Genotype-guided dosing of warfarin: GIFT wrap-up

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January 2018—In an ideal world, clinical research data would be applied with immediate and beneficial effect to clinical practice, especially when the data come from a well-controlled, well-run trial that meets the gold standard of being large, randomized, and blinded. However, as the Sept. 26 publication of the Genetic Informatics Trial to evaluate genotype-guided dosing of warfarin demonstrates, reality is far more complicated (Gage BF, et al. *JAMA.* 2017;318[12]:1115–1124).

Despite GIFT showing that genotype-guided dosing prevents more adverse outcomes than clinically guided dosing, pharmacogenetic testing to improve warfarin initiation may not become widespread practice anytime soon.

GIFT was designed to do what the earlier COAG and EU-PACT trials had failed to do: provide the definitive answer to the question of whether genotype-guided warfarin dosing provided statistically significant clinical benefit to patients undergoing anticoagulant therapy. The inconsistent results of the prior trials—the COAG study found no benefit, EU-PACT did—were all the more puzzling because the effects of allelic variation in genes related to warfarin metabolism are well known and well characterized. (The results of both were published Dec. 12, 2013 in the *New England Journal of Medicine*, along with the results of a third study not of warfarin but of two other vitamin K antagonists.)

GIFT, which was a study of patients undergoing elective hip or knee arthroplasty, differed from the earlier trials in important respects that led investigators to hope it would provide a clearer answer to the question. GIFT was larger (1,597 patients compared with 1,015 in COAG and 455 in EU-PACT) and differed in the length of time the dosing algorithms were used. (EU-PACT found a higher percentage of time in the therapeutic INR range but wasn't powered to assess for differences in clinical outcomes.)

Dr. Eby

"We were optimistic that the trial could show a difference favoring pharmacogenetic testing because of some pretty important details," says investigator Charles S. Eby, MD, professor of pathology and immunology and co-chief of the Division of Laboratory and Genomic Medicine, Washington University School of Medicine.

"One, we had, under [principal investigator] Brian Gage's leadership, developed dosing adjustment algorithms that went all the way to day 11 of warfarin treatment [versus four or five days in COAG and EU-PACT] and allowed for additional fine-tuning of the warfarin dose using both the known genetic information for the patients randomized to that arm plus how their INR was changing in those first 11 days."

"We basically had more detailed algorithms to make dose refinement adjustments," Dr. Eby explains.

A second advantage is that GIFT investigators included the polymorphism *CYP4F2*, which has been shown to have minor impact on steady state warfarin dose, he says, because the product of that gene is a protein involved in metabolizing vitamin K. "If vitamin K metabolism is slower, it means there will be more vitamin K inside of liver cells that has to be antagonized by warfarin, and it actually predicts a slightly higher warfarin dose," Dr. Eby says.

The third advantage was a different population. GIFT investigators enrolled patients undergoing major surgery who

historically have a higher rate of deep vein thrombosis in the first 30 days than nonsurgical patients started on warfarin. “We anticipated that we would have more clinical events to further help differentiate the benefits of the pharmacogenetic-based dosing algorithm,” Dr. Eby says. “We estimated that based on preexisting risks for DVT, a sample size of 1,600 would give us the power to see a difference in the composite outcome of VTE, major bleeding since patients undergoing major surgery had higher bleeding risks, INR of four or greater, and death.”

Coauthor Gwendolyn A. McMillin, PhD, medical director of toxicology and pharmacogenetics at ARUP Laboratories, says the biggest flaw of the prior studies (she was involved in COAG also) was the short period of time the genotype-guided algorithm was applied to warfarin dosing. “It takes four or five days for someone to reach steady state with warfarin if they have normal metabolism. If they have impaired metabolism, it’s going to take even longer, and then we also have to consider the kinetics of eliminating the clotting factors,” she says, noting that these temporal relationships had largely not been incorporated into previous study designs. “Most of the early studies switched back to the clinical monitoring before the genotyping really had any time to impart its effects.”

Dr. McMillin, who is also a professor of pathology at the University of Utah School of Medicine, says the incorporation in GIFT of the additional allele was important and that 42 percent of the study population was heterozygous for it. Brian F. Gage, MD, MSc, professor of medicine at Washington University School of Medicine and medical director of the Barnes-Jewish Hospital Blood Thinner Clinic, says there is a five to eight percent increase in dose per *CYP4F2* allele and that he hopes to use the GIFT data to quantify this effect more precisely.

