# Trends-in-Medicine

**August 2007**
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# Quick Pulse



**Trends-in-Medicine**
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## FDA Highlights Value of Genetics in Dosing of Warfarin and Codeine

In two separate advisories in one week, the FDA, as part of its Critical Path Initiative, flagged genetics as a potential factor when it comes to prescribing the correct dose of two drugs – warfarin (Coumadin) and codeine. Both will get new labels describing the genetic factors involved and tests available to determine whether a patient may need a lower dose.

The FDA called the announcements a look into the "window of the future of genomics and individualized medicine." The FDA is not recommending the genetic tests, but it is asking doctors to consider them.

The FDA's Critical Path Initiative, which began in 2004, focuses on the pathway medical products travel from early development to use in patients. It also highlights specific scientific projects most likely to modernize and transform the development and use of medicines, including the use of genetic factors to determine how patients will respond to therapy.

Dr. Janet Woodcock, FDA Deputy Commissioner and Chief Medical Officer, said, "This is a theme we're trying to develop that looks at scientific bases for why people respond differently, so that we can predict and prevent safety problems in people, based on these known mechanistic causes. It's part of our Critical Path Initiative, which seeks to apply new science – in this case, genomic science – to drug development and evaluation. In the case of warfarin and codeine, these are old drugs that have been around a long time, and in drug development we can apply the same new science to drugs just being studied and investigated and have more information on how to use them more properly. This is our overall goal in the Critical Path Initiative, and the codeine advisory is a good example of how we can prevent various side effects."

One of the most promising Critical Path projects, according to the FDA, is a collaboration with the University of Utah, the Critical Path Institute (C-Path) in Arizona, and the FDA to establish an evidence-based framework for determining the clinical usefulness of cardiovascular biomarkers. One of the Cardiovascular Drug Safety and Biomarker Research Program's first projects is warfarin dosing.

### Warfarin

The FDA announced that the warfarin label will be changed to include new information describing the role of genetics in dosing. The label will suggest that a lower initial dose of 2-5 mg "should be considered for patients with certain genetic variations." While Medicare covers the one-time genetic tests, which cost $125-$500, major insurance companies have not been covering them, claiming there is not enough proof that the tests reduce patient risks.

Larry Lesko, PhD, director of the FDA's Office of Clinical Pharmacology in the Center for Drug Evaluation and Research (CDER), said the label change will show physicians and patients that they have another option. Warfarin is prescribed as an anticoagulant, but excessive doses can cause bleeding and even death. After insulin, the drug (warfarin) is the second most likely drug to send patients to the emergency room.

**Reason for the label change.** Dr. Lesko said that the FDA decided to re-label warfarin because of the large percentage of adverse effects associated with the drug, "The Office of Drug Safety in 2003 did a survey of adverse events using the FDA database and published literature and found that, along with the increase in the use of warfarin over the years (as much as 40% over four years), the drug consistently was in the top 10 for the largest number of serious adverse events – as much as 15%. This is the second most popular drug in the early part of the 21st century, and in terms of causing adverse events was the second most common drug in hospitalized patients with adverse events. The use of the drug, in total, was associated with risk. The paper was published in July (2007), and looking at what the risk factors were led us down the path to re-labeling. When one began to look at the risk factors, they didn't in and of themselves seem to be associated with this high percentage of adverse events."

**Genes involved.** Dr. Lesko said that two genes can be tested to help determine a patient's response to warfarin: CYP2C9 (called 2C9 for short) and VKORC1. He explained, "2C9…is a gene member of a super family of enzymes, predominantly located in the liver. The role is to catalyze the metabolism of warfarin and other drugs, and the rate of metabolism depends on the gene variance in that gene. So, that gene affects the relationship between giving a dose to a patient and how much warfarin they have in the blood. We call that exposure. VKORC1 is an abbreviation for a vitamin K target site…This gene represents the site of action of the drug, and gene variance in that gene affects the sensitivity of a patient to the drug. Together, both the genes affect the necessary dose and response to the drug of the patient. Both of these gene tests are widely available; labs across the country offer these tests together. When one orders a 2C9 test, one gets the other automatically."

Dr. Lesko described the gene variants: "With 2C9, the most severe variant would be what we call Star 3 Star 3 (2C9*3*3). There are two variants in that gene, and those (people) with two would be most at risk. There will be people at moderate risk who may have one gene variant. The number of gene variants will affect eventual maintenance dose. In the VKOR gene, one can have one or two gene variants. If you add those up, a patient will have from zero to four total gene variants for the combined tests, and as the number of those variants go up, so does the risk and the potential lower dose."

