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Health Care Savings from Personalizing Medicine Using Genetic Testing: The Case of Warfarin*

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Executive Summary

Progress towards realizing a vision of personalized medicine—drugs and drug doses that are safer and more effective because they are chosen based on an individual's genetic makeup—has been slower than once forecast. The Food and Drug Administration has a key role to play in facilitating the use of genetic information in drug therapies because it approves labels, and labels influence how doctors use drugs. Here we evaluate one example of how using genetic information in drug therapy may improve public health and lower health care costs.

Warfarin, an anticoagulant commonly used to prevent and control blood clots, is complicated to use because the optimal dose varies greatly among patients. If the dose is too strong the risk of serious bleeding increases and if the dose is too weak, the risk of stroke increases. We estimate the health benefits and the resulting savings in health care costs by using personalized warfarin dosing decisions based on appropriate genetic testing. We estimate that formally integrating genetic testing into routine warfarin therapy could allow American warfarin users to avoid 85,000 serious bleeding events and 17,000 strokes annually. We estimate the reduced health care spending from integrating genetic testing into warfarin therapy to be $1.1 billion annually, with a range of about $100 million to $2 billion.

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1. Introduction

The vision of personalized medicine—drugs and drug doses that are safer and more effective because they are chosen according to an individual's genetic makeup—has grown closer with the Administration's request for six million dollars in funding for the Critical Path Initiative of the Food and Drug Administration (FDA).[1] This Initiative can protect and promote public health by generating information needed to identify patients likely to benefit from a treatment as well as patients more likely to respond adversely to a drug.[2] Through collaboration with the new Critical Path Institute (C-Path) and the University of Utah, the FDA is already working to establish an evidence-based framework for determining the clinical utility of cardiovascular biomarkers. These include genetic variants that determine the response to warfarin —a commonly used anticoagulation drug whose wide range of efficacy in different individuals can expose many tens of thousands of patients to severe under- or over-dosing.[3] Improving warfarin therapy by integrating genetic testing into dosing protocols will require not only the collection of additional data demonstrating the clinical value of such testing, but also changes to warfarin labeling. FDA thus plays a key role because it approves drug labels describing appropriate use and these, in turn, influence physician practice.[4] The case of warfarin dosing illustrates how FDA is uniquely positioned both to cooperate in clearing scientific hurdles that impair improvements in medicine and to facilitate adoption of these improvements by improving labeling. As we demonstrate below, the case of warfarin also illustrates how FDA-facilitated improvements in drug dosing based on newly available genetic tests can simultaneously improve public health and offer large savings to health care payers.

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[1] Department of Health and Human Services News Release, HHS Proposes $689 Billion Budget for Fiscal Year 2007, February 6th 2006, http://www.hhs.gov/news/press/2006pres/20060206a.html.

[2] Food and Drug Administration, Budget Formulation and Presentation, The Critical Path to Personalized Medicine, February 2006, http://www.fda.gov/oc/oms/ofm/budget/2007/HTML/4CPPOM1.htm.

[3] Food and Drug Administration, FDA Drug Safety Initiative: Fact Sheet, 2006 http://www.fda.gov/oc/factsheets/initiative.html.

[4] Warfarin is included in the FDA's Critical Path Initiative. See Food and Drug Administration, "FDA Drug Safety Initiative: Fact Sheet," 2006, http://www.fda.gov/oc/factsheets/initiative.html.

The anticoagulant medication warfarin is used to prevent and treat blood clots. Approximately 2 million persons start taking warfarin each year; physicians commonly prescribe it for patients with a history of atrial fibrillation, recurrent stroke, deep vein thrombosis, or pulmonary embolism, as well as for patients who have had heart valve replacements. A major challenge in treating patients with warfarin is that the optimal dose varies greatly from person to person. Further, if the dose taken is too high, users are subject to increased risk of serious bleeding. Indeed, warfarin is the second most common drug—after insulin—among those implicated in emergency room visits for adverse drug events, causing an average of more than 43,000 cases per year in 2004-2005.[5] Finally, if the dose is too low, users are subject to increased risk of stroke.

Currently, the appropriate dose is determined by monitoring the level of anticoagulation through blood tests and altering the dose if it is too high or too low. Recent research shows genetic tests can, to some extent, identify which patients require higher and lower doses and may be a cost effective way to reduce bleeding events from warfarin.[6] We estimate that formally integrating genetic testing into routine warfarin therapy could allow American warfarin users to avoid 85,000 serious bleeding events and 17,000 strokes annually.

