Published in final edited form as:

J Law Med Ethics. 2016 March ; 44(1): 194–204. doi:10.1177/1073110516644210.

Contrasting Medical and Legal Standards of Evidence: A Precision Medicine Case Study

Gary E. Marchant*, Kathryn Scheckel, and Doug Campos-Outcalt

Precis

As the health care system transitions to a precision medicine approach that tailors clinical care to the genetic profile of the individual patient, there is a potential tension between the clinical uptake of new technologies by providers and the legal system's expectation of the standard of care in applying such technologies. We examine this tension by comparing the type of evidence that physicians and courts are likely to rely on in determining a duty to recommend pharmacogenetic testing of patients prescribed the oral anti-coagulant drug warfarin. There is a large body of inconsistent evidence and factors for and against such testing, but physicians and courts are likely to weigh this evidence differently. The potential implications for medical malpractice risk are evaluated and discussed.

Our medical system is shifting from a one-size-fits-all approach to a new paradigm centered on personalized or precision medicine – targeting health care to a patient's unique molecular and genetic profile. President Obama recently announced a major new initiative to speed the clinical implementation of precision medicine, described as “an innovative approach to disease prevention and treatment that takes into account individual differences in people's genes, environments, and lifestyles.”¹ One of the key elements of precision medicine is pharmacogenetics, the study of genetic differences that impact individual response to drugs.

The clinical implementation of precision medicine generally, and pharmacogenetics specifically, has been much slower than many experts originally anticipated. A number of factors have contributed to this slow implementation, including the lack of validated biomarkers, insufficient evidence of clinical utility, regulatory uncertainty, lack of reimbursement, and outdated business models. But another important impediment has been the unfamiliarity and reluctance of health care providers to integrating genetic tests into clinical decision-making.²

With increasing availability of genetic and molecular data, there is a growing potential for divergence between medical practice and applicable legal standards of care. Physicians are often slow to uptake new medical technology.³ This is due in part to inertial forces having to do with the individual physician's training and knowledge, cost and reimbursement issues, lack of clear clinical guidelines, and the transaction costs of learning and applying new technologies. But this reticence to take up new technologies is also based on caution about premature adoption of technologies with unproven clinical value. Many of the expectations

*Corresponding author: Phone: 480-965-3246 (office); 480-388-7004 (cell); 480-727-6973 (fax); gary.marchant@asu.edu.

about the clinical use of genetics have been overly-optimistic, and in many cases may not comport with an evidence-based medicine approach.⁴

The legal system tends to be less reticent, and will often push actors to adopt new technologies more quickly than would otherwise occur. This is in part because the legal system is usually looking at the case of a specific patient after an injury has already occurred. From this hindsight perspective,⁵ the case for delaying implementation of a technology that may have prevented the injury is much less compelling than how it may have looked prospectively to the physician at the time of the initial clinical recommendation. In part due to this divergence between medical and legal perspectives, new medical technologies are one of the most important drivers of medical malpractice liability.⁶

For many years, experts have warned that liability concerns may influence (perhaps inappropriately) the decisions of health care providers to recommend genetic testing.⁷ As access to genomic information becomes more ubiquitous and affordable, providers can identify particular genes that affect drug response. This changing genomic landscape has resulted in uncertainty about the medical and legal standards of care for prescribing such drugs with known genetic influences on safety. Physicians who fail to recommend genetic testing that might avoid adverse drug effects may be at risk of medical malpractice lawsuits. Yet, when the medical evidence in favor of such genetic testing is mixed or ambiguous, how should the physician counsel the patient, who will usually lack the sophistication to understand the nuances of different types and results of medical studies? Given that the patient is likely to follow the physician's express or implied cues, failure to recommend testing may create a liability risk if an adverse event occurs, whereas recommending testing of uncertain benefit may impose unnecessary costs on the health care system and the patient, especially when health insurance will not cover the cost of the genetic test.