To some extent, GIFT did what it was designed to do. The study met its primary endpoint of the four composite outcomes of major bleeding, INR of four or greater, VTE, and death. There were no deaths in the trial and the three other outcomes favored the genotype-guided algorithm group. “We were glad to see that genotype dosing worked,” Dr. Gage says of the overall results. “We also were part of the COAG trial, so some of my colleagues had grown skeptical about the potential of genome-guided dosing. However, GIFT squeezed more benefit from genotype-guided dosing by using genotype for days one through 11 of therapy and by including SNPs in another gene [*CYP4F2]*.”

Dr. Gage

Although the primary endpoint was statistically significant, the significance was driven largely by the differences in INR greater than four. “The 27 percent relative risk reduction in adverse events was very similar to what we hypothesized,” Dr. Gage says. He adds: “The surprise was how well these elderly patients did after elective hip and knee replacement. Only 1.6 percent of 1,597 patients had a symptomatic deep venous thrombosis or PE. No one died during surgery or during his or her 90-day follow-up. Of course, most of the credit goes to the excellent teams caring for these patients” at Hospital for Special Surgery, Washington

University, Intermountain Healthcare, University of Utah, Rush University Medical Center, and University of Texas Southwestern. “The only intracranial hemorrhage occurred in a patient who fell a couple months after he stopped his warfarin therapy,” Dr. Gage says.

The small number of adverse events made the statistical data challenging for the investigators and clinicians to interpret. Moreover, the results are indicative of the challenge of relying on historical data to make statistical power calculations, particularly in a medical setting where constant improvement in outcomes is the aim.

Are the results applicable to other clinical settings and patient populations? Says Dr. Gage: “I think the results of

GIFT are generalizable to other populations who have access to accurate, timely genotyping at the time of warfarin initiation. However, the absolute benefits of genotype dosing will depend on that population's baseline rate of adverse events." This speaks to the fact that GIFT took place in major medical centers and used a relatively homogeneous and well-defined patient population that underwent regular INR testing.

The trial also used a 2×2 randomization to help orthopedic surgeons answer the question of whether there are safety differences between an INR goal of 1.8 or 2.5. The data comparing potential differences in safety have not yet been published and are still under review, but the fact that half the patients had a lower INR target may have reduced bleeding complications.

GIFT compared pharmacogenetic-guided dosing to a refined clinical algorithm that is not yet the standard of care. "It's one thing to estimate what the therapeutic dose would be," Dr. McMillin says, "but it's another to tell you how to get there using a refined electronic algorithm. It's like the difference between using a GPS rather than just a map or an address. You could redirect based on how a patient was responding. When you have well-managed coagulation clinics, particularly in major medical centers, the performance of the clinical algorithm is very good and it's hard to demonstrate an improvement. It was actually rather astounding that GIFT was able to show a difference." Better results might be seen if pharmacogenetic dosing were tested in a more real-world situation, she adds.

Although the use of an electronic algorithm (for example, Gage, et al., warfarindosing.org) has never been compared with trial-and-error dosing, Dr. Eby believes it would be an improvement. Both are used at Washington University and the goal is to integrate the clinical algorithm into the new electronic health record system slated to come online this year. "The integration of the algorithm would be a short-term goal," Dr. Eby says, "and I don't think it comes at an additional cost. It's one of the attractions of using the clinical algorithm. The information is already available and we can be optimistic it would improve INR control and precision even if we have not compared it to the trial-and-error standard of care."

Using clinical algorithms rather than pharmacogenetic-guided dosing might be a more practical way to improve warfarin dosing, wrote Jon D. Emery, MBBCh, DPhil, professor of primary care cancer research at the University of Melbourne, in an editorial accompanying the GIFT results. Genotype-guided warfarin dosing probably has clinical utility, he wrote, "but it might be simpler and less expensive to implement wider use of clinical dosing algorithms to reduce the harms of anticoagulation."

At the University of Utah, Dr. McMillin says, GIFT has reignited a discussion of the best way to administer warfarin, and the university is reconsidering whether to recommend genotyping. Before GIFT, physicians were reluctant to order the additional laboratory test or to integrate an electronic algorithm into their warfarin dose decision-making. The trial has changed that.

Two other changes have come out of GIFT. First is a recognition that it's important to combine genes, Dr. McMillin says. "We in our community have been focused on single gene-drug pairs, and it's very shortsighted, a little monovision. I love the warfarin example—a study where we've used three different genes because they all play a different role and they're all important. So one outcome that's already impacting the pharmacogenomics community is there are more people thinking about multi-gene impact." Second, GIFT demonstrates success with an electronic algorithm—which is not standard of care now—whereby physicians consult an electronic resource to select drugs and doses. "This demonstrates it actually can work," Dr. McMillin says.