Our model may underestimate the full benefits of integrating genetic information into warfarin dosing because it includes the effects of over-dosing warfarin in only some genetic variants-- the presence of one or more 2C9 variant alleles. Sconce et al.[7] show polymorphisms at a second genetic locus, VKORC, are independently strongly correlated with the warfarin maintenance dose. Variation in the VKORC enzyme is, therefore, another risk factor for bleeding. Genetic_testing for both CYP2C9 and VKORC could reduce bleeding events and

[5] Daniel S. Budnitz et al., "National Surveillance of Emergency Department Visits for Outpatient Adverse Drug Events." *JAMA* 2006; 296: 1858-1866. The cases that are seen in emergency departments represent a subset of total adverse drug events but the precise fraction they represent is uncertain. An estimate of total adverse drug events would include those occurring among hospital and nursing home inpatients, those treated in clinics, offices, and homes, and those not treated – in addition to those treated in emergency departments.

[6] Tom Schalekamp et al., "CYP2C9 Genotyping in Acenocoumarol Treatment: Is It a Cost-Effective Addition to International Normalized Ratio Monitoring?" *Clinical Pharmacology and Therapeutics* 2006; 79: 511-520.

[7] Elizabeth A. Sconce et al., "The Impact of CYP2C9 and VKORC1 Genetic Polymorphism and Patient Characteristics upon Warfarin Dose Requirements: Proposal for a New Dosing Regimen." *Blood* 2005; 106: 2329-2333.

strokes that occur in warfarin therapy by more than the annual estimates of 85,000 and 17,000 developed here.[8]

Excluding the potential benefits of testing for VKORC variation, we estimate the net monetary benefits of integrating genetic testing into warfarin therapy to include $1.1 billion annually in reduced health care spending, with a range from $100 million to $2 billion annually.

These estimates of potential benefits illustrate the gains that might be achieved through successful implementation of one part of the FDA's Critical Path Initiative. The Initiative seeks to identify ways of predicting drug safety and efficacy, and to develop standards and other innovations that facilitate application of basic scientific advances to the improvement of patients' health. In many cases, the gap between science and improved outcomes results from institutional, regulatory, or other barriers. In such cases, FDA has a unique role to play in closing this gap because it alone has access to all of the confidential business information provided by medical product developers who seek approval to market their products. In addition, FDA regulates drug labels that convey to doctors how to use drugs in a manner known to be safe and effective.

In the next section of this paper, we provide background information on the uses and risks associated with warfarin dosing. We then describe the methods and assumptions we use to estimate the benefits associated with integrating genetic testing with warfarin therapy. In the following section we present our results, as well as the results of our uncertainty and sensitivity analysis. Our conclusion stresses the public health significance of our results.

2. Background

Warfarin has a problematic safety profile in part because it has a narrow therapeutic range and in part because patients vary greatly in the dose needed for adequate anticoagulation. The consequences of under-dosing and over-dosing are severe: including elevated risk of death

[8] If the VKORC1 genotype is as widespread as the CYP2C9*2 and CPY2C9*3 polymorphisms and as useful as a guide to dosing, the benefits of integrating genetic typing with warfarin dosing could be twice as high as we have estimated here, Although we are not yet able to estimate the additional health benefits and cost savings from VKORC genotyping, the correlation between this genetic locus and warfarin metabolism strongly implies that the ranges of health benefits and cost savings shown in tables 2 and 3 likely understate the full gains from integrating genetic testing with warfarin therapy.

from stroke from under-dosing, and bleeding from over-dosing. The highest risk is the first 30 to 60 days after beginning warfarin therapy.

Individual characteristics and behavior, such as sex and diet, account for the variation in appropriate warfarin dose across individuals. In addition, roughly one-third of the population carries one or both of the CYP2C9*2 and CPY2C9*3 polymorphisms that are associated with slower metabolization of warfarin, which in turn increases the likelihood of over-anticoagulation and the associated risk of serious bleeding.[9] Identifying persons with these genetic variants could allow physicians to prescribe more appropriate initial dosing of warfarin. Personalized dosing would reduce the number of serious adverse events and the associated costs of those adverse events to the health care system.