**The new label.** Dr. Dwaine Rieves, deputy director of the FDA's Division of Medical Imaging and Hematology Products in CDER, outlined the key label changes: "With respect to the major clinical portions of the label, the alterations are in the precaution section. There are two paragraphs somewhat altered in the precaution section, and one change in the administration section…These enzyme-genetic tests we're talking about provide somewhat more of a subjective tool physicians can use in choosing the doses. The label doesn't say that performance of the tests is required. In fact, the label emphasizes the unknowns."

1. **Precaution #1.** The label will now read: "Numerous factors alone or in combination, including changes in diet, medications, botanicals, and genetic variations ***may*** influence the response of the patient to warfarin." Dr. Rieves pointed out a key word is "may."
2. **Precaution #2.** The label will now read: "Certain genetic variations…may increase the need for monitoring and lowering warfarin doses." Dr. Rieves said, "There is quite a list of factors prescribers need to consider when prescribing both initial doses and then how to adjust the doses. Some of these are subjective such as fragility and diet. The label alteration to identify these lab tests is just another one of the potential tools the doctor may consider in prescribing warfarin."
3. **Administration.** In the administration section, the initial recommended dose is 2-5 mg per day. The modified text says that the lower initial dosage should be considered "for persons with certain genetic variations, as well as elderly, debilitated patients."

**Message for physicians.** Dr. Woodcock said that one unanswered question is how genetic information will affect how physicians prescribe drugs. She said, "There are going to be some randomized trials that look at using the genetic information vs. standard of care. The point is that doctors have to figure out a way to try and get the best dose of warfarin. What they (currently) do is trial and error when they start the dose, and every patient comes back, and tests are done, and the dose is adjusted. Up to this point, that's been the workaround. There are some variabilities due to diet and factors not related to genetics. We have to test how good it will be to use genetic information vs. the current methods… Everyone knows that people respond differently to the same drug, and that isn't just by chance. There is a scientific reason – some of that is genetic, and some is what happens in your environment – what you eat and so forth…We think we can now find out why some people respond to drugs differently."

*Asked how the genetic test would work relative to factors such as age and diet when it comes to determining dose*, Dr. Lesko said, "The predominant risk factor is age…Body weight and size contribute very little more than age. Genetics becomes important in the percentage of contribution it makes to the overall variability in the dose and response. It is estimated that 30%-35% of variability in dose to response is in the two

genes we're talking about…A combination of age, along with genetics, would be the best approach now to figure out the initial dose. When patients continue to the maintenance phase, the INR (International Normalized Ratio) becomes the dominant way of regulating dose.

Dr. Woodcock said that the new warfarin label will ***not*** require physicians to do genetic tests, but she said that recommending tests is not out of the question in the future: "This re-labeling …is not a directive to doctors that they should use (the genetic test). We will await the results of outcome studies for that type of label if, in fact, the data show that it is necessary for the drug to be used safely. The information in the label is more informational to doctors...There are several steps down this pathway (which may) stimulate the investigation in getting conclusions about what the role of genetic testing is at this point in the use of warfarin therapy."

*Asked why the FDA didn't recommend the tests in the labeling*, Dr. Rieves said, "The clinical data available today are not sufficient in our judgment to alter the recommendations in the label such that we require or even strongly encourage – beyond what we described in the current label – the use of these tests. There are so many considerations. The subsequent clinical tests may prove that the tests are essential, and if the data turn out that way, we expect the labeling will be changed to reflect that…Hopefully, over the next few years, we will have information so that we can optimize the use of the tests. We're seeing now the early stages of the use of these types of tests in clinical practice. We're not quite to the point where we can say that doctors must perform these tests. Doctors can still practice good medicine without necessarily doing these tests, but the tests are available, and that's one of the major points we make with the (label) change." Dr. Lesko added that to mandate the test would make it a prerequisite that the test is widely available: "We don't want to put any physicians in a situation where they don't have access to the test, and, in addition, we encourage the diagnostic industry to submit the approval of these gene tests to the FDA."

*Asked if the label change will cause a greater demand for the tests*, Dr. Lesko said, "The language in the label is important. We felt an obligation to share the information that we have and the level of evidence that we have. Physicians may want to consider these tests. We do know from the adverse event literature that that the drug is problematic, and people may use it as part of the solution to better management of INR control."