The anti-coagulant drug warfarin (also known by its brand name Coumadin[®]) may be the poster child for potential medical malpractice liability relating to pharmacogenetics. Warfarin presents unique challenges due to its narrow therapeutic index and large, inter-individual variation in metabolism. Risks from too low of dose may be stroke, and from too high of dose, excessive bleeding. Variants in at least two genes (*VKORC1* and *CYP2C9*) are a significant factor in the variability in warfarin response. This role for genetics may create legal duties to physicians with regard to recommending genetic testing before prescribing warfarin.

This article compares and contrasts the medical versus legal perspective of the evidentiary case for physicians to recommend genetic testing prior to prescribing warfarin. The next section provides background on warfarin, including its risks and benefits, followed by a discussion of the role of genetics in predicting potential adverse effects. Next, we examine the diverse evidence and professional opinions on whether genetic testing is warranted before prescribing warfarin. Finally, we contrast the hierarchy of evidence utilized by the medical and legal systems in evaluating any duty to recommend genetic testing before prescribing warfarin, and consider the broader liability implications of pharmacogenetic testing.

Background on Warfarin

Warfarin is an oral anticoagulant first approved in 1954 that is prescribed to over 30 million U.S. patients annually for myocardial infarction, atrial fibrillation, stroke, venous thrombosis, or prosthetic heart valve replacement.⁸ Warfarin reduces the risk of forming blood clots by inhibiting the enzyme vitamin K epoxide reductase, thereby disrupting the vitamin K cycle essential for blood coagulation.⁹ By slowing the blood coagulation process, warfarin helps prevent blood clots that may result in a heart attack, stroke, or other thrombotic event.

Two aspects of warfarin are particularly relevant with regard to proper prescribing and the standard of care. The first factor is the delicate balance between over-dosing and under-dosing warfarin. Warfarin has one of the narrowest therapeutic ranges of any prescribed drug.¹⁰ If given at too low of a dose, there remains a significant risk of stroke or a blood clot. On the other hand, too high a dose can result in excessive bleeding, including intracranial bleeding, the most serious outcome.¹¹ Major bleeding episodes have been reported in 1–3.4% per year in patients prescribed warfarin, with death occurring in as many as 0.1–0.7% of cases each year.¹² Warfarin is one of the most frequent causes of serious adverse events including deaths from prescribed drugs,¹³ and is the leading cause of hospitalizations related to adverse drug events among older adults in the U.S. – accounting for 33% of such hospital admissions.¹⁴

The second important factor is the high degree of patient variability in response to warfarin, with a 20-fold inter-patient variation in therapeutic dose requirements.¹⁵ Dosage optimization of warfarin is influenced by both genetic factors and non-genetic factors, including age, weight, height, alcohol use, diet and other medications.¹⁶ The warfarin dosage must therefore be optimized for each patient to avoid complications from bleeding. Proper dosing of warfarin is monitored using a diagnostic called the International Normalized Ratio (INR). This method involves testing the blood's ability to clot properly using the prothrombin time (PT) test, which measures (in seconds) the body's ability to coagulate blood, and compares this to the expected value in healthy people, to produce the INR ratio. The risk of bleeding can be reduced by over 50 percent with frequent, appropriate monitoring of the INR. The standard practice has been to give every patient a fixed starting dose and then to conduct blood testing every several days until the INR is stabilized, often after a dose adjustment is indicated. Following stabilization, further monitoring is recommended at least once per month. The goal is to maintain the INR of a patient on warfarin in the range of 2.5–3.0.¹⁷

Warfarin is the most commonly prescribed anti-coagulant. Yet, in significant part due to concerns about bleeding risks and the need for frequent monitoring of the INR, anti-coagulants are under-prescribed, resulting in significant risks of stroke and other thrombotic events in many patients. This problem demonstrates the need for better approaches for safer anti-coagulation.¹⁸

One approach for safer anti-coagulation has been the development of several new oral anticoagulants (“NOACs”) as alternatives to warfarin in recent years, including dabigatran