We estimate the public health benefits and savings in health care costs that could accrue from more accurate, genotype-driven dosing decisions at the initiation of warfarin therapy. We take current medical outcomes and health care costs for those taking warfarin as the baseline, and then calculate the changes that would occur if the entire population of warfarin users underwent genetic testing.

3. Assumptions and Methods

To estimate the annual savings of health care costs attainable when genetic testing guides warfarin dosing, we employ estimates of the following variables:

- the number of people who start taking warfarin each year,
- the prevalence of variant genotypes among patients prescribed warfarin,
- the reduction in bleeding events from more accurate dosing,
- the cost of bleeding events avoided,
- the reduction in strokes from more accurate dosing,
- the cost of strokes avoided, and
- the accuracy and cost of genetic testing.

[9] Mitchell K. Higashi et al., "Association Between CYP2C9 Genetic Variants and Anticoagulation-Related Outcomes During Warfarin Therapy." *JAMA* 2002; 287: 1690-1698.

All of these elements involve some uncertainty, which we build into our calculations through simulations and sensitivity analysis.

4. Number and Prevalence of Varient Genotypes Among People Who Start Taking Warfarin Each Year

We estimate that roughly 2 million persons start taking warfarin in the United States annually. [10] With more accurate dosing, that number could change but we do not build such a response into the model. We assume that genetic testing will identify a genotype for 95 percent of these 2 million, and fail to identify the genotype of 5 percent.[11] We further assume that one-third of those whose genotype is identified are of variant genotypes.[12] Figure 1 illustrates the relative size of the several variant and non-variant populations. [13]

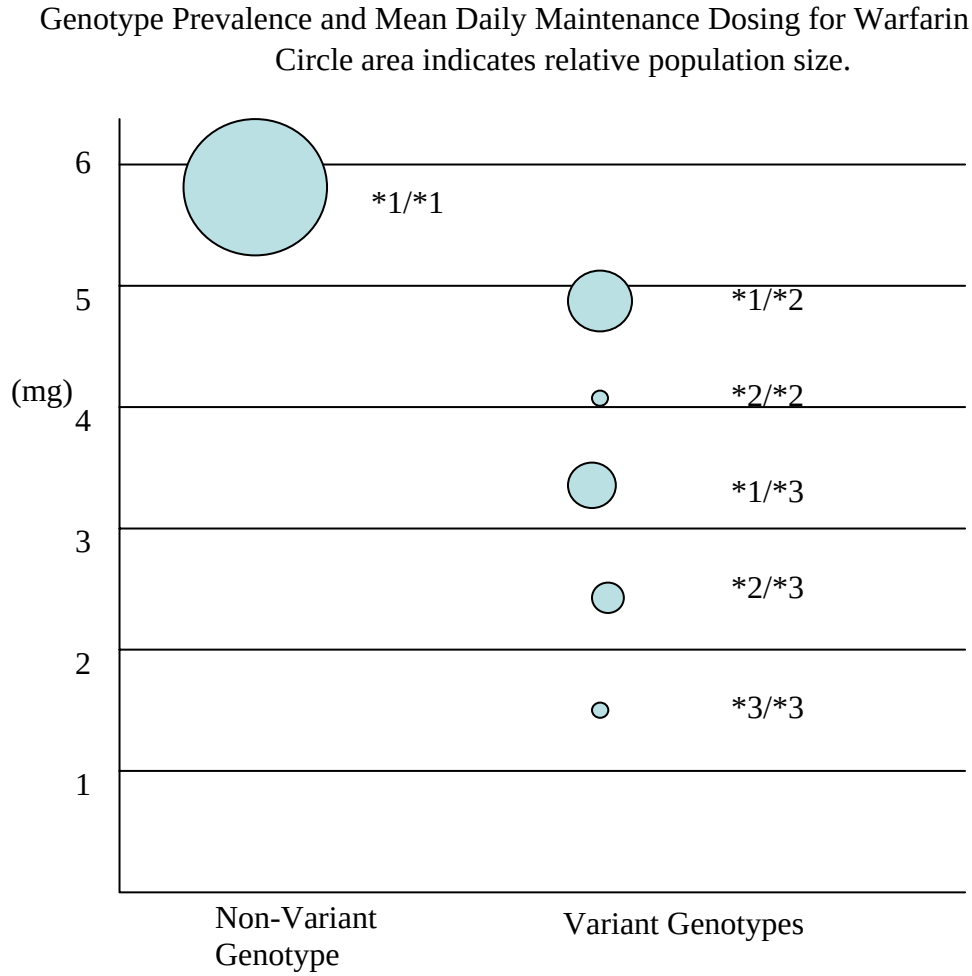
[10] Data from IMS Health™, IMS National Sales Perspective™, 2005, extracted September 2005, shows that, in 2005, in 2005, 7 to 10 million patient years of warfarin therapy were sold. This overstates the number of patients starting therapy each year, as many patients use warfarin for periods longer than a year. If the average patient uses warfarin 3 years, roughly 2 million individuals start warfarin therapy annually.

