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Newly Proposed PAMA Rates for 2018 Confirm Lab Industry's Worst Fears

The Centers for Medicare and Medicaid Services' (CMS') preliminary 2018 prices for clinical laboratory tests issued under the Protecting Access to Medicare Act (PAMA) came as a big disappointment to the laboratory industry. First, other than for some advanced tests, the prices were lower than expected. Secondly, implementation of the new PAMA payment system will not be delayed and will take effect Jan. 1, 2018. Lastly, CMS stuck to its controversial approach of excluding hospital laboratories from its pricing formula.

The intent of PAMA is to base Medicare payments for specific tests on the weighted median of private payer rates for that test. Since 2014, CMS has been gathering data from "applicable laboratories" to calculate these rates. The proposed Clinical Laboratory Fee Schedule (CLFS) for 2018 represents the agency's first attempt at setting prices using the new formula.

While embracing the idea of market-based pricing, the laboratory industry has objected to CMS' methodology of not including hospital and community labs in its definition of "applicable laboratories." Because these labs charge higher rates, excluding their pricing data was bound to artificially skew rates in a downward direction, the laboratory industry argued.

Payment Cuts

The CMS's CLFS proposal confirms the laboratory industry's concerns, making even deeper and more widespread cuts than feared. The 2018 CLFS would cut payments for approximately 75 percent of lab tests. The only upside for laboratories is that the majority of the rate cuts (58 percent) will be phased in due to CMS's 10% per year cap on reductions from 2018 to 2020. CMS claims that the new rates will save Medicare Part B about $670 million in 2018.

"If these draft rates were finalized, the impact would be devastating," according to Julie Khani, president of the American Clinical Laboratory Association, in a statement. "We fear the impact on laboratories serving the most vulnerable Medicare beneficiaries, laboratories serving rural areas, and those with high Medicare volumes would be the most severely impacted."

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Below is G2's analysis of the key takeaways about the proposed 2018 CLFS.

Reference Labs Suffer the Deepest Cuts

While, if implemented, the proposed rate cuts would have widespread effects across the industry, big reference laboratories, like Quest Diagnostics and LabCorp, will be particularly negatively impacted. In a note to investors, Piper Jaffray analyst William Quirk writes that the expected revenue decline of approximately 8 percent in the first three years is even worse than Wall Street's initial expectations of a 6 percent drop in 2018 followed by a leveling in 2019 and 2020.

Both companies have issued statements criticizing the preliminary rates as not being market-based because they exclude payment data from hospital labs. According to Quest CEO Steve Rusckowski, "Hospitals and physician office labs comprise half of Medicare CLFS volume and lab spending, but only accounted for 8.5 percent of the reported lab volume used by CMS to calculate the rates."

Molecular Testing Relatively Unscathed

Proprietary tests would fare better than more common tests provided by large numbers of hospital and reference laboratories. While a few molecular tests would suffer deep cuts (including tests for Lynch syndrome [CPT 81435] and TRB gene rearrangement direct probe [CPT 81341]), molecular assays generally see smaller declines and even a few rate increases.

Sampling of Molecular Test Pricing Changes

Test	Proprietary Manufacturer(s)	2017 Rate	Proposed 2018 PAMA Rate	% Change
CPT 81519 (Oncotype DX for breast cancer recurrence)	Genomic Health	$3,443.36	$3,873	+12.4
CPT 81525 (Oncotype DX for colon cancer recurrence)	Genomic Health	$3,126	$3,116	-0.3
CPT 0008M (Prosigna for breast cancer recurrence)	Nanostring	$3,443	$900	-73.9
myRisk Hereditary Cancer (based on CPT 81211 and 81213)	Myriad Genetics	$2,781	$2,949	+6.0
CPT 81490 (Vectra DA rheumatoid arthritis test)	Myriad Genetics	$591	$841	+42.3
CPT 81450 (hematological malignancies)	--	$541.81	$648.40	+19.7
CPT 81445 (targeted next-generation sequencing of 5 to 50 genes panels	--	$602.10	$597.91	-0.7
CPT 81432 (Invitae hereditary cancer panel)	Invitae	$931	$838	-10.0
CPT 81528 (Cologuard colon cancer screen)	Exact Sciences	$512	$509	-0.6
CPT 81420 (prenatal testing)	Illumina, Natera, et al.	$802	$759	-5.4
CPT 81435 (Lynch syndrome test)	--	$802	$38	-95.3