(Pradaxa[®]), rivaroxaban (Xarelto[®]) and apixaban (Eliquis[®]). These NOACs have been demonstrated to be at least as efficacious and safe as warfarin for patients with atrial fibrillation.¹⁹ The key advantage of these NOACs is that they do not require the regular INR monitoring necessary with warfarin.²⁰

However, several factors have slowed the adoption of NOACs. First, the new NOACs are significantly more expensive than warfarin, resulting in many patients staying with the less expensive option of warfarin.²¹ Second, there are no antidotes currently available for the NOACs, unlike warfarin whose effect can be quickly reversed. This has resulted in a significant number of deaths and resulting litigation for the NOACs.²² Third, the NOACs have not been shown to be effective as warfarin for treating some conditions (e.g., patients with mechanical heart valves or chronic kidney disease).²³

For these reasons, warfarin remains the most commonly prescribed anti-coagulant,²⁴ and is likely to be widely prescribed for the foreseeable future, even if its market share gradually declines in favor of the NOACs.²⁵ The need for safer administration and dosing of warfarin therefore continues. One promising approach for improving the safety of warfarin may be to use genetic testing to select the appropriate dose of the drug for each patient.

Genetics and Warfarin

Genetics is the largest factor affecting variation in warfarin response. As many as thirty genes affect the drug's metabolism, of which the two most important are *CYP2C9* and *VKORC1*. *CYP2C9* produces an enzyme that is involved in the metabolism of warfarin, and variations in this gene (*CYP2C9*2* and *CYP2C9*3*) result in a slower metabolic breakdown of warfarin than does the normal *CYP2C9*1* form of the gene. This results in increased anticoagulation that is associated with INR peaks above the therapeutic range and an increased risk of excessive bleeding.²⁶ *VKORC1* codes for the vitamin K epoxide reductase complex, which is the target molecule of warfarin. A frequently occurring variant of *VKORC1* produces a less effective enzyme which is more susceptible to the inhibiting effect of warfarin, potentially producing excessive anticoagulation that can result in bleeding.

These two genes (*CYP2C9* and *VKORC1*) work in combination to influence optimal warfarin dosing. Together, variants in these two genes are estimated to account for 10–45% of the variability in response to warfarin, depending on the population studied.²⁷ Most studies reported to date examining the role of pharmacogenetic testing in warfarin dosing have only looked at variants in these two genes. However, more recent studies show that additional variants play an important role, especially in different ethnic subgroups. For example, a variant of the *CYP4F2* gene may have the largest effect in some groups on major bleeding risks associated with warfarin, but has not been assessed in most clinical trials on warfarin genetics.²⁸

Given that genetics is the most significant factor affecting variation in warfarin response, the question is presented whether physicians should genetically test patients before prescribing warfarin. In August 2007, the FDA revised the label for warfarin to state that *CYP2C9* and *VKORC1* genotypes “may be useful” in determining the optimal initial dose of warfarin,²⁹

which was updated in 2010 to include a table recommending initial dosing ranges for patients with different combinations of *CYP2C9* and *VKORC1* genotypes.³⁰ Pharmacogenetic dosing algorithms have been developed that predict an appropriate starting dose that more closely approximates the stable therapeutic dose than those derived from a clinical algorithm without genetic information or the more traditional fixed starting dose approach.³¹ Several genetic tests for warfarin responsiveness have been approved by the FDA, and are commercially available.³² Tests range from \$125 to \$500, depending on the laboratory conducting the tests.³³

The question is whether such genetic testing is justified, which turns on two factors: clinical utility and cost-effectiveness. Clinical utility will depend on whether genetic testing results in achieving the appropriate INR ratio sooner and more consistently in patients, and more importantly, reduce significant adverse events (in particular stroke and serious bleeding events). The cost-effectiveness will depend on whether the benefits of genetic testing justify the additional cost and delay that such testing will entail. The available evidence on these two factors is summarized next.

Divergent Evidence and Recommendations

Many different types of evidence and recommendations are currently available on the clinical utility and cost-effectiveness of genetic testing prior to prescribing warfarin. This evidence is summarized by category below.