[11] Higashi et al. identified genotypes for 190 of 200 patients (95 percent).

[12] Thirty-eight percent of those genotyped in the Higashi et al. study were of warfarin sensitive genotypes. Other studies show the prevalence of Warfarin sensitive genotypes to be closer to 30 percent. We use 33 percent here as a middle estimate of prevalence.

[13] Higashi et al., tables 2 and 3. The labels on the figure (*1/*1, *1/*2, *2/*2, and so on) identify the non-variant (or "wild type") and variant alleles of the enzyme CYP2C9.

Figure 1. Genotype Prevalence and Mean Daily Maintenance Dosing for Warfarin



We base our estimate of the health gains from more accurate warfarin dosing on the recent paper by Higashi et al., which found that the mean maintenance dose for the variant population was much lower than the mean maintenance dose for the non-variant or "wild" [14] population. The study found 16 of the 58 variant carriers had serious or life-threatening bleeding events after initiation of warfarin therapy, as opposed to 16 of 127 in the non-variant population. If the numbers from their study are approximately representative of the entire population, then about 27.6 percent of the variant population taking warfarin experience adverse bleeding events, whereas 12.6 percent of the non-variant population experience such events. We use these results

[14] In this context "wild" refers to the baseline genotype against which other genotypes are compared.

to generate a preliminary estimate of the potential reduction in the rate of serious and life-threatening bleeding events.

Lower initial dosing could reduce the rate of serious and life-threatening bleeding events in the variant population. Because we do not have data on the reduction in bleeding events among the variant population, we assume that accurate dosing would reduce the rate of adverse bleeding events in the variant population to the lower rate of the non-variant population. Under this assumption, more accurate warfarin dosing would reduce the incidence of serious bleeding in the variant population taking warfarin by approximately 15 percent (27.6 percent - 12.6 percent).[15]

Testing has the potential to reduce not only the incidence of serious bleeding in warfarin therapy, but also the health care costs associated with serious bleeding, According to Ansell et al., most investigators categorize serious bleeding as bleeding associated with a defined drop in hemoglobin level, leading to transfusion of some number of units of blood or to hospitalization.[16] The most common serious bleeding associated with warfarin use is gastrointestinal bleeding, followed by intracranial bleeding. You et al, estimates the average direct medical cost of gastrointestinal hemorrhage (with and without complication and co-morbidity) at $11,635 in 2001. [17] Adjusting this estimate for inflation yields an average direct medical cost of roughly $13,500. [18]

5. <u>Reduction in Strokes and Costs Saved from More Accurate Dosing</u>

Correctly identifying non-variant individuals could also improve anticoagulation in the non-variant population if physicians, wary of bleeding risk, now under-dose or under-prescribe warfarin therapy. According to the Agency for Healthcare Research and Quality's Healthcare Utilization and Cost Project, strokes account for over 400,000 annual hospital discharges. We assume that 10 percent of those strokes are preventable. Because we do not know the efficacy of more accurate warfarin dosing, we assume that 50 percent will be prevented by more accurate dosing. The actual efficacy may be lower or higher. We estimate the average stroke resulted in

[15] Higashi et al.
[16] Jack Ansell et al., "Managing Oral Anticoagulant Therapy," *Chest* 2001; 119:22S-38S.
[17] Joyce H .S. You et al., "The Potential Clinical and Economic Outcomes of Pharmacogenetics-Oriented Management of Warfarin Therapy – A Decision Analysis." *Thromb Haemost*. 2004; 92:590-597.
[18] Bureau of Labor Statistics, Consumer Price Index for Medical Care, 2002-2006.

