes a long way toward resolving the CMS Decision’s clinical validity concerns with two- to ten-day turnaround times. However, given that the

health intervention, and the number of years that the suboptimal health condition is expected to last. Id. at 1256–58.

For instance, part one of the QALY measurement would be $1,000, if that is the cost of a health intervention. For part two, a number between zero and one is assigned that represents the quality of life based on the state of a person’s health. Milligan, supra note 133, at 158. A person’s optimal health has a quality number of one; a person’s death has a quality number of zero. Weinstein et al., supra note 134, at 1256. If a health intervention improves a patient’s quality of life from .4 to 1, then the difference in the quality, .6, is part two of the QALY measurement. See Weinstein et al., supra note 134, at 159. Part three is the length of the health condition. A chronic condition is measured by the number of years remaining for that person’s life expectancy. Id. at 158. In this example, assuming a 20 year life expectancy for a chronic condition, the QALY would be $12,000: ($1,000 health intervention cost) · (.6 quality of life) · (20 years).

Milligan, supra note 133, at 159. Although the $50,000 breakpoint was established in 1982, it is still widely used. Id. at 159, n. 185.

Mark H. Eckman et al., Cost-Effectiveness of Using Pharmacogenetic Information in Warfarin Dosing for Patients With Nonvalvular Atrial Fibrillation, 150 ANNALS OF INTERNAL MED. 73, 78 (2009).

Nanosphere’s test takes 45 to 90 minutes to get results. Even the more complex AutoGenomics system has same day results. Ray (Oct. 10, 2007), supra note 124.

Once a patient in the warfarin pharmacogenetic testing group enrolled in the study, the patient’s physician only had to prescribe one warfarin dose without knowing the patient’s genetic information. McBane et al., supra note 48.
pharmacogenetic test is unlikely to cost less than $500,139 that $200 QALY scenario is unlikely.

Clinicians may decide against using warfarin pharmacogenetic testing to determine initial warfarin dosing because of the above clinical utility and cost effectiveness analyses shortcomings. However, the Warfarin Consortium and Medco-Mayo studies show that when clinicians only take a patient’s phenotypical attributes into account (such as standard starting dosages, age, “race”, and medication interactions), the net result is that they accept status quo warfarin dosing for their patients that are replete with high ADEs.140 Neither clinical utility nor cost effectiveness analyses address how a clinician can effectively predict who the few high risk patients are, as identified in the Medco-Mayo study,141 without warfarin pharmacogenetic test results.

c. **Private Insurance Coverage**

Private insurers often follow Medicare’s lead on coverage issues, sometimes paying a percentage of what Medicare charges.142 Since Medicare has decided not to cover warfarin pharmacogenetic tests,143 that may eliminate coverage by a number of private insurers. Unlike Medicare, private insurers also evaluate the cost effectiveness of a pharmacogenetic test in order to determine whether or not the policy will cover it.144 The current private insurance tally for CYP2C9 and VKORC1 pharmacogenetic testing is as follows: five have determined that the testing is investigational or experimental because there is not sufficient clinical validity or utility information,145 and one covers

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139 See *supra* notes 121–32 and accompanying text.
140 See *supra* notes 95–101 and 110–18, and accompanying text.
141 The Medco-Mayo study found that 4% of its patient-subjects who had pharmacogenetic testing had high sensitivity to warfarin and 2.6% more had very high sensitivity, for a total of 6.6%. The difference in warfarin dosage was .5–2 mg in these two groups versus 5–7 mg for those patients who had normal sensitivity. See *supra* notes 63–64 and accompanying text.
142 Milligan, *supra* note 133, at 155.
143 See *supra* notes 106–09 and accompanying text.
144 Milligan, *supra* note 133, at 155.
Without Medicare and most private insurance coverage, patients may choose to forego clinician-recommended pharmacogenetic testing. Clinicians who weigh patient cost concerns along with conflicting CMS and FDA 2010 warfarin label recommendations may hesitate to recommend warfarin pharmacogenetic testing.

III. LEGAL IMPETUS FOR WARFARIN PHARMACOGENETIC TESTING

A. FDA’s Labeling Requirements as Applied to Warfarin

1. FDA’s Decision to Reconsider its 2007 Coumadin Label

In August of 2007, the FDA revised the Coumadin label to include a discussion of CYP2C9 and VKORC1 pharmacogenetic factors without making a clear recommendation for pharmacogenetic testing. At the time of that 2007 revision, the FDA had not approved any CYP2C9/VKORC1 pharmacogenetic testing.


147 Conti et al., supra note 120, at 6.

148 BRISTOL-MYERS SQUIBB CO. (2007), supra note 7, at 25
tests. That soon changed in September of 2007 when the FDA approved the first of five such test systems.\textsuperscript{149}

Against this backdrop of FDA-approved CYP2C9/VKORC1 pharmacogenetic tests and conflicting clinical utility findings, the FDA evaluated the 2009 Warfarin Consortium study.\textsuperscript{150} Unlike CMS, the FDA’s Center for Drug Evaluation and Research (“CDER”) Director Woodcock and Office of Clinical Pharmacology (“OCP”) Director Lesko supported the Warfarin Consortium study’s conclusions.\textsuperscript{151} The study evaluated the efficacy of pharmacogenetic testing for predicting warfarin dosing,\textsuperscript{152} finding that 46% of warfarin patients benefited from the Warfarin Consortium study’s pharmacogenetic dosing algorithm.\textsuperscript{153} FDA officials Woodcock and Lesko opined that pharmacogenetic testing is the only way to determine in advance which 46% are likely to benefit from warfarin dosing based on pharmacogenetic factors.\textsuperscript{154}

2. 2007 and 2010 Coumadin Label Similarities
   a. Pharmacogenomic Studies

   In January of 2010, the FDA revised the 2007 Coumadin label.\textsuperscript{155} All of the studies relied upon in the 2007 label\textsuperscript{156} are similarly relied upon in the 2010 label.\textsuperscript{157}

   In 2007, under the Clinical Pharmacology heading, the FDA added a Pharmacogenomics subheading that did not exist in prior warfarin labels.\textsuperscript{158} That subheading and all of its contents remain