DTET

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Advanced Diagnostic Laboratory Tests (ADLTs)

Another category of tests that fared relatively well are advanced diagnostic laboratory tests (ADLTs), which CMS defines as tests developed and offered by a single lab that use a unique algorithm to analyze multiple DNA, RNA, or protein markers, and provide new clinical diagnostic information that cannot be obtained by any other test. Two noteworthy ADLT test codes that would get payment increases are:

- CareDx's AlloMap for cardiac transplant rejection risk (CPT 81595): a 14 percent increase, from $2,841 to $3,240; and
- Veracyte's Affirma Gene Expression Classifier for classifying thyroid nodules (CPT 81545): a 12 percent increase from $3,222 to $3,600.

Crosswalk Codes

CMS also issued crosswalk- and gap-filling-based preliminary rates for 58 HCPCS codes that received no private payor data.

Takeaway: CMS is expected to issue final rates in November. In the meantime, the laboratory industry has not given up on its efforts to persuade the agency to change the pricing formula to include hospital laboratories or delay the new PAMA rates from taking effect on Jan. 1, 2018.

IDWeek Tackles Improved Ordering Strategies

IDWeek, the combined annual meeting of the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, the HIV Medicine Association, and the Pediatric Infectious Diseases Society, was held Oct. 4 to 8 in San Diego.

DTET examined abstracts presented and identified a common theme of trying to improve appropriateness of infectious disease test ordering. Below is a sampling of presented abstracts that highlight the need to improve reflex testing, electronic-based methods to increase the appropriateness of test ordering, as well as an examination of renewed interest in alternative, non-blood based specimens for rapid testing.

Low Frequency of Reflex Flu Testing Seen

Despite, national guidelines, provider compliance with recommendations for reflex polymerase chain reaction (PCR) testing for negative rapid flu results are low.

Intermountain Healthcare (IH) operates a nonprofit system of 22 hospitals, 41 urgent care centers, and more than 185 physician clinics serving the Intermountain West. The researchers identified orders for rapid flu tests (BD Veritor) during a high-activity period in the 2016-2017 flu season (December 2016 to March 2017). Tests were ordered at any one of the IH locations. The proportion of reflex tests ordered within 48 hours of rapid flu testing was calculated.

The researchers, led by E. Kent Korgenski, from University of Utah School of Medicine in Salt Lake City, identified 9,623 patients assessed during the study

period and determined the overall reflex to PCR within 48 hours occurred in 9.6 percent of patients. Reflex testing frequency was much higher in the hospital setting, particularly in the emergency department (20.5 percent) and among inpatients (30.4 percent), compared to ambulatory care settings (2.0 percent) and urgent care clinics (0.6 percent).

The researchers found that mean weekly C. diff testing rates declined significantly before and after the intervention (146 pre-intervention versus 119 post-intervention).

The Impact of 'Hard Stops' for C. Diff Test Ordering

An abstract presented at IDWeek 2017 assessed the impacts of implementing "hard stops" in electronic medical records (EMR) as a means of improving appropriateness of C. difficile (C. diff) test ordering. The study found that EMR alerts reduced inappropriate testing, without negatively impacting patient outcomes.

In the Johns Hopkins University School of Medicine study, EMR alerts were triggered for C. diff tests ordered in a patient with previous test (14 or 7 days for positive or negative) or receipt of laxative within the last 48 hours. The initiative began at an academic hospital in October 2016 and at two community hospitals in December 2016 and January 2017.

The researchers found that mean weekly C. diff testing rates declined significantly before and after the intervention (146 pre-intervention versus 119 post-intervention). The average number of weekly EMR alerts was 51 (26 for laxatives, 14 for previous negative test, three for previous positive test, and eight for undetermined reasons).