$24,601 in hospitalization costs in 2002, [19] and that hospitalization costs account for 70 percent of the first year direct costs of a stroke.[20] Adjusting these estimates for inflation, we calculate direct first year costs of about $39,500 per stroke. [21] If these outcomes and costs could be reduced by genetic testing for CYP2C9 phenotypes, the cost savings and health gains would be large. Because we do not have any data to estimate the number of strokes avoided, we assume that better dosing through genetic testing would cut the number of preventable stroke in half.[22] We use simulations to show the effect of different assumptions on the reduction in preventable strokes when genetic testing helps determine initial warfarin doses.

6. Accuracy and Cost of Genetic Testing

The net benefits from more accurate dosing rely on the ability of the test to distinguish patients with variant genotypes from patients with non-variant genotypes, as well as the cost of the test.[23] Incorrectly identifying a variant carrier as a non-variant carrier could increase the risk of overdosing and bleeding, especially if genetic testing leads physicians to increase the initial warfarin dosing of non-carriers. Incorrectly identifying non-variant individuals as variants could similarly cause the non-variant population to be under-dosed, at least initially. Figure 2 summarizes the consequences of testing accuracy and inaccuracy.

[19] Weighted national estimates from HCUP Nationwide Inpatient Sample (NIS), 2002, Agency for Healthcare Research and Quality (AHRQ), based on data collected by individual States and provided to AHRQ by the States.
[20] Thomas N. Taylor et al., "Lifetime Cost of Stroke in the United States." *Stroke*, 1996; 27: 1459-1466.
[21] Bureau of Labor Statistics, Consumer Price Index for Medical Care, 2002-2006.
[22] A recent review and meta-analysis suggests that this assumption understates the reduction in preventable strokes. See Matthew W. Reynolds et al, "Warfarin Anticoagulation and Outcomes in Patients with Atrial Fibrillation." *Chest* 2004; 126: 1938-1945.
[23] Joyce H. S. You et al., "The Potential Clinical and Economic Outcomes of Pharmacogenetics-Oriented Management of Warfarin Therapy – A Decision Analysis." *Thromb Haemost*. 2004; 92:590-597.

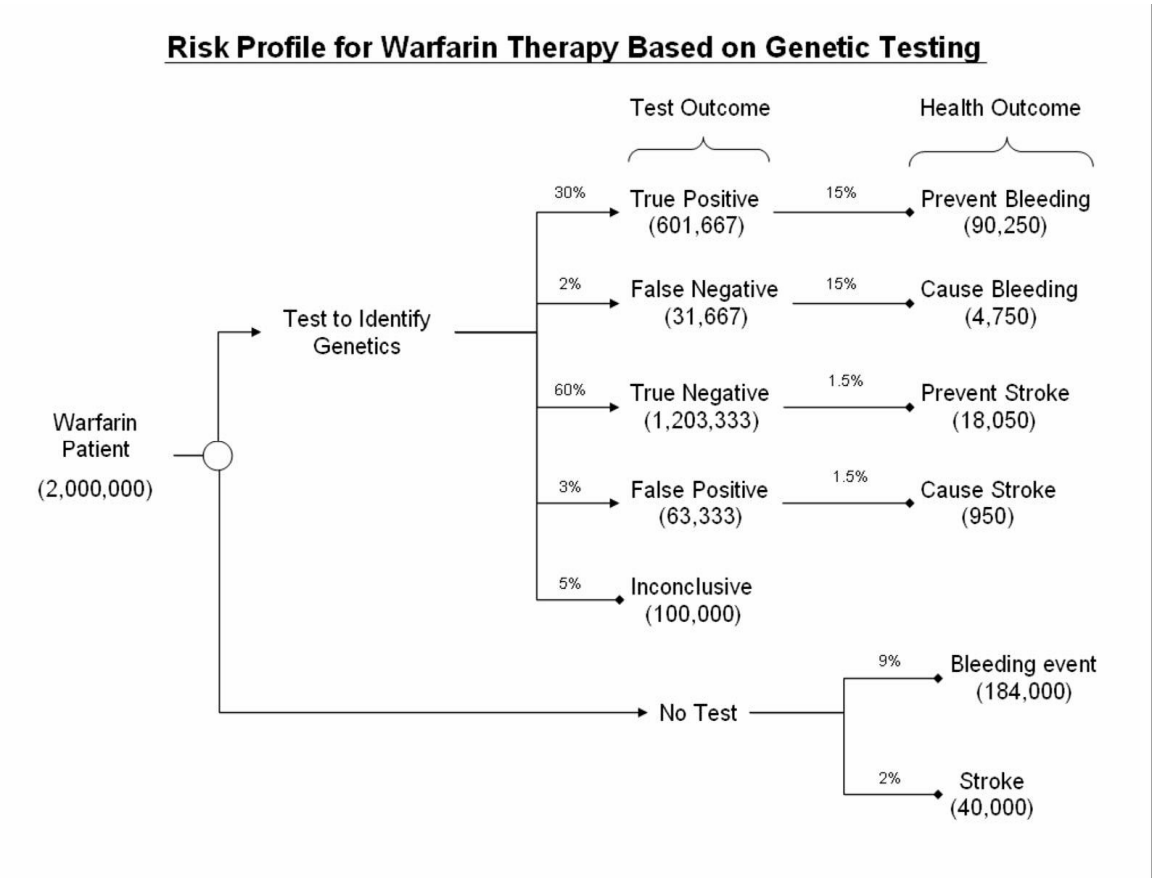
Figure 2. Testing Accuracy and Consequences