Clinical Guidelines

Clinical guidelines produced by various medical associations and authorities are the most frequently relied on practice recommendations for providers, although they are applied infrequently in medical malpractice cases.³⁴ Clinical guidelines produced by the American College of Chest Physicians call for no routine genetic screening prior to initiating warfarin treatment.³⁵ In contrast, the Clinical Pharmacogenetics Implementation Consortium guidelines recommend incorporating *existing* genotype information into warfarin dosing decisions.³⁶

Randomized Control Trials

Randomized control trials (RCTs) are generally considered the “gold standard” for evaluating the utility and safety of medical interventions. Several RCTs have now been reported on pharmacogenetic-guided dosing for warfarin, and others are pending. The first reported RCT was the CoumaGen study published in 2007 which found no difference in out-of-range INRs between a genotype-guided or standardized dosing regime.³⁷ In 2011, the Marshfield RCT reported that genotyping more accurately predicted the appropriate therapeutic warfarin dose for patients, but did not improve the percentage of time in the therapeutic range (PTTR).³⁸

Two recent RCT studies for warfarin genotyping were published in the *New England Journal of Medicine* in late 2013 with divergent results. The first, the Clarification of Optimal Anticoagulation Through Genetics (COAG) trial examined 1015 patients who were given either a genotype-guided algorithmic treatment, or a clinically-guided algorithmic treatment

for warfarin dosing in the first five days. After four weeks, there was no significant difference in the PTTR, time to first therapeutic INR, or in adverse event rates, although there was a non-significant reduction in serious bleeds in the genotype-guided group (4 vs. 10, $p=0.13$).³⁹ Supplementary data not included in the published manuscript showed that there was a statistically-significant decrease in major bleeding events ($n=7$, 1% vs. $n=19$, 4%, $p=0.021$) in patients with genotype-guided dosing in the six month follow-up to the study.⁴⁰

COAG has been the most influential study to date weighing against genetic testing prior to commencing warfarin treatment, but there are some significant uncertainties raised by this study.⁴¹ One third of the study participants were African Americans, who on average spent less time in the therapeutic range and had a higher incidence of INR values above 3 (although no increase in bleeding or other effects) with pharmacogenetic dosing. Subsequent data suggests that the two genes considered in the COAG study (*CYP2C9* and *VKRC1*) are not highly predictive of adverse events from warfarin in the African American population, and instead other gene variants unique to that population are more relevant.⁴² The failure to appropriately adjust the dose for the large percentage of African Americans in the COAG study based on their distinct genetic risk factors likely diluted any positive results in the study,⁴³ although analysis of non-blacks only in the COAG study found a small positive but still not statistically significant benefit of genotyping.⁴⁴

The second RCT reported in late 2013 was the European Pharmacogenetics of Anticoagulant Therapy (EU-PACT), which randomized 455 patients to genotype-dosing or fixed dosing regimes and found that genotyping resulted in significantly greater PTTR, fewer patients with INR above 4, and less time to achieve therapeutic INR levels, although no difference in bleeding or thromboembolic event rates.⁴⁵ This study was done in a homogenous European population without the demographic complications presented by the diverse COAG population.

In summary, while the available RCT studies give somewhat inconsistent results, the overall weight of evidence from these studies has generally been interpreted to not support inclusion of genotype information in the dosing algorithm for warfarin initiation.⁴⁶ However, the existing studies were generally small, and were not powered to assess adverse (i.e., serious bleeding) event rates, but rather were designed to measure surrogate markers such as INR statistics.⁴⁷ Moreover, any benefits of genotyping may have been masked by the fact that these RCT studies were conducted in specialized anticoagulation clinics with frequent INR monitoring, which is not representative of many warfarin patients served by community clinics with less frequent INRs.⁴⁸

A larger RCT ($n=1600$) currently underway, known as the Genetics Informatics Trial of Warfarin to Prevent DVT (GIFT), in contrast to the earlier studies, is specifically designed to statistically assess the rate of adverse events rather than surrogate endpoints relating to INR.⁴⁹ The results of this study, expected in 2015, are likely to significantly help clarify the clinical utility of genotyping warfarin patients.