**Dosing recommendations.** Dr. Rieves said that dosing recommendations are not changing with the new label, "The most clinically applicable portion of the label hasn't changed with respect to the recommended dose. What is available is in the language and precaution section. Genetic testing is one of the many tools that physicians consider when they select one of the recommended doses, but the actual recommendations for dosing and monitoring have not changed."

*Asked about the potential for genotype-driven dosing algorithms*, Dr. Woodcock said, "A variety of groups are looking at this. The C-Path Institute has given us some valuable input, but there is a fair amount of work that would have to be done before the biomedical community would consider this to be standard therapy. This is right now one of the factors to consider when dosing warfarin, so we hope under Critical Path that we will continue to collaborate with several groups in terms of nailing down the level of contribution of genotyping in the management of patients who need anticoagulation."

A third of the U.S. population has a variant in the 2C9 gene. Dr. Lesko said, "We are primarily focused on the relationship between the gene variant and final maintenance. Also, INR control is important as a prerequisite to optimal or suboptimal therapy. From a combination of trials, gene variants are associated with better INR control and lower doses than the usual 5 mg dose. That type of evidence led to consideration of the label update…We had to stop short of recommending specific doses for specific genotypes, and that's what additional studies will focus on. The VKOR gene variants are a little bit wider than the 2C9."

Dr. Rieves said, "This labeling recommendation does not change how physicians alter their dosage in response to INR results, and none of the recommendations for either initial dose or subsequent doses has changed. What this does is highlight the availability of these tools, of these tests for the physician to test patients. If the patient has a genotype for these gene variations, then it's logical to use the lower initial dose. The recommended initial dose is somewhere between 2-5 mg. As it stands right now, physicians could use very subjective factors, and the dosing of warfarin right now involves a great deal of subjectivity. The genetic testing impacts the choice of initial dose – whether to start a patient on the lower end or the 5 mg. That is an important consideration during the first few days of starting warfarin therapy. Subsequent doses are based on PT (prothrombin time)/INR goals, and the dose adjustment paradigm has not changed."

**Race and ethnicity.** There are racial and ethnic differences in the distribution of these genes, Dr. Lesko said, adding, "In interpreting the data, what physicians and patients have to think about is the number of gene variants in a given patient for both genes. The larger the number of variants, most likely the lower the dose and potentially higher risk for adverse effects or for INR control."

- **Caucasians.** Most of the information so far is on Caucasians, and about 60% of Caucasians have at least one variant in that gene.
- **African-Americans.** One in four African-Americans has the variant.
- **Asians.** About 80% of Asians have a variant in the gene.

**Genetic test availability.** Many companies make the genetic test, including Kimball Genetics and others, but Dr. Lesko said the testing companies had not asked for the re-labeling, "No one has gone through the approval process at the FDA, although several of them are under consideration, and other companies have publicly said that they intend to submit applications to the FDA. These lab tests are regulated in terms of quality and analytical quality by Clinical Laboratory Improvement Amendments (CLIA) regulations under CMS (Centers for Medicare and Medicaid Services)."

*Asked how long test results take*, Dr. Lesko said, "Genetic testing depends on the setting. If it's a major medical center with more volume and research, the turnaround time could be one day or less. With a commercial lab, it could take around five days to get the results back. It depends on where the practice is and the frequency of people using it."

**Ongoing studies.** Dr. Lesko said that there are several ongoing studies looking at genetic factors in warfarin dosing, and a University of Alabama study published in early August 2007 found an association prospectively between the risk of hemorrhage and 2C9. He said that many drugs have genetic information included in their labeling, but traditionally much of that was descriptive and found in the pharmacology part of the label. Several older approved drugs have had some genetic information included on updated labels over the past four years, including mercaptopurine (a leukemia drug), and irinotecan (Pfizer's Camptosar) for colon cancer has been associated with a high risk of severe neutropenia in a population subset, so the FDA included specific dosing in that label. Dr. Lesko said the FDA also is looking at the breast cancer drug tamoxifen and which patients might not respond to that, adding, "Warfarin becomes the next in line."

*Asked about an FDA genetic study of 800 patients that was to have begun in November 2006*, Dr. Lesko said that the study (with Kaiser Permanente) was never conducted because of funding issues.