\textsuperscript{149} See supra notes 75–77 and accompanying text.
\textsuperscript{150} See supra notes 94–98 and accompanying text.
\textsuperscript{151} Woodcock & Lesko, supra note 80, at 811–13.
\textsuperscript{152} The International Warfarin Pharmacogenetics Consortium, supra note 35, at 753–65.
\textsuperscript{153} See supra notes 99–103 and accompanying text for a discussion of the study.
\textsuperscript{154} Id.
\textsuperscript{155} BRISTOL-MYERS SQUIBB CO. (2010), supra note 6, at 1.
\textsuperscript{156} BRISTOL-MYERS SQUIBB CO. (2007), supra note 7, at 4, 28–30.
\textsuperscript{157} BRISTOL-MYERS SQUIBB CO. (2010), supra note 6, at 5, 29–31.
\textsuperscript{158} BRISTOL-MYERS SQUIBB CO. (2007), supra note 7, at 4.
in the 2010 revision. In accordance with Title 21 of the Code of Federal Regulations, section 201.57(c)(2)(i)(B), both labels discuss the studies’ results regarding the variations in the CYP2C9 and VKORC1 genes and other subgroup variables (race, sex, age, etc.).

b. Pharmacogenetic Testing Issues

21 C.F.R. § 201.57(c)(2)(i)(C) requires that a drug label state the “identity” of specific tests “necessary” for monitoring or selecting patients that need the drug. Both of the recent label revisions stop short of identifying by name the specific pharmacogenetic tests that a clinician might order to provide the above warfarin pharmacogenetic data. At least one scholar has argued that this regulation requires FDA to name a pharmacogenetic test within the label.

Although including the name of the test would clearly provide more guidance to the clinician prescriber, it is less clear that the FDA has the authority to do so. If the FDA requires that Manufacturer A (a drug company that manufactures warfarin) cross-label to a product produced by Manufacturer B (a device company that manufactures CYP2C9/VKORC1 pharmacogenetic tests), then Manufacturer A would have to make frequent, costly updates as new pharmacogenetic tests become available. Furthermore, such cross-labeling has the potential to make Manufacturer A liable for a defect in Manufacturer B’s product. Given such burdensome results, this author maintains that the FDA

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163 Id. at 786.
Pharmacogenetic testing for warfarin did not intend 21 C.F.R. § 201.57(c)(2)(i)(C) to require cross-label branding.

Even if the FDA only specifies the type of warfarin pharmacogenetic test, its recommendation will quickly become outdated as warfarin pharmacogenetic test manufacturers create new types of tests. This would still probably require the drug manufacturer to make frequent, costly label updates, but it would seem to satisfy 21 C.F.R. § 201.57(c)(2)(i)(C), as well as provide the clinician with some guidance.

3. 2007 and 2010 Coumadin Label Distinctions
   a. Clinical Pharmacology

      Under the Clinical Pharmacology heading, the excretion subheading follows the Pharmacogenomics subheading in the 2007 label, but precedes it in the 2010 version. Other than a different subheading order, the two label versions include the same Clinical Pharmacology material. In fact, the content of the two labels are virtually identical except for differing provisions under one Dosage and Administration subheading: Initial Dosing.

   b. Dosage Recommendations

      The Code of Federal Regulations chapter 21, § 201.57(c)(2)(i)(B) requires that a drug’s label include available evidence of the drug’s effectiveness and safety in a subgroup of the larger population. The rule cites effectiveness for a specific age group as an example of a population subgroup. If effectiveness and safety evidence only supports the drug’s use within select

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164 Id.
165 As pointed out by Professor Roth, the FDA has precedent for generally mentioning the availability of pharmacogenetic testing with mercaptopurine in the 2003 label, even when that pharmacogenetic testing is not FDA approved. Roth, supra note 162, at 281–82.
population subgroups, the label must include evidence of the drug's "limitations of usefulness."\textsuperscript{170}

Warfarin is not effective and safe unless dosing considerations include its differing effects on myriad population subgroups.\textsuperscript{171} Among them, mixtures of racial and ethnic subgroups are difficult to quantify.\textsuperscript{172} Warfarin pharmacogenetic testing objectively identifies genetic distinctions in warfarin sensitivity that are influenced by racial and ethnic differences, but that are not easily discernable through subjective racial and ethnic phenotypes.\textsuperscript{173} Thus, 21 C.F.R. § 201.57(c)(2)(i)(B) requires that the warfarin drug label include evidence of warfarin's "limitations of usefulness." The 2010 label, and to a lesser extent, the 2007 label, addresses the requisite usefulness limitations under Dosage and Administration.\textsuperscript{174}

21 C.F.R. § 201.100(b)(2) requires that a prescription drug label state either the drug's "recommended" dosage or its "usual" dosage.\textsuperscript{175} 21 C.F.R. § 201.57(c)(3)(i) clarifies that under the Dosage and Administration heading, the label must state what the "recommended dose" is including dosage modifications for "special patient populations" such as "in groups defined by genetic characteristics."\textsuperscript{176}

In both label versions under Dosage and Administration, the first paragraph ends with the following statement in bold type: "The best available information supports the following recommendations for dosing of COUMADIN."\textsuperscript{177} This is followed by information under five subheadings of disease states

\textsuperscript{170} Id.
\textsuperscript{171} 21 C.F.R. § 201.57(c)(3)(C) (2010) requires that the label state appropriate dosages for each subpopulation.
\textsuperscript{172} See supra notes 48, 62–64, and 103 and accompanying text.
\textsuperscript{173} Id.
\textsuperscript{174} BRISTOL-MYERS SQUIBB Co. (2007), supra note 7, at 22-27; BRISTOL-MYERS SQUIBB Co. (2010), supra note 6, at 24-29.
\textsuperscript{175} 21 C.F.R. § 201.100(b)(2) (2010).
\textsuperscript{176} 21 C.F.R. § 201.57(c)(3)(i)(H) (2010).
\textsuperscript{177} BRISTOL-MYERS SQUIBB Co. (2007), supra note 7, at 23; BRISTOL-MYERS SQUIBB Co. (2010), supra note 6, at 24.
or medical conditions. Under each of those subheadings, the label does not state specific dosage recommendations. Rather, each label recommends dosage adjustments to achieve recommended INR ranges. The sixth Dosage and Administration subheading is Initial Dosing, the only category containing substantial differences in content between the 2007 and 2010 labels.