• True Positive o Warfarin Sensitive Individual Correctly Identified o Lower Initial Warfarin Dosing – Fewer Bleeding Events	• False Negative o Sensitive Individual Falsely Identified as Non-Sensitive o Higher Initial Warfarin Dosing Increases Risk of Bleeding Events
• False Positive o Individual Incorrectly Identified as Sensitive o Initial Warfarin Dose Too Low – Increased Stroke Risk	• True Negative o Individual Correctly Identified as Non-Sensitive o Higher Initial Warfarin Dosing Decreases Risk of Stroke

We do not have data on the sensitivity and specificity of the genetic tests for these variant polymorphisms. For our baseline estimates of the effects of genetic testing, we assume that the rate of false positives and false negative is the same as the rate of inclusive tests. By one estimate, 5 percent of genetic tests for variant polymorphisms are inconclusive.[24] Allowing for human and testing error, we assume that genetic testing

[24] Higashi et al. were unable to genetically type 10 of 200 blood samples.

Figure 3. Risk Profile for Warfarin Therapy Based on Genetic Testing



correctly identifies 95 percent of variant population as variant and correctly identifies 95 percent of the non-variant population as non-variant. We also show the results for different sensitivities and specificities of the tests compared with the base case of 95 percent for both sensitivity and specificity. Figure 3 shows the health outcomes with and without genetic testing under these assumptions about the accuracy of the tests.

The cost of genetic testing includes the cost of the test itself and the costs of drawing blood samples, making samples available for testing, and reporting results. Genelex, a private company offering direct to consumer genetic testing, charges approximately $250 for a single genetic test for CYP2C9 genotyping, although prices would be lower for a larger volume of tests. Genelex has done approximately 1,200 individual tests since 2000, implying that, if genetic testing were to be widely adopted, companies could charge less for testing, as the costs of testing equipment could be spread across more tests.

A new genetic test based on nanotechnology is also being developed. The test attaches gold nano-particles to genetic probes that are designed to bind to genetic variations in DNA. The nano-particles identify genetic variations by changing colors. This test has the potential to substantially reduce the cost of genetic testing for warfarin sensitive genotypes.[25]

We assume that the labor involved in drawing blood and related activities, such as record keeping, will be up to 3 hours. At a full compensation of about $33 per hour (for hospital workers)[26], the additional costs are about $100.

Results

We estimate the health effects and the net change in health care costs associated with generic testing for warfarin dosing.[27] We estimate the number of bleeding events avoided as the number of bleeding events prevented in persons with variant genotypes correctly identified (true positive tests) minus the number of bleeding events caused in persons with variant genotypes incorrectly identified as non-variant (false negative tests). Under the assumptions we have described, genetic testing would reduce serious bleeding events among the variant population in warfarin therapy by roughly 85,000 annually. If each event leads to health care costs of $13,500, genetic testing would reduce annual healthcare costs from bleeding events by about $1.15 billion.