Among the 83 patients who had an EMR alert, but for whom the clinician did not pursue testing, outcome review showed that for 36 diarrhea resolved, for 21 an alternate cause found, 11 had subsequent C. diff testing later in the admission (6 negative, 5 positive results), 12 patients were discharged home, and three died from non C. diff infection-related etiology.

Test Names Can Optimize Ordering Patterns

Despite guidelines to the contrary, the emergency department at University of Wisconsin-Madison had a high number of Group A Streptococcus (GAS) reflex culture orders were being placed for adults with negative results from rapid antigen detection testing (RADT).

In November 2016 the institution changed its ordering language. To differentiate the ordering pathways for children and adults, with the goal of increasing guideline compliance, the word "peds" was added for RADT with reflex culture orders, while the word "adult" was added for RADT without reflex culture. The number of GAS reflex culture orders for adult patients in the emergency department was tracked for six-months following the change and compared to data from the year before.

The researchers found that pre-intervention, the average number of adult GAS reflex cultures per month was 66, which fell to 34 following the change in ordering language. The percentage of total RADT tests that underwent reflex culture changed from 99.5 percent to 49.0 percent before and after the intervention, while the number of RADT tests with no reflex culture ordered showed a proportional increase. The number of add-on culture orders was

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>
> — Chelsea Shannon

also tracked, but there was no marked increase in these orders during the intervention period.

Oral Fluid For Syphilis Testing

A group of University of California Los Angeles researchers tested whether saliva could be used to replace whole blood as the specimen of choice for rapid syphilis testing (qualitative immunoassay).

Oral fluid samples (1 mL) were collected from 72 participants using the Super•SAL Oral Fluid Collection Device (Oasis Diagnostics), but were tested using the SD Bioline Syphilis 3.0 rapid test (Alere Diagnostics) following manufacturer directions for whole blood. TP particle agglutination (TPPA) and rapid plasma reagin (RPR) results, abstracted from participants' medical records, were used as reference values.

Assessing TPPA reactivity, the test's sensitivity was sensitivity 83.3 percent. Assessing TPPA and RPR reactivity, the test had 86.4 percent sensitivity. Finally, using TPPA reactivity and RPR titer above 1:4, the test's sensitivity was 100 percent. Specificity was 47.2 percent. The authors suggest that false positive results may be due to the presence of non-venereal treponemal antibodies in oral fluid.

"The high sensitivity of the SD Bioline Syphilis 3.0 test using oral fluid suggests a strong potential for the development of accurate rapid oral syphilis tests," conclude the researchers, led by Chelsea Shannon.

New Strategies Seek to Expand Genetic Counseling Capacity, Remove Workforce Constraints on Testing

Geneticists and genetic counselors are in short supply. The shortage has even been a bottleneck for expanded clinical use of large molecular panels and whole-exome sequencing, which require patient counseling. It has been presumed that increasing the workforce capacity of these genetics experts, could remove workforce issues as a barrier to testing and increase comfort among nongenetics specialists ordering and counseling patients about results of complex, genetic tests.

The annual conference of the National Society of Genetic Counselors was held Sept. 13-16 in Columbus, Ohio. Many presentations focused on how to expand workforce capacity in order to improve access to services. Below is a sampling of studies that examined alternative strategies, including web-based, on-demand, and telemedicine options, to extend the reach of genetic counselors in clinical settings.

Web-Based Education about Exome Sequencing Okay

The best "full member" abstract award at the conference went to researchers at the National Human Genome Research Institute who tested a web-based alternative to in-person carrier results return. They designed a web platform that integrated education regarding carrier results with individualized test results.

A total of 462 participants were randomized to receive either web-based or counselor-delivered results. One to seven carrier results were returned to each participant. The web was non-inferior to the counselor at six months after return of results for the following outcomes: knowledge, distress, risk worry, and decisional conflict. There were no significant differences between the two groups in disclosure rates to children, siblings, or providers.

"[The results] should spur efforts to shift the communication of certain information about genomic test results from the clinic to the Internet to improve efficiency and reduce health care costs, allowing genetic counselors to prioritize in-person return of more threatening health risk information from sequencing," conclude the authors led by Barbara Biesecker, Ph.D.