Under Initial Dosing, the 2007 label recommends that the clinician initiate Coumadin at two to five milligrams daily as adjusted by PT/INR results. In contrast to that dosage recommendation, the 2007 revision suggests considering the following changes for special populations:

The lower initiation doses should be considered for patients with certain genetic variations in CYP2C9 and VKORC1 enzymes as well as for elderly and/or debilitated patients and patients with potential to exhibit greater than expected PT/INR responses to COUMADIN....

Unlike the 2007 label, the 2010 revision’s Initial Dosing subheading does not specifically state a “recommended” initial Coumadin dose. The latter label discusses several factors that “influence” the dose needed to maintain (not to initiate) PT/INR target results: clinical (a patient’s weight, age, sex, race, comorbidities, and concomitant medications) and genetic factors

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183 BRISTOL-MYERS SQUIBB CO. (2010), supra note 6, at 26–27.
(CYP2C9/VKORC1 genotypes), acknowledging the existence of other unknown variables that affect dosing. The new label does not repeat the 2007 label’s recommendation of starting initial dosing at two to five milligrams daily. Instead, it evinces a non-mandatory preference for pharmacogenetic testing: “[i]f the patient’s CYP2C9 and VKORC1 genotypes are not known, the initial dose of COUMADIN is usually 2 to 5 mg per day”, which may be a reference to the 21 C.F.R. § 201(b)(2) “usual dosage.”

Under the Initial Dosing subheading, the current label also adds a dosing chart, reprinted in Table 2 below, that incorporates the known warfarin genetic factors. Despite the 21 C.F.R. § 201.57(c)(3)(i) requirement for a “recommended dose” under the label heading, Dosage and Administration, the dosing chart contains expected doses, but does not specify that the FDA recommends these doses.

### Table 2: Range of Expected Therapeutic Warfarin Doses Based on CYP2C9 and VKORC1 Genotypes

<table>
<thead>
<tr>
<th>VKORC1</th>
<th>CYP2C9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>*1/*1</td>
</tr>
<tr>
<td>GG</td>
<td>5–7 mg</td>
</tr>
<tr>
<td>AG</td>
<td>5–7 mg</td>
</tr>
<tr>
<td>AA</td>
<td>3–4 mg</td>
</tr>
</tbody>
</table>

Ranges are derived from multiple published clinical studies. Other clinical factors (e.g., age, race, body weight, sex, concomitant medications, and comorbidities) are generally accounted for along with genotype in the ranges expressed in the table. VKORC1 –1639 G>A (rs9923231) variant is used in this

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184 Id. at 26. However, the 2010 label later states that a patient’s clinical factors are generally accounted for in their dosage chart that adjusts dosages solely based on a patient’s genetic factors, obviating the need to consider those clinical factors if the clinician obtains the patient’s CYP2C9 and VKORC1 genotypes. Id. at 27.
185 Id. (emphasis added).
186 Id. at 27.
187 Id. at 24–29.
188 BRISTOL-MYERS SQUIBB CO. (2010), supra note 6, at 26-27.
Other co-inherited VKORC1 variants may also be important determinants of warfarin dose. Patients with CYP2C9 *1/*3, *2/*2, *2/*3, and *3/*3 may require more prolonged time (>2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen.\footnote{\textit{Id.} at 27.}

On its surface, the 2010 label does not appear to be in compliance with the 21 C.F.R. § 201.57(c)(3)(i) requirement of a “recommended dose” under Dosage and Administration. Though there are recommendations for INR levels and a recommendation against loading doses, the Initial Dosing verbiage contains no specific recommendations for the actual doses.\footnote{\textit{Id.} at 26-27.}

It is an axiom of administrative law that “agencies are entitled to a presumption that they ‘act properly and according to law.’”\footnote{Kohli v. Gonzales, 473 F.3d 1061, 1068 (9th Cir. 2007) (quoting FCC v. Schreiber, 381 U.S. 279, 296 (1965)).} Given this assumption, it is appropriate to presume that the FDA intended the 2010 label to comply with the C.F.R. dosage recommendation requirement. In order to do so, the FDA must have intended its reference to “the following recommendations for dosing of COUMADIN”\footnote{\textit{Bristol-Myers Squibb Co.} (2010), \textit{supra} note 6, at 24.} to apply to the content of all of the Dosage and Administration subheadings following that bolded statement. Therefore, a reasonable construction of the FDA’s 2010 statement of preference for initial dosing based on the “patient’s CYP2C9 and VKORC1 genotypes”, the FDA’s dosing chart, and the 2–5 mg genotype starting dose when the genotype is unknown is that those are the FDA’s initial dosage recommendations. Although the FDA gave allowances for situations where the genotype is unknown, it indicated a preference for using the pharmacogenetic information, stating that “when available, [it] can assist in selection of the starting dose.”\footnote{\textit{Id.} at 26.} A necessary corollary to this dosing recommendation preference is that the FDA must also be recommending pharmacogenetic testing, though not the branded name of that test, to discover CYP2C9 and VKORC1 genotypes.
because those genotypes are integral to the FDA’s dosing recommendations.\textsuperscript{194}

B. Liability Issues Arising from 2010 Coumadin Label

The PPACA authorizes the immediate establishment of an independent, non-government, Washington, D.C. non-profit corporation known as the Patient-Centered Outcomes Research Institute ("Institute").\textsuperscript{195} The Institute will compare “health outcomes and the clinical effectiveness, risks, and benefits of 2 or more medical treatments, services, and items"\textsuperscript{196} taking into account various subpopulations, such as individuals with different "genetic and molecular sub-types."\textsuperscript{197} If “feasible and appropriate,” the studies must include members of those subpopulations.\textsuperscript{198} The Institute’s governing board must identify research priorities; establish a research project agenda; and carry out that agenda by assessing past and future research, conducting primary research, and contracting for research.\textsuperscript{199}

The Institute’s governing board may decide to grant research priority to establish the clinical effectiveness of warfarin

\textsuperscript{194} The 2007 label contains the same language as the 2010 label regarding “the following recommendations for dosing of Coumadin.” \textbf{BRISTOL-MYERS SQUIBB Co.} (2007), \textit{supra} note 7, at 23. Two pharmacy professors at the University of California-San Diego and a genetics professor at the University of Florida College of Pharmacy-Gainesville agree that the 2007 Coumadin label also recommends pharmacogenetic testing. Shin et al., \textit{supra} note 65, at 630.