Clinical benefits aside, a central question remains: reimbursement. The CMS funded GIFT and is reviewing the data, but a decision is not expected soon. Dr. Gage was a coauthor of a cost-effectiveness analysis of using pharmacogenetic information in warfarin dosing for patients with nonvalvular atrial fibrillation (Eckman MH, et al. *Ann Intern Med.* 2009;150[2]:73–83). He and his coauthors concluded: "For genetic testing to cost less than $50,000 per QALY, it would have to be restricted to patients at high risk for hemorrhage or meet the following optimistic criteria: prevent greater than 32% of major bleeding events, be available within 24 hours, and cost less

than $200.” Although these three criteria were met in GIFT, he says, the cost-effectiveness studied in 2009 was for a different population.

Even as newer anticoagulants displace some warfarin use, warfarin is still likely to have an important place in the care of patients, Dr. Eby says, such as those with severe renal failure and mitral valve prosthetics and where financial resources are limited. But so far, the early promise of major pharmacogenomic benefit on patient care, including on warfarin dosing, has not been realized and cost-benefit questions loom large. Preemptive genotyping is one way to lower the cost and increase the benefit. As the cost of gene sequencing declines, it makes more sense clinically and economically to have pharmacogenetic data on a broad range of drugs as part of a patient’s record, which would remove time to result, among other benefits. Dr. McMillin cites the Ubiquitous Pharmacogenomics program in the European Union as the wave of the future. An 8,000-patient clinical trial is underway in the Netherlands, Spain, United Kingdom, Italy, Austria, Greece, and Slovenia to preemptively genotype 4,000 patients across 13 genes that affect the metabolism of 40 commonly prescribed drugs. Outcomes will be compared in the three-year study with those of 4,000 control patients. If the trial is successful, the goal would be to extend the U-PGx program to all EU residents.

Dr. McMillin

“The EU made a major commitment to pharmacogenomics because they think it’s worth it,” Dr. McMillin says. “There are a number of institutions in the U.S. that are doing work on preemptive genotyping and implementing smaller pieces, but it would be a problem for our health care system to implement a Ubiquitous approach because we’re not socialized enough.”

Absent a European-style centralized health authority, preemptive genotyping is a chicken-and-egg situation: Clinical demand is needed to drive positive reimbursement, and positive reimbursement is needed to drive clinical demand. Another necessity would be electronic decision support. “Such a system would do what the warfarindosing.org website does but automatically,” Dr. McMillin says. “It would take the genetic information that is preexisting, combine it with the clinical information that’s extracted, and provide that information directly to the clinician with some additional prediction of risk. The costs in that case have already been expended, so it comes down to the medical evidence that it is going to benefit the patient.” Clinicians will adopt preemptive genotyping, in her view, when it is incorporated into the clinical decision support components of electronic health records. “That’s really what it’s going to take.”

Before this can happen, Dr. McMillin says, there are a few nontechnical obstacles to overcome, and chief among them are the proprietary commercial algorithms. “One of the more unfortunate things in the marketplace right now is the development of proprietary algorithms. There are some companies that are charging huge amounts of money to guide drug and dose selection with their algorithms, and they are proprietary so it prevents access. To use psychiatry as an example, there are now over 20 algorithms that are out there, they’re all proprietary, and none have been compared head to head. The algorithms and the data behind them should be shared for everyone.”

A broader question concerns the future of clinical research like GIFT in a cost-constrained environment dominated by reluctant third-party payers. Why spend the money for the research if there is no way to pay for the benefit? The future may be some combination of using real-world data and sophisticated informatics and artificial intelligence tools, perhaps in partnership with third-party payers with incentives to save money and improve care.

The challenge, Dr. Eby says, is that randomized clinical trials can't be conducted to answer every clinical question. "Although I am optimistic that clinical research will still drive and provide compelling evidence to change both the funding and practice of medicine, I think the dependence on randomized, controlled trials is what has to change." Other reliable ways based on clinical experience have to be found to guide medical decisions and reimbursable practice. "This gets into a discussion of how clinical informatics and computational expertise can use real-world data to guide decision-making. And could this same way of analyzing existing data provide convincing data that the outcomes would be better or cheaper if certain practices were adopted?"

The combination of data from trials such as GIFT, the declining cost of genotyping, and advances in clinical informatics may finally allow the field of pharmacogenomics to fulfill its early promise. Though genotyping of warfarin might be hard to justify today given the cost and logistics, warfarin would most certainly merit priority placement on any pharmacogenomic panel of the future.
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