## CODEINE

In another action designed to focus attention on how genetics and genomics can influence people's metabolism of drugs, the FDA issued a public health advisory, and the FDA asked manufacturers of drugs containing codeine to revise their drug labels. The actions came because the FDA found a very rare – but serious – side effect can occur with codeine when it is used by breast-feeding mothers who metabolize the drug very quickly, possibly putting their infants at higher risk of a morphine overdose. The FDA said that it had found only one case of morphine overdose in a newborn but that women who are breast-feeding and taking pain medication should be aware that some people metabolize codeine differently, and it may affect their infants.

Codeine, an ingredient in many prescription pain relievers and over-the-counter (OTC) cough syrups, breaks down into morphine in the body. Rear Admiral Dr. Sandra Kweder, deputy director of the FDA's Office of New Drugs in CDER, said, "There is clear evidence that genetics and genomics can influence people's individual metabolism of drugs. This is important new information about a very rare but serious side effect in nursing infants whose mothers are taking codeine, and differences in metabolism among mothers taking codeine, which can contribute to side effects in nursing infants. Infants of nursing mothers taking codeine have an increased risk of narcotic, particularly morphine, overdose if the mother is an ultrarapid metabolizer of codeine. When codeine enters the body, it changes to morphine, and it's the morphine that relieves pain…Ultrarapid metabolizers are more likely to have higher levels of morphine in the blood when they use codeine at regular doses. Nursing mothers may also have higher morphine levels…in their breast milk, and these higher levels of morphine in breast milk can affect the baby and lead to severe, even life-threatening, side effects in nursing babies."

The use of codeine to manage pain after birth is very common, but reports of serious side effects are extremely rare, according to Dr. Kweder, who said that the FDA learned of the rare side effect in ***Lancet*** last year, which described a 13-day-old breast-fed baby in Canada who died of an overdose. High levels in the baby's blood and genetic testing showed that the mother was an ultrarapid metabolizer of morphine. Dr. Kweder said, "There was no question that this was a clear-cut case of ultrarapid metabolism in a mother, and it was the first case so well reported. We went back and looked through FDA's adverse events database looking for any reported cases we might have of similar adverse events, and we were unable to find anything this clear-cut…After our look at the science that went into this particular case report, we felt it worth highlighting to the public because it gives us a window into the future of genomics and individualized medicine."

She said that the FDA, in issuing the public health advisory, is telling doctors that when prescribing codeine for a nursing mother, they should:

- Prescribe the lowest dose for the shortest amount of time to nursing mothers to relieve pain or a cough.
- Talk to nursing patients about how to recognize signs of high morphine levels in themselves and their babies.
- Tell new mothers that if a baby shows signs of increased sleepiness, breathing difficulties, or limpness, they should call the baby's doctor or take it to the emergency room right away.

Manufacturers of codeine products are being asked to include this information, and particularly concerns about breast-feeding, on labels for all codeine-containing drugs. Dr. Woodcock said that there are "dozens" of companies that make codeine-containing products, most of which are generic. She added that ultrarapid metabolizers can also be affected by

other narcotics, but other narcotics are not converted directly to morphine as codeine is, and "that is what's expected to be most problematic in breast milk and infants."

FDA officials pointed out that there is an FDA-cleared test – called the CYP2D6 metabolism test – which can identify patients with the ultrarapid metabolizer profile. The test is widely available in specialty labs, but there is not a lot of information about its use in the general population looking specifically at its application to codeine. From 1%-10% of Caucasians, about 3% of African-Americans, and about 1% of Hispanics and Asians fit that profile. Inexplicably, about 16%-28% of Ethiopians and Saudis also fit the profile. Dr. Kweder commented, "It (the test) can be useful, but it is not a substitute for a doctor's judgment."

*Asked if women should consider having the test before breast-feeding*, Dr. Kweder said, "That is not advice we have enough evidence to give very broadly right now. Codeine-containing products are the most commonly utilized products in new moms. The drug doesn't hang around for a very long time and is usually cleared from the system quickly. It also has been used for decades. It is one of the oldest and tried-and-true types of pain medication utilized…Our point is (for doctors to) pay attention."

*Asked why there haven't been more cases reported of infant codeine overdoses from breast-feeding*, Dr. Kweder said, "The prevalence is estimated to be in the range of 1%-10% in Caucasians, and there are probably some people who express this genetic type more strongly than other people. The case that was reported was a very dramatic case, and it may well be that other people with the same profile may be less affected or more affected by it, even if the genes are there. The question of how your body expresses the gene can vary tremendously."

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