Other Peer-Reviewed Clinical Studies

Numerous non-RCT peer-reviewed studies have demonstrated that variants in the *CYP2C9* and *VKORC1* genes are associated with increased risk of INR peaks and serious bleeding events, including comparative effectiveness studies and prospective observational studies.⁵⁰ One of the largest such studies was the CoumaGen-II study which compared the clinical effectiveness of warfarin in 504 genotype-guided patients with 1866 patients in a standard dosing control group and found significant benefits from genotyping, including less frequent INRs out of the desirable range as well as higher PTTR and fewer serious adverse events.⁵¹ A prospective study involving a collaboration between the Mayo Clinic and Medco found that the hospitalization rate for bleeding or thromboembolism decreased 46% in the group using genotype-based dosing (n=896) relative to an age- and sex-matched control group with no genotyping (n=2688).⁵² Most recently, a prospective study of almost 5000 patients genotyped for both *CYP2C9* and *VKORC1* found that patients with the sensitive genotypes were significantly more likely to be over-coagulated and had a significantly increased risk of bleeding.⁵³ Several earlier peer-reviewed non-randomized studies also found benefits from using pharmacogenetics to calculate warfarin dose.⁵⁴ These non-RCT studies find that genotyping warfarin patients does provide some benefits, but the value of such studies are limited by their small size, non-randomized protocols, and inconsistent statistical significance.

Meta-Analyses

Two recent meta-analyses have reviewed the impact of genotyping on warfarin dosing effects. One meta-analysis examined nine randomized control studies of coumarins (warfarin and its analogues) that had enrolled a total of 2812 patients into genotype-guided versus standard dosing groups, and found marginal benefits that were not statistically significant between the aggregated groups in TTR, INR >4, major bleeding events, and thromboembolism.⁵⁵ Another meta-analysis included seven warfarin clinical trials and compared genotype-dosing patients with control arms that were either fixed initiation dose (the usual practice in clinical care) or non-fixed dose (i.e., initial dose based on clinical algorithm that did not include genotype). There were significant improvements in TTR in the genotyped group compared with fixed-dose controls, but not with non-fixed-dose comparators.⁵⁶

Cost-Effectiveness Studies

A series of studies have examined the cost-effectiveness of pharmacogenetic testing associated with warfarin. Meckley et al. found a range of outcomes depending on assumptions used, concluding that there is approximately a 46% probability that genotyping would be cost-effective at a \$50,000 per QALY threshold level.⁵⁷ Eckman et al. calculated that genotype-based dosing would have a marginal cost-effectiveness ratio of almost \$172,000 per QALY, with only a 10 percent chance of the cost-effectiveness falling below the \$50,000 generally accepted social threshold for willingness to pay.⁵⁸ A key factor driving the relative cost-ineffectiveness of genotype-based dosing was the three day turnaround for genetic testing results to be available; if the delay decreased to 24 hours as might occur with in-hospital genotyping, the cost-effectiveness would improve to \$51,000

per QALY, very close to the \$50,000 willingness to pay threshold.⁵⁹ Other studies have found that genotype-guided dosing of warfarin may be potentially cost-effective for at least some patients.⁶⁰

A 2014 review of the pharmacoeconomic data concluded that the available data do not show that genetic testing is a cost-effective option for guiding warfarin therapy, but as the costs and delays associated with genetic testing continue to drop, genetic testing may become a viable option in the not too distant future.⁶¹ The development of point-of-care testing devices was identified as a particularly promising technology for making genetic testing for warfarin feasible.⁶² The cost-effectiveness of warfarin genotyping also becomes stronger if recent proposals to increase the cost-effectiveness threshold to \$100,000 or \$150,000 per QALY are applied.⁶³