\textsuperscript{195} \textbf{Patient Protection and Affordable Care Act of 2010}, Pub. L. 11-148, 124 Stat. 119 § 6301(a) (2010) (amending Social Security Act § 1181(b)(1)–(2), (d)(2)(A)(i)), 42 U.S.C. § 1320e(b)(1)–(2), and (d)(2)(A)(i)) (2006)). It is unclear who has the authority to establish this Institute; though, the Comptroller General of the United States has the responsibility to appoint its Governing Board and Methodology Committee members. Social Security Act § 1181 (d)(6), (f)(1)(C) (as amended by PPACA § 6301(a) (2010)).

\textsuperscript{196} Social Security Act § 1181(a)(2)(A) (as amended by PPACA § 6301(a) (2010)).

\textsuperscript{197} \textit{Id.} § (d)(2)(D).

\textsuperscript{198} \textit{Id.} The United States Comptroller General must appoint a governing board and methodological committee whose members will include patients/consumers, a federal agency/program, National Institutes of Health, Agency for Healthcare Research and Quality, health care workers, and private payers. \textit{Id.} § (d).

\textsuperscript{199} \textit{Id.} § (d)(1)–(2).
pharmacogenetic testing given the disparity among the CMS study, the Medco-Mayo study, and the FDA’s 2010 Coumadin label recommendations. This possibility is even more likely if the Comptroller General includes an FDA member as its representative of “a Federal health program or agency” on the governing board.  

Since any such review or study must incorporate patients in subpopulations with a propensity for warfarin genetic susceptibilities, such as those of African and Asian ethnicities, the results ought to contain more of the genetic outliers who require substantially increased or decreased warfarin in initial dosing.

An independent Institute analysis is more likely to result in a decision favoring warfarin pharmacogenetic sensitivity testing. However, it will take at least two years after the Institute is established before its governing board can initiate such an analysis. In the meantime, manufacturers, pharmacists, health

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200 Id. § (f)(6).

201 See supra notes 48, 62–64, 103, and accompanying text.

202 See supra notes 80–83, 151–54 and accompanying text for a discussion of these outliers as identified by FDA Center Directors Woodcock and Lesko.

care institutions, physicians, and other health care workers must navigate through an uncertain legal minefield.

1. **Manufacturer Product Liability—Caution Issues**

Under product liability law, a prescription drug manufacturer is liable if it sells or distributes a defective prescription, the defect causes a person harm, and at the time of the sale or distribution any of the following occur:

- The prescription drug manufacturer does not give reasonable instructions or warnings of foreseeable risks of harm to:
  - The health care provider (including the prescriber), if the health care provider would have been able to reduce those risks at the time of the sale or distribution had the health care provider received the manufacturer’s instructions or warnings; or
  - The patient, if the manufacturer had reason to know that the health care provider would have been able to reduce those risks had the health care provider received the manufacturer’s instructions or warnings;

- A reasonable health care provider, knowing the foreseeable treatment risks and benefits, would not have prescribed the drug “for any class of patients; or”

- The defect results from the product’s design.

In each of the above instances, the manufacturer is liable regardless of whether the manufacturer exercised reasonable care, a strict liability standard.

a. **Learned Intermediary Defense**

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205 ld. § 6(b)(3), (d)(1).
206 ld. § 6(b)(3), (d)(2).
207 ld. § 6(b)(2), (c).
208 ld. § 6(a)–(b) (1), 2(a).
209 ld. §§ 2, 6.
The learned intermediary doctrine limits a prescription drug manufacturer's liability to the patient by warning the clinician, the learned intermediary, of the drug's risks to the patient. The premise of this defense is that the manufacturer-provided drug information is directed to the health care clinician who acts as the intermediary between the manufacturer and the patient to avoid patient injury. Under this theory, if a warfarin manufacturer places sufficient patient genetic-susceptibility information on the warfarin prescription label, the manufacturer has fulfilled its obligation to warn the patient.

In 1966, the judge in *Sterling Drug v. Cornish* first gave the learned intermediary doctrine its name. Since that time, courts have retreated from the notion that manufacturers have no obligation to provide pertinent medication information directly to potential patients. Courts have increasingly granted patients the right to participate in decisions regarding their own medical care. Just as it is no longer solely within physicians' discretion to decide whether patients should have access to their own medical information, sometimes it is no longer within manufacturers' sole discretion to only provide the learned intermediaries with patient medication information. Over the last fifteen years, manufacturers have targeted patients through direct to consumer ("DTC") prescription drug advertising. This DTC advertising certainly seems to obviate the premise behind the *Sterling Drug v. Cornish* learned intermediary doctrine that the doctor is acting as the intermediary. At least two state supreme courts agree with this trend; in 2007, West Virginia followed New Jersey's lead in

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210 Sterling Drug, Inc. v. Cornish, 370 F.2d 82, 85 (8th Cir. 1966).
212 *Sterling*, 370 F.2d at 85.
213 Castagnera & Gerner, *supra* note 211, at 123.
214 Id.
215 Id.
eliminating the defense.\textsuperscript{217} In \textit{Perez v. Wyeth Laboratories}, the court ruled that the New Jersey statute that codifies the learned intermediary doctrine “does not confer on pharmaceutical manufacturers a license to mislead or deceive consumers when those manufacturers elect to exercise their right to advertise their product directly to such consumers.”\textsuperscript{218}

However, one of the reasons that the learned intermediary doctrine has had such staying power is that it recognizes that the real issue with manufacturer liability is causation. It is more difficult to prove that the manufacturer’s actions are the direct cause of the patient’s injuries when the health care provider’s treatment decision adds an intervening cause for those injuries.