We estimate the number of strokes avoided as the number of strokes avoided in non-variants correctly identified (true negative tests) minus the number of stokes caused in patients with non-variant genotypes incorrectly identified as variants (false positive tests). The simulations also predict a reduction of about 17,000 strokes. If strokes, on average, lead to health

[25] Jon Van, "Small Innovation in Genetic Tests for Drugs." *Chicago Tribune*, September 25, 2006.
[26] Bureau of Labor Statistics, Employer Costs for Employee Compensation: Health Care Employees in Hospitals, June 2006.
[27] For those patients with a genotype identified by the test, the following formulas give the possible test outcomes, where p is the frequency of variant genotypes, e is the probability of a false negative test for a variant genotype, and s is the probability of a false positive test for a variant genotype:

1. True negative, non-variant correctly identified: (1-p) x (1-e)
2. False positive, non-variant incorrectly identified: (1-p) x e
3. True positive, variant correctly identified: p x (1 – s)
4. False negative, variant incorrectly identified: p x s

The health benefits are the strokes prevented among the true negative patients net of the additional strokes caused among the false positive patients, plus the bleeding events prevented among the true positive patients net of the bleeding events caused among the false negative patients.

care costs of $39,500, genetic testing would reduce healthcare cost by about $675 million per year.

With full costs of genetic testing of about $350 per test, annual testing costs equal $700 million (2 million tests x $350 per test). We estimate the net health care savings of integrating genetic testing into warfarin therapy to be about $1.1 billion ($1.15 billion in reduced bleeding costs + $675 million in reduced stoke costs - $700 million testing costs). From the standpoint of an individual patient or payer for that patient, the use of genetic tests reduced expected health care by about $900, at a cost of about $350 for an expected net saving of $550. [28] These direct monetary savings substantially understate full social benefits because they do not include the value of the health improvements among warfarin users.

Uncertainty and Sensitivity Analysis

Monte Carlo simulations show, that with plausible assumptions about the distributions of the key variables, the public health benefits and cost savings of integrating genetic testing with warfarin therapy remain substantial. We derive the distributions for the bleeding events prevented from the values in Higashi et al. For stroke prevention, we have less quantitative information, so we use a uniform distribution (zero to 100 percent effectiveness) to model the uncertainty.[29]

The simulation incorporates uncertainty by using the distributions for many base values shown in Table 1. The results, shown in Table 2, contrast the mean outcomes with the 5th and 95th percentile outcomes of the simulation. As the table shows, the 90 percent confidence intervals are 26,000 to 150,000 for serious bleeding events prevented, 1,690 to 32,700 for strokes avoided, and $70 million to $2.2 billion for net healthcare cost savings.

These estimated benefits are most sensitive to the reduction in the rate of bleeding following genotype-based dosing, the reduction in preventable strokes, and the accuracy of testing. To show this sensitivity, we estimated the benefits using selected values for these key variables. The results of these calculations are shown in Table 3.

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[28] We calculate the expected gross cost savings per warfarin patient as bleeding cost savings plus stroke cost savings divided by the number of patients, or ($1.15 billion + $675 million) / 2 million patients.

[29] We generated the mean results and the percentile estimates with a Monte Carlo computer simulation using Palisade™ @Risk™, version 4.5.

We assume that the reduction in the rate of serious bleeding is the difference between the rate in the variant and non-variant populations. The assumption that better dosing would reduce serious bleeding rates in the variant population to the same rate as that of the non-variant population has no basis in the evidence but is plausible. The reduction in the bleeding rate, however, could be less than or possibly even greater than the difference between the bleeding rates of the two populations in the Higashi et al. study. The estimates of the health gains are therefore too high if the reduction is less than the difference in bleeding rates, and too low if the reduction is greater than the difference. To show this sensitivity, we estimate benefits using the 5^{th} percentile estimate of the difference in bleeding rates between variant and non-variant populations (5 percent) and the 95^{th} percentile difference (26 percent).

The number of preventable strokes avoided is highly uncertain. We know that more aggressive warfarin dosing for the non-variant patient population will reduce strokes, but the percentage reduction could lie anywhere between zero and 100 percent. For the basic calculation, we chose the midpoint of 50 percent. In the simulations we use a uniform distribution running from zero to 100 percent. For the sensitivity analysis, we show the effects of a 5 percent and a 95 percent reduction in preventable strokes.