FDA Label

As described above, FDA revised the label for warfarin in 2007 to suggest the benefits of genetic testing in determining the initial dose of warfarin, and then updated that label in 2010 to provide a table with dosing suggestions for specific genotypes. In its media release announcing the 2007 label change, the FDA stated: “The labeling change highlights the opportunity for healthcare providers to use genetic tests to improve their initial estimate of what is a reasonable warfarin dose for individual patients. Testing may help optimize the use of warfarin and lower the risk of bleeding complications from the drug.”⁶⁴ However, at a press conference announcing the 2007 label change, Dr. Larry Lesko, Director of the FDA Office of Clinical Pharmacology, suggested that “[w]ith this information in the labeling, doctors and other health professionals *may well decide* to incorporate genetic information along with more traditional factors in estimating their patients’ initial doses.”⁶⁵ He added though “we’re not quite to the point where we can say that doctors must perform these tests, if you will. Doctors can still practice good medicine without necessarily doing these tests.”⁶⁶ FDA revised the warfarin label again in 2010 to provide specific dosing data for different genotypes, but unlike in 2007 issued no press release and held no press conference to announce its label change and its significance.

Reimbursement

Insurance coverage is another important factor for the uptake of a medical product or procedure. In 2009, the Centers for Medicare and Medicaid Services (CMS) issued a national coverage determination that it would only reimburse genetic testing in the context of warfarin prescribing if the patient was enrolled in a randomized clinical trial.⁶⁷ Private insurers also generally do not currently reimburse for genetic tests relating to warfarin prescriptions.⁶⁸

Peer Practice

A key factor in many jurisdictions for determining the standard of care in medical malpractice cases is the practice of similarly situated practitioners. Most physicians who prescribe warfarin today do not use genotyping to calibrate starting dose.⁶⁹ For example, in 2012 genotype-guided dosing became the standard of care for warfarin at the University of Illinois Hospital & Health Sciences System, but this decision in favor of routine genetic

testing for new warfarin prescriptions was discontinued after publication of the COAG trial in 2013.⁷⁰

Overview of Evidence

There is substantial peer-reviewed and other evidence both for and against genotyping patients before initiating warfarin therapy. The overall weight of the evidence at this time likely weighs against using genetic-based dosing, and many expert commentators have come out in favor of that position.⁷¹ Consistent with that assessment, most physicians today are not genotyping patients before prescribing warfarin. There is not unanimity on this point of view however, as a number of top experts from leading institutions argue that the weight of the evidence supports routine genetic testing before prescribing warfarin.⁷²

Moreover, there are contexts in which the weight of medical opinion and/or evidence may weigh in favor of genetic testing. For example, at present, the delay and cost of genetic testing lowers its utility, diminishing physician uptake. As more patients start obtaining their own genotype data through direct-to-consumer genetic testing or whole genome sequencing, the case for doctors using such pre-existing genotype information to determine dosing in individual patients will become much stronger.⁷³ The CPIC guidelines, and leading experts who do not presently support genetic testing prior to prescribing warfarin,⁷⁴ do recommend using the genetic data if it is already available at the time of prescribing. This suggests that a physician of a patient with consumer genetic information showing a warfarin sensitivity may have a different standard of care than for a patient without such information.

Moreover, almost of all of the clinical studies evaluating genetic testing for warfarin dosing have involved state-of-the-art anticoagulation clinics where INRs are tested frequently.⁷⁵ For a patient who lives far away from the prescribing physician's office, or is otherwise unavailable for frequent INR monitoring, genetic testing (assuming it is conveniently available at such sites) in combination with other algorithm factors may be prudent to maximize the safety of the patient. Finally, recent analyses have shown that differential frequencies and effects of genetic variables between racial groups may explain some of the discordance in study results, and that race-stratified studies are needed to clarify the potential benefits of genetic testing for warfarin dosing.⁷⁶ This effect of race, and the uncertainty about how it may have affected previous studies in the literature which did not stratify by race, creates an additional level of ambiguity for physicians trying to decide whether to recommend genetic testing before prescribing warfarin.