This is especially true when the clinician lawfully prescribes a medication off-label, either for a different use or for a different dosage than recommended on the prescription drug label.\textsuperscript{219} The manufacturer makes safety and efficacy claims based on clinical study results with the backing of FDA-approved uses and dosages.\textsuperscript{220} The clinician’s intervening off-label prescribing breaks the chain of causation between the acts of a prescription drug manufacturer and the patients’ injuries. Warfarin-injured patients will have difficulty reaching into a warfarin manufacturer’s deep pockets if the patients’ clinicians prescribe warfarin off-label and without pharmacogenetic testing (unless a manufacturer illegally


\textsuperscript{218} \textit{Perez v. Wyeth Laboratories}, 734 A.2d 1245, 1264 (N.J. 1999).

\textsuperscript{219} Clinician off-label use of prescription drugs is lawful. However, its off-label promotion can violate several federal laws. The FDA usually regulates manufacturers’ off-label promotions of prescription drugs under federal misbranding statutes. For a more in-depth discussion of FDA’s authority in this area, see \textit{Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices}, \textit{FOOD & DRUG ADMIN.} (Jan. 2009), \url{http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm}. The safe harbor provision of the Food and Drug Administration Modernization Act (“FDAMA”) relied upon in \textit{Washington Legal Found. v. Henney}, 128 F. Supp. 2d 11 (D.C. 2000) has since been repealed. Without the FDAMA safe harbor provision, the legal effect of FDA’s current guidance on Good Reprint Practices is murky.

\textsuperscript{220} \textit{Id.}
promotes off-label prescribing, or warfarin is not reasonably safe because of unclear or inadequate instructions).

b. **Specific Causation Defense**

Despite movement toward more patient health care autonomy, the few plaintiffs who have brought genetic susceptibility lawsuits against prescription drug manufacturers have had little success. Plaintiffs have been stymied by their failure to prove specific causal connections between their injuries and genetic susceptibility to the manufacturers’ product.

_Easter v. Aventis Pasteur, Inc._ is an illustrative example. The plaintiffs alleged that the defendant manufacturer’s thimerosal-containing vaccine caused their autistic son’s numerous comorbid neurological conditions. The Easters conceded that they could not prove that thimerosal caused their son, Jordan’s, autism because he does not fit the genetic profile for alleged thimerosal susceptibility. The Easters sought to have their expert testify that there is a correlation between Jordan’s neurological conditions and his combined thimerosal exposure. The court ruled that a plaintiff must prove both general and specific causation. General causation in the _Easter_ case would have been present if the plaintiff had proved that thimerosal caused the same type of injuries claimed by the plaintiff. Specif
causation would have been present if the plaintiff had proved that thimerosal caused the injuries to this specific plaintiff.\textsuperscript{230}

In order to determine that the defendant’s thimerosal-containing product specifically caused Jordan’s neurological conditions, the plaintiffs’ expert would have to eliminate other potential causes for Jordan’s injuries.\textsuperscript{231} Even if thimerosal caused autism in some recipients, other factors caused autism in patients who were not thimerosal recipients.\textsuperscript{232} Since Jordan admittedly did not have a genetic susceptibility to thimerosal, the court reasoned that Jordan’s neurological conditions were really aspects of his autism.\textsuperscript{233} Without Jordan having a genetic susceptibility to thimerosal, the Easters could not prove specific causation, that thimerosal caused Jordan’s neurological conditions.\textsuperscript{234} The court excluded the plaintiffs’ expert’s testimony of a thimerosal-neurological injury correlation because a thimerosal correlation would not be relevant to this specific patient who is not genetically susceptible to thimerosal.\textsuperscript{235} Thus, the proposed testimony would not provide evidentiary proof of specific causation.\textsuperscript{236} Presumably, if the plaintiffs had offered evidence demonstrating that Jordan had the polymorphism that confers this genetic susceptibility, the judge would have allowed the plaintiffs’ expert to testify at the hearing. In order to prevail in the lawsuit, the Easters would then have had to prove the causal relationship between the manufacturer’s thimerosal-containing vaccine and autism in individuals with that particular genetic susceptibility.

c. Failure to Warn

Manufacturers will often counter plaintiffs’ failure to warn causes of action with the learned intermediary or other causation defenses.\textsuperscript{237} A failure to warn cause of action may prove successful in jurisdictions that eliminate the learned intermediary defense

\textsuperscript{230} Id. at 576.
\textsuperscript{231} Id.
\textsuperscript{232} Id. at 577.
\textsuperscript{233} Id. at 579.
\textsuperscript{234} Id.
\textsuperscript{235} Id.
\textsuperscript{236} Id.
\textsuperscript{237} See supra Part III.B.1.a and Part III.B.1.b.
when a manufacturer engages in deceptive DTC advertising.\textsuperscript{238} The learned intermediary is also not a defense to the manufacturer’s failure to warn in vaccine lawsuits.\textsuperscript{239} Thus, a manufacturer’s failure to warn patients of potential genetic susceptibilities to a vaccine may be relevant to plaintiffs harmed by undiagnosed warfarin genetic susceptibilities.

In \textit{Cassidy v. SmithKline Beecham}, LYMErix vaccine patients filed a lawsuit against SmithKline Beecham alleging that the manufacturer’s LYMErix vaccine caused the patients’ treatment-resistant arthritis due to the patients’ HLA-DR4 genetic susceptibility.\textsuperscript{240} The patients argued that the manufacturer had a legal duty to warn the LYMErix vaccine’s patient recipients of the vaccine’s arthritis potential in patients who have the HLA-DR4 genetic polymorphism.\textsuperscript{241} The defendant argued that people who have that HLA-DR4 genetic polymorphism have an independent genetic susceptibility risk for treatment-resistant arthritis. The vaccine does not increase that risk.\textsuperscript{242} The parties settled the case prior to trial.\textsuperscript{243}

The manufacturer’s stance was probably correct. Although the plaintiffs may have been able to prove that they had both the HLA-DR4 genetic polymorphism and treatment-resistant arthritis, proving general causation would have been problematic. The

\textsuperscript{238} See supra notes 216–18 and accompanying text.