The accuracy of the genetic tests matters. The lower the rates of false positive and false negative tests, the greater will be the effectiveness of dosing based on those tests. For the basic calculations, we assume that 95 percent of tests identify the genotype as variant or non-variant. We further assume that 95 percent of the tests that identify patient genotypes as variant are correct and 95 percent of the tests that identify patient genotypes as non-variant are correct. We run sensitivity tests using 70 percent and 99 percent as alternative rates of sensitivity and specificity.

We also include the sensitivity of the results to the costs of testing. We show the results for testing costs of $200 ($100 test plus $100 collection costs) and $500 ($400 test plus $100 collection costs). Clearly, the lower the cost of testing, the higher are net healthcare savings. A low test cost reflects possible declines in the cost of the test as the amount of testing increases; a high test estimate reflect possible increases in costs that might occur if several tests are necessary to identify sub-variant genotypes.

Table 3 shows the results of several of the sensitivity tests. As we expected, the results are highly sensitive to the effectiveness of warfarin dosing and the accuracy of the test. The cost

savings run from under $100 million per year to more than $2 billion, depending on the specification. Unless we assume low effectiveness for genotype-drive warfarin dosing, high rates of false positive and false negative tests, or extraordinarily high testing costs, the estimated healthcare savings remain positive.

Conclusion

Rapid progress toward personalized medicine may require trials appropriate to justify changes to FDA-approved drug labels. This analysis of warfarin illustrates that both public health improvements and significant reductions in health care spending may result from adoption of genetic information in clinical decisions about drug therapy. To generate estimates of health improvements and savings, we take current medical outcomes and health care costs for those taking warfarin, and then calculate the changes that would occur if the entire population of warfarin users underwent genetic testing that would be used to adjust initial doses of warfarin. In this case, the 85,000 serious bleeding events prevented and 17,000 strokes avoided come with a reduction in $1.1 billion in health care costs. The expected cost savings per patient exceed $500. Although these benefits estimates are quite uncertain, the existence of these benefits is much less so. Under many different plausible alternative assumptions, our analyses show that integrating genetic testing into warfarin therapy significantly improves health outcomes and reduces healthcare costs.

Table 1. Values and Distributions Used to Estimate Health Benefits and Cost Savings

	Mean or assumed value	Distribution
Population of warfarin users	2 million per year	None. Benefits would change in direct proposition to the change in population.
Probability of variant genotype	33 percent	None.
Frequency of test identifying a genotype	Test identifies a genotype 95 percent	Beta (190,10)
Accuracy of genotype testing	Probability of false positive or false negative is 5 percent; sensitivity and specificity are therefore both 95 percent	Uniform (0, 10 percent) for probabilities of false positive and false negative tests for variant genotypes
Probability of bleeding event in variant population	27.6 percent	Beta (16, 42)
Probability of bleeding event in non-variant "wild" population	12.6 percent	Beta (16, 111)
Number of preventable strokes	40,000	None.
Reduction in preventable stokes following integration of genetic testing into warfarin therapy	50 percent	Uniform (0,100 percent)
Cost per severe bleeding event	$13,500	None.
Cost per stroke	$39,500	None.
Test cost	$350. $250 for test plus $100 for costs of collecting and processing the sample	Truncated normal: mean = $250, standard deviation = $50, minimum = $25, maximum = $475. Add $100 for costs of collecting and processing the sample.

Table 2. Health Benefits and Cost Savings
(Dollar values are in millions per year)

	Mean	5th percentile	95th percentile
Reduction in bleeding events	85,400	26,000	150,000
Reduction in strokes	17,100	1,690	32,700
Net healthcare cost savings	$1,130	$70	$2,240

Table 3. Selected Results of Sensitivity Analysis
(Dollar values are in millions per year)

	Reduction in bleeding events	Reduction in strokes	Net healthcare cost savings
Genetic testing reduces bleeding by 5 percent	28,500	17,100	$347
Genetic testing reduces bleeding by 26 percent	148,200	17,100	$1,917
Genetic testing reduces strokes by 5 percent	85,400	1,710	$487
Genetic testing reduces strokes by 95 percent	85,400	32,490	$1,702
Sensitivity and specificity of genetic test are both 70 percent	38,000	7,600	$98
Sensitivity and specificity of genetic test are both 99 percent	93,000	18,600	$1,255
Test cost is $100 plus $100 collection costs	85,400	17,100	$1,394
Test cost is $400 plus $100 collection costs	85,400	17,100	$794