Defining the Standard of Care: Medical vs. Legal Perspectives

Under the archetypical standard of care for medical malpractice, which is based on the local custom of practitioners in the relevant field, there should be little risk of liability for a physician who fails to recommend genetic testing before prescribing warfarin, given that the dominant current practice is not to recommend such testing. However, many jurisdictions are moving away from the custom rule to a reasonableness standard that is more consistent with other negligence contexts, where existing custom and practice is just one factor in determining the appropriate standard of care.⁷⁷ In a jurisdiction that determines the appropriate standard of care based upon reasonableness, the factfinder (jury or judge) would

consider several types of evidence that would be considered relevant to the reasonableness of the physician's actions. The list of relevant factors, and the weight given to each, may differ for a legal factfinder than for a practicing physician.

Table 1 compares a clinical versus legal evaluation of warfarin genetic testing, with significant factors rated by number of asterisks ("*") to show strength of importance of each category of evidence, with three asterisks indicating the evidence given the greatest weight and no asterisks the least evidentiary weight. The final column indicates whether the overall weight of evidence for that category of evidence supports genetic testing for warfarin administration. From this analysis, it is clear there is an imbalance between clinician weight and legal weight on a variety of factors that influence the judgment on whether warfarin prescribing should include a recommendation of genetic testing.

The factors that weigh most heavily for clinical decision-making – including clinical guidelines, RCTs, cost-effectiveness and reimbursement – all arguably weigh against genetic testing for warfarin patients at this time. It is therefore perhaps not surprising that most medical practitioners are not recommending genetic testing with warfarin. In the litigation framework, however, the balance of evidence is more contested. The most influential factors in the courtroom, other than peer practice, are either equivocal or supportive of genetic testing, including the complete body of peer-reviewed, published studies, litigation experts, and the FDA label. A substantial number of peer reviewed studies support genetic testing for warfarin, and although other studies may weigh against testing, those negative studies consistently report results that are in the direction of favoring genetic testing, but are classified as negative studies because their results are not statistically significant. While doctors give the most weight to RCTs, examples such as the Vioxx litigation demonstrate that juries tend to give as much if not more weight to observational studies that tend to involve more real-world exposure scenarios than the somewhat artificial context of RCTs, and there are a number of peer-reviewed observational studies that support genetic testing for warfarin.

Under evidence-based medicine methods, studies are ranked by likelihood of bias. RCTs, if well conducted should trump observational studies. However, good observational studies with consistent results might trump poor RCTs. Given the mixed bag of evidence for warfarin genetic testing, the legal decision on whether a doctor had a duty to recommend genetic testing is a question of weighing the evidence, rather than a threshold determination of admissibility for the judge, and thus a case is likely to advance through motions practice to be presented to the jury.

Once a malpractice case gets to the jury, the outcome is highly individualized and often unpredictable, often turning on the skills and effectiveness of the attorneys and expert witnesses involved, as well as the specific circumstances of the particular patient and the actions of the health care professional being sued. While the physician makes his or her decision based primarily on studies of group data, the focus on the individual patient in the litigation context can shine a very different light on the available evidence. For example, while prospective decision-making based on cost-effectiveness is rational and even necessary, such weighing can look very different after-the-fact when considered in the

context of an individual plaintiff who has been injured. Juries have tended to punish with large punitive damage awards manufacturers who relied on such cost-benefit weighing for making decisions affecting human safety.⁷⁸ Moreover, juries are subject to “hindsight bias,” in which a physician’s culpability may look very different after harm has occurred.⁷⁹ Thus, prospective decisions based on group or population data can suggest very different outcomes than retrospective searches for blame for injuries to a specific individual.

There are a number of other possible individualized factors that could tilt the decision on the appropriateness of warfarin genetic testing for an individual plaintiff in the litigation hindsight context. An injured plaintiff that already had possession of his or her genetic data from direct to consumer testing, which was not used by the physician in decision making on warfarin dosing, or a plaintiff who lives in a location without easy availability of frequent INR monitoring, would likely be able to make the strongest case for a duty to use genetic data in calibrating the warfarin starting dose. Moreover, there already is significant litigation against health care professionals for alleged failure to properly manage warfarin treatment.⁸⁰ It would likely be useful for the plaintiffs’ lawyer in such cases to invest a few hundred dollars to genetically test their client and if they have a susceptible genotype, include a claim in the pending complaint for failure to recommend genetic testing.