\textsuperscript{239} The National Vaccine Injury Compensation Program establishes a no-fault compensation process through the vaccine courts. A vaccine manufacturer is not liable for injury from a faulty vaccine unless the plaintiff first tries the case through the vaccine court, rejects the vaccine court’s judgement, and then files a civil lawsuit in a state or federal court. 42 U.S.C. § 300aa-11 (2006). In situations outside of the vaccine court, the manufacturer can be liable for damages. According to the Restatement (Third) of Torts, the learned intermediary defense is not available to a manufacturer in a vaccine case or in other cases in which the health care provider has less of an intermediary role between the manufacturer and the patient. \textit{Restatement (Third) of Torts: Prod. Liab.} § 6(d)(2), cmt. e (1998). Thus, the manufacturer has a duty to directly warn the patient who receives the vaccine. \textit{Id.}


\textsuperscript{241} \textit{Id.}

\textsuperscript{242} \textit{Id.}

\textsuperscript{243} \textit{Id.}
Centers for Disease Control and Prevention found no adverse event evidence to substantiate linking those factors to the LYMErix vaccine.244

A plaintiff claiming warfarin dosing injuries might successfully sue a warfarin manufacturer for failure to warn patients of potential genetic susceptibility to high or low warfarin dosages. Unlike the situation in Cassidy, there should be no general causation hurdles. There is ample evidence of warfarin sensitivity with specific CYP2C9 and VKORC1 polymorphism combinations and FDA label recommendations for pharmacogenetic testing. Borrowing the rationale from the Easter case, the manufacturer might effectively argue that there is an absence of specific causation if the plaintiff does not prove that the plaintiff has a particular genetic susceptibility. In order to support an alternative causation defense, the manufacturer could also petition for a court order that would require the plaintiff to undergo genetic testing for other genetic traits that might explain the plaintiff’s injuries.245 Similar to the plaintiffs’ issue in the Easter case, a warfarin manufacturer raising an alternative causation defense is not likely to prevail unless the testing shows that the plaintiff actually has those alternative genetic traits.246

If a Plaintiff can show a genetic basis to prove specific causation, general causation may be a moot issue:

By shifting the specific causation inquiry from statistical rules of thumb or subjective medical assessments to molecular changes within the plaintiff’s own cells, genetic biomarkers such as gene expression signatures have the potential to make specific causation significantly more

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246 Id.
objective and reliable. It may even obviate the need for general causation, because if a party can directly show, using gene expression markers, that a particular toxic agent caused (or did not cause) his or her toxic response, that party establishes causation without any need to make a separate general causation finding.\textsuperscript{247}

If specific causation issues are resolved, it is conceivable that a patient with CYP2C9*3/*3, VKORC1–1639 AA alleles who is injured by too high of an initial warfarin dose might argue that the warfarin manufacturer failed to warn patients of this genetic possibility. In the age of the Internet, a manufacturer may have less success asserting the learned intermediary doctrine as its defense. In response to this defense, might the plaintiff find purchase arguing that a warfarin manufacturer has a duty to recommend pharmacogenetic testing on its warfarin web site because such sites amount to DTC advertising?

Similar DTC advertising issues arise with the warfarin label which is also available online. Both the 2007 and 2010 Coumadin labels contain the Information for Patients subheading under Precautions.\textsuperscript{248} Neither labels’ Information for Patients discusses the patients’ genetic susceptibility. The labels recommend that patients should receive a manufacturer’s Medication Guide, which is at the end of the labels.\textsuperscript{249} Yet neither patient Medication Guide warns patients of their potential genetic susceptibility, an omission that may result in manufacturer liability.

2. \textit{Pharmacist and Health Care Institution Liability}

A pharmacist has a legal duty to exercise “reasonable care” when selling a prescription drug.\textsuperscript{250} If a patient’s injury is caused by the pharmacist’s failure to exercise that reasonable care, then the pharmacist may be subject to liability.

\begin{footnotesize}
\textsuperscript{247} \textit{id.} at 27.
\textsuperscript{248} \textit{Bristol-Myers Squibb Co.} (2007), supra note 7, at 19–20; \textit{Bristol-Myers Squibb Co.} (2010), supra note 6, at 20–21.
\textsuperscript{249} \textit{Bristol-Myers Squibb Co.} (2007), supra note 7, at 31–34; \textit{Bristol-Myers Squibb Co.} (2010), supra note 6, at 34–39.
\textsuperscript{250} \textit{Restatement (Third) of Torts: Prod. Liab.} § 6(e)(2) (1998).
\end{footnotesize}
Reasonable care encompasses duties beyond the physical processing of the prescription. This is a negligence, not a strict liability, standard. A pharmacist’s professional responsibility is based on the knowledge that the pharmacist is expected to have. This knowledge determines whether the harm to the patient was foreseeable. However, this presumed knowledge base expands as pharmacists increasingly become more involved in patient care, as when pharmacists manage anticoagulation clinics.

In Jeffries v. United States, the plaintiff, Mr. Eason, received anticoagulation therapy treatment at a veteran’s hospital anticoagulation clinic managed by Dr. Paysinger, a clinical pharmacist. Dr. Paysinger lowered the patient’s warfarin prior to the patient’s planned dental surgery. The plaintiff alleged that Mr. Eason’s subsequent stroke resulted from Dr. Paysinger continuing Mr. Eason on warfarin, despite an INR well below the patient’s target treatment range, instead of administering a faster-acting heparin product. Dr. Paysinger testified that she did not administer a heparin product because she was concerned about the patient’s bleeding risks.

The court agreed that Dr. Paysinger’s conduct fell below the standard of medical care based on the plaintiff’s two physician experts and partially on the defendant’s physician expert testimonies. Although the defendant’s physician agreed with the plaintiff’s experts as to a physician’s standard of care, he testified

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252 Id.
253 Id.
254 Id.
256 Id. at *7–8.
257 Id. at *10.
258 Id. at *7–8.
that he was not familiar with a pharmacist’s standard of care. The court quoted the appropriate, objective standard of care as one that is "ordinarily possessed and exercised by a minimally competent and reasonably diligent, skillful, careful, and prudent physician in that field of practice...."

The concern with this decision for future pharmacist liability is that the court held Dr. Paysinger to a physician’s standard of care despite the fact that Dr. Paysinger is a pharmacist, not a physician. However, the broader implication may be that health care institutions are particularly vulnerable due to the depth of their pockets. It is important to note that the defendant in this case was not Dr. Paysinger; it was the veteran’s hospital. Perhaps one lesson for a health care institution is that its responsibility for a physician medical care standard in its anticoagulation clinic cannot be delegated to create a lower standard of care threshold. With the 2010 warfarin pharmacogenetic testing label recommendations, a health care institution may be held liable for their pharmacist or other health care provider employee who does not order or correctly interpret warfarin pharmacogenetic testing.

3. Physician Liability

Physicians, as well as other health care professionals, are liable for standards of care based on negligence, not the strict liability standard to which pharmaceutical manufacturers are held. That
standard of care for physicians encompasses patient diagnosis and making patient treatment decisions with the patient by getting informed consent for treatment. This involves providing enough material information so that the patient can weigh the risks and benefits to be able to give informed consent. The physician must accomplish all of this while adhering to the standards inherent in their fiduciary relationship with their patients: to look after their patients' best interests by staying current in their fields of specialty.

Pharmacogenetics adds another interesting wrinkle. Physicians may have a fiduciary duty to make pharmacogenetic treatment recommendations. This would require the physician to know when to order genetic tests, which tests to order, where to send the patient to be tested, and how to interpret the results. In the case of warfarin sensitivity, with conflicting clinical utility assessments, their roles have become much more complex.

a. Genetics Quandary

It was not until December 27, 2001 that the American Society of Human Genetics and the Association of Professors of Human and Medical Genetics developed guidelines recommending genetic classes in medical schools' core curriculum. Consequently,

(2009). This analysis is also applicable to nurse practitioners, and other health care professionals who provide the same role as physicians with regard to a patient's warfarin therapy management. Id.

265 Id. at 855.
266 Id.
267 Id.
268 Id.

physicians who graduated from medical school prior to 2002 may not have had much in the way of genetics training.

In a more perfect world, a physician might rely on the services of professionally-trained geneticists. Unfortunately, there are few board certified genetic counselors and medical geneticists, the professionals best equipped to explain genetic test results. For example, in Arizona there are only twenty-seven genetic counselors who are members of the National Society of Genetic Counselors, and limited certified geneticist curriculums exist in Arizona. There are approximately 509 physician-geneticists scattered unevenly across the United States; Arizona has between one and five of them.

The few genetic counselors who are available nation-wide are seldom subject to any state licensing regulations. Yet, they and physician-geneticists are far better equipped to recommend, interpret, and explain pharmacogenetic tests than medical providers untrained in genetics. By default, physicians who are


272 The American Board of Genetic Counseling certifies genetic counselors.

273 Gary E. Marchant, Executive Director & Faculty Fellow, Center for Law, Science & Innovation at Arizona State University College of Law, Class lecture in Genetics and the Law (Aug. 29, 2008).


275 Id.


277 Prior to 2002, physicians were not routinely trained in genetics. See APHMG/ASHG, supra note 269 and accompanying text.
not geneticists must increasingly risk liability to perform these genetic functions.\textsuperscript{278} It is not surprising that many physicians resist changing their practices to include pharmacogenetic testing when they have so little access to both genetic training and genetics experts to help them.\textsuperscript{279} Yet, physicians and other health care professionals with little genetics training have the most risk of liability for their failure to incorporate pharmacogenetics.\textsuperscript{280}

b. Issues in Determining the Standard of Care

It is difficult for a physician to establish what the standard of care is for treating warfarin patients. One of the problems is that by its very nature, patient CYP2C9 and VKORC1 warfarin sensitivity testing occurs at the same time as the initial warfarin dosing.\textsuperscript{281} Therefore, it is difficult to determine whether the clinical utility is from the warfarin or from the warfarin pharmacogenic test.\textsuperscript{282} An adverse event related to the test may be reported as a failure of the medication and vice versa:

For drugs with known or suspected genetic variability of patient response, adverse-event reports may need to include information about whether a TAB [treatment-adaptive biomarker] test was performed at all and, if so, which specific test was used; what the test result was; and whether the clinician's decision to prescribe the drug was in line with the current understanding of which drugs are appropriate for patients with similar test results. This level of detail is needed to support future improvements in drug targeting . . . .\textsuperscript{283}

In part, this may explain the disparate warfarin study results. The fact remains that often the only way physicians can identify the warfarin patients at either extreme of sensitivity is from the results of their patients' FDA label recommended CYP2C9/

\textsuperscript{278} Michael J. Malinowski, \textit{Coming into Being: Law, Ethics, and the Practice of Prenatal Genetic Screening}, 45 Hastings L.J. 1435, 1493 (1994).


\textsuperscript{280} Id.

\textsuperscript{281} See supra Part II.

\textsuperscript{282} Evans, supra note 162, at 761.

\textsuperscript{283} Id. at 771.
VKORC1 testing. Patients’ phenotypical characteristics have not been as reliable for predicting safe initial dosing.\textsuperscript{284}

A plaintiff could conceivably argue that the 2010 Coumadin revised label dosing recommendations create a new standard of care that requires warfarin pharmacogenetic testing concurrent with initial warfarin dosing. An issue inherent in that argument is whether the FDA’s regulatory actions that produced these new label recommendations preempt more lenient physician prescribing practices under state tort law.

In most jurisdictions, a plaintiff who sues a physician for medical malpractice must prove that the defendant did not meet the standard of care (knowledge and skill) of physicians “in good standing in similar communities.”\textsuperscript{285} Thus, a physician will likely respond to the plaintiff’s argument by asserting that the FDA’s dosing recommendations do not necessarily represent local medical practice standards of care. In fact, in some situations where the FDA label has not kept pace with scientific discoveries, off-label use may constitute the safest standard of care in the medical community.\textsuperscript{286} However, other off-label uses may be dangerous if physicians ignore screening tests which indicate that the patient is at high risk for having an adverse reaction\textsuperscript{287} (as when a physician prescribes an average warfarin dose despite the patient’s genotypical results indicating a very high warfarin sensitivity and hemorrhage risk). In the latter scenario, with the gathering of individualized patient pharmacogenetic information, FDA “product regulation necessarily touches matters traditionally

\textsuperscript{284} See supra notes 48, 62–64, 103 and accompanying text.

\textsuperscript{285} RESTATEMENT (SECOND) OF TORTS § 299A (1965).


seen as medical-practice issues....", hence, the need for a *Wyeth v. Levine*289 permitted FDA preemption in this area.