Other factors could affect a decision in either direction, for instance insurance coverage. If a payer does not pay for warfarin metabolism gene testing, who is liable if the patient decides not to pay for this additional test and they suffer an adverse event? How much responsibility does the physician have to explain the uncertainty of benefits so the patient can make an informed decision, and can the physician be held liable for not advocating for a potentially beneficial test to spare the patient expense? It is questionable how informed a patient can truly become on a topic such as warfarin metabolism genes and the uncertainties of potential benefits from its use. If a physician monitors their patient frequently, adjusting the warfarin dose to keep the INR within the recommended limits, not knowing a patient’s warfarin metabolism would only affect the initial dose estimate thus creating a more likely successful plaintiff if the adverse event happens in the early stages of therapy.

V. CONCLUSION

Warfarin was thought to be the “poster child” for pharmacogenetic testing before prescribing a drug. Yet, very little genetic testing is occurring in clinical practice involving prescribing warfarin. Just as physicians have been reluctant to uptake genetic testing for warfarin, malpractice attorneys have been slow to bring lawsuits against providers who fail to recommend genetic testing for warfarin patients that die or are injured by bleeding events associated with excessive over-anticoagulation. The resistance by physicians and trial lawyers are inter-dependent – trial lawyers will be reluctant to bring lawsuits when the customary practice of physicians is not to recommend genetic testing, and physicians will be under no pressure to test if trial lawyers lack the expertise, precedent and incentive to bring lawsuits. This equilibrium may not be stable however, as more states evolve to a “reasonableness” rather than “custom” standard of care, and as more patients have already obtained their genetic information through whole genome sequencing or direct to consumer genetic testing, the legal arguments for a duty to consider genetics in prescribing warfarin

will become stronger. If such lawsuits are brought, the analysis provided in this paper suggests that the factors and weighing that physicians rely on to guide their practice will not align with those used by juries to judge the physician's actions. And the dynamics of litigation are that if some lawsuits start to succeed with significant verdicts, the trickle of such cases can quickly become a torrent. The future of malpractice liability for failure to genetically test before prescribing warfarin, and for failure to recommend genetic testing in other contexts, therefore remains cloudy.

Acknowledgments

Funding for this work was provided by NHGRI ELSI Grant #R01HG006145-01A1

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Biographies

Gary Marchant is Regents’ Professor and Lincoln Professor of Emerging Technologies, Law & Ethics at the Sandra Day O’Connor College of Law at Arizona State University. He is also the Faculty Director of the Center for Law, Science & Innovation at ASU. He has a Ph.D. (Zoology) from the University of British Columbia, Vancouver, B.C., Canada (1986), a J.D. from Harvard Law School, Cambridge, MA (1990) and a M.P.P. from the Kennedy School of Government, Cambridge, MA (1990).

Kathryn Scheckel is Assistant Director, Special Projects in the Office of University Affairs at Arizona State University. She is a Masters student in Public Policy at ASU, Tempe, AZ (anticipated 2016). She holds a B.S. in Molecular Biosciences & Biotechnology and a B.A. in Piano from ASU, Tempe, AZ (2012).

Doug Campos-Outcalt is a Medical Director of Mercy Care Plan, Phoenix Arizona. He has a M.D. from the University of Arizona (1979) and an M.P.A. from Arizona State University (1985).

Table 1

Clinical versus legal evaluation of warfarin genetic testing.

Factor	Clinician	Legal	Support for Genetic Testing?
Clinical Guidelines	***	*	No
Systemic Evidence Reviews	**	*	No
Reimbursement	***	-	No
Randomized Control Trials (RCTs)	***	**	No
Other Peer Review Studies	*	***	Equivocal
Cost-Effectiveness	***	*	No
Litigation Experts	-	***	Equivocal
Peer Practice	**	***	No
FDA/Label	*	**	Yes