In *Wyeth*, the Vermont courts found that the plaintiff’s arm was amputated due to gangrene caused by a clinician’s use of an intravenous ("IV")-push method to inject a medication into the plaintiff’s arm instead of the safer IV-drip method.290 The Vermont Supreme Court affirmed that the drug’s manufacturer, Wyeth, was liable to the plaintiff due to Wyeth’s failure to warn clinicians of the heightened gangrene risks associated with the IV-push injection method.291 Wyeth appealed the decision to the United States Supreme Court arguing that the FDA’s actions in approving the drug’s label without the IV-push injection gangrene warning preempted the state’s product liability claims.292

In denying Wyeth’s federal preemption claim, the Court noted that the FDA sets federal labeling standards as “minimal standards” or “a floor upon which States could build” by adding state labeling requirements.293 *Wyeth* does not preclude federal preemption on a case by case basis depending “on the substance of state and federal law.”294 The Court has given some deference to an agency’s preemption position in cases where “the subject matter is technica[l] and the relevant history and background are complex and extensive.”295

The *Wyeth* decision points out that the state standard, requiring the IV-push method gangrene warning, disclosed more consumer safety risks than the minimum standard in the FDA label which omitted that warning.296 Whereas, a state standard, initiating warfarin dosing without warfarin pharmacogenetic testing, would disclose less consumer safety risks than the FDA’s 2010 label

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288 *id.*
290 *id.* at 1191–92.
291 *id.* at 1193.
292 *id.*
293 *id.* at 1202.
294 *id.* at 1200–01.
296 *id.* at 1196–97.
.recommending that testing. Applying *Wyeth*, it would certainly be plausible for a court to rule that the warfarin label’s pharmacogenetic dosing recommendation sets a minimum federal safety standard that warrants federal preemption when state law fails to meet that minimum standard, especially given the extensive, complex, technical debate regarding the clinical utility of warfarin pharmacogenetic testing.

### IV. CONCLUSION: BETWEEN A ROCK AND A HARD PLACE

#### A. The Status Quo

Will the FDA’s 2010 changes to the warfarin label finally provide the legal impetus for warfarin pharmacogenetic testing? The legal impetus exists, but cost considerations may ultimately defeat the promise of warfarin pharmacogenetic testing. One of the problems that physicians and other health care providers may encounter with their new found genetic duties is that a typical ten minute office visit will be insufficient. Health clinicians who want to take advantage of warfarin pharmacogenetic testing for their patients must have the time to explain the feasibility of genetic testing needed in order to get the patient’s informed consent, and to later explain the results of that testing.

Patient out-of-pocket cost for the extra office visits and the pharmacogenetic testing result in a health care conundrum. The logistics for acquiring timely third party coverage for warfarin pharmacogenomic testing is daunting. Most patients who are prescribed warfarin are older than average; many will be on Medicare. The clinician would have to prescribe the Medicare patient’s first warfarin dose while simultaneously enrolling the patient in a Medicare approved clinical trial that studies the clinical utility of warfarin pharmacogenetic testing. Otherwise, Medicare will not cover the pharmacogenetic costs, or presumably, the associated counseling required. Most private insurers also do not cover CYP2C9/VKORC1 warfarin sensitivity testing. If the patients are unwilling or unable to pay for the testing, the clinicians are effectively prevented from providing their patients with what may be the appropriate standard of care: pharmacogenetic testing concurrent with initial warfarin dosing.
Consequently, the net result of the 2010 label changes may be a giant paper shuffle. Attorneys will advise clinicians to document their patient recommendations for warfarin sensitivity testing. The health care provider will then produce a form and ask their patients to sign off that they are making informed decisions to waive their rights to have the testing. Finally, the form will need to contain a statement that the patients will not hold the clinicians liable for the patients’ testing refusals.

B. Recommendations for Change

The warfarin pharmacogenetic testing clinical utility and funding debacle is a harbinger of the battles that lie ahead for personalized medicine. In particular, there will be an inevitable increase in pharmacogenetic testing prompted by new genetic-medication associations. There need to be more efficient, flexible processes to both evaluate and take advantage of pharmacogenetic advances.

The 2010 Patient Protection and Affordable Care Act clinical effectiveness testing and uniform health care standards mandating this insurance coverage should eventually help to alleviate some of these roadblocks, but the Act requires some administrative actions in order to achieve PPACA’s benefits in two areas.

First, before implementing an independent analysis of the clinical utility of pharmacogenetic testing versus an alternative, the government must establish an independent, non-government, non-profit corporation, the Patient-Centered Outcomes Research Institute. Funding for the Institute is available in a trust fund beginning in 2010, but PPACA does not specify who is authorized to establish this nonprofit corporation. Congress needs to either amend PPACA § 6301(a) to grant that authority or pass clarifying regulations so that the Institute can be established. With all of the built in waiting periods, it will still take some time after the Institute’s establishment before it can become functional. Second, the Secretary of Health and Human Services (“HHS”) has

yet to define the specifics of what constitutes basic “essential health benefits” in year 2014. HHS rules need to explicitly address whether PPACA uniform health care standards and essential health benefits require pharmacogenetic private and public insurance coverage.

In the meantime, Congress and the FDA have a role to play by implementing new legislation and FDA regulations. Despite the confusion over clinical utility for warfarin pharmacogenetic testing, there have been no serious issues raised as to the clinical validity of the testing to detect warfarin sensitivity.

Applying the rationale in Wyeth, the FDA should draft a regulation for public comment that FDA label recommendations, that apply to pharmacogenetic testing for dosing recommendation, set a minimum federal safety standard. That minimum standard should warrant federal preemption when the state law standard falls below the FDA’s. The rationale justifying federal preemption in this limited area is reiterated in Wyeth, “the subject matter is technical and the relevant history and background are complex and extensive.” Alternatively, the FDA could again revise the Coumadin label to make FDA approved warfarin pharmacogenetic testing mandatory. However, that would require frequent, costly warfarin label revisions to address changing parameters of what constitutes a warfarin pharmacogenetic test since technological advances are likely to result in updated tests.

Ideally, in order to avoid the litigation that would likely follow the above two alternatives, Congress should amend the Food and Drug Administration Amendments Act of 2007 to give the FDA more statutory authority to determine when it should require pharmacogenetic testing for existing prescription medications to mitigate risks of serious injury in susceptible patients.