Remote Genetic Counseling Improve Clinical Decision-Making

Researchers from Invitae (San Francisco, Calif.) tested a novel model for hereditary cancer risk assessment where 14 community-based breast cancer surgeons had "on-demand" access to a remote laboratory-based genetic counselor for consultation about testing eligibility and selection. The multiple participating clinical sites did not have a genetic counselor as part of their practice. Physicians could opt to utilize remote genetic counselors to discuss results or they could refer to traditional genetic counseling services.

Over the study period 236 patients were evaluated. Physicians used risk assessment tools (BRCAPRO and the Hughes Risk model) on 98 percent of patients. Nearly two in three patients (65 percent) met National Comprehensive Cancer Network guidelines for testing. After discussion with a genetic counselor, breast surgeons changed their test selection 21 percent of the time. Clinicians called to discuss results in just under half of cases (47 percent). Furthermore, based on these discussions with a remote genetic counselor, medical management changes were incorporated in 15 percent of these cases.

Non-invasive Prenatal Screening Results Management

Use of non-invasive prenatal screening (NIPS) has grown dramatically and is increasingly offered by nongenetics specialists. Yet, all major guidelines recommend that patients with both negative and positive results be counseled regarding limitations of testing.

Researchers from Counsyl (South San Francisco, Calif.) evaluated their "next-generation" counseling model. It consists of: provider notification of results availability; patient notification, if negative, in which a patient receives automated email to access results through a secure portal where she may watch tailored informational videos, request on-demand genetic counseling, schedule a later consult, or decline all of the above; direct patient contact by the ordering provider or Counsyl genetic counselors if the results are positive.

Over a 29-month period, 27,827 NIPS results were issued through the Counsyl system. Of these, 1,975 patients elected genetic counseling, 96.6 percent of whom received negative results. Of those wanting genetic counseling, 65.2 percent of patients with negative results and 72.1 percent of patients with positive results selected on-demand consult. For positive results, average consultation time was 15 minutes and seven minutes for negative results.

The average patient satisfaction rating for consultations was 4.9 out of 5.0.

Patient Satisfaction

The Providence Health and Services hospital system conducted a seven-question survey to assess patient satisfaction with three models of genetic counseling: one-on-one telegenetic counseling, in person group counseling, and traditional one-on-one in person counseling.

The researchers found that 100 percent (202/202) of patients surveyed report being satisfied with their visit, regardless of type of genetic counseling (telegenetic [n = 89], group [n = 20], or traditional [n = 88] counseling). The groups did not significantly differ with regard to ease of use, recommending the service to a friend, comfort in communicating, or time spent in the visit. The only significant difference seen was related to visit experience versus expectations. Patients seen in the traditional setting more often stated that the visit was "better" than expected versus the alternative models (91 percent traditional, 50 percent group, and 18 percent telegenetic).

"Based on this preliminary data, it appears that both alternative models may be acceptable to patients as a substitute for traditional counseling," conclude the authors, led by Monica Helm.

Telegenetics from Counselor's Perspective

Researchers from Virginia Commonwealth University conducted semi-structured interviews with board certified genetic counselors, who had conducted both a telegenetics and an in-person new patient appointment within the last 5 years. The researchers identified 20 themes from participants' answers, the most frequent of which were recognition that telegenetics increases accessibility for patients and technological errors pose difficulty in telegenetics session. While the respondents said overall, telegenetics sessions were similar to in-person appointments and they do offer benefits for the patients, most counselors still prefer in-person counseling due to the perceived difficulty with psychosocial assessment.

FDA Considering Self-Collection Sample Regulation

The U.S. Food and Drug Administration (FDA) may be considering self-collection of samples for cervical cancer screening. The agency is seeking guidance on the evaluation of cervical sample self-collection devices for cervical cancer screening of patients, according to a Sept. 8 announcement in the *Federal Register*. But experts say that FDA's consideration of self-collection devices could have broader implications for over-the-counter testing than just for cervical cancer screening.

The announcement says the FDA will hold a public workshop entitled "Self-Collection Devices for Pap Test" on Jan. 11, 2018. Additionally, the agency is collecting comments comment until Feb. 14, 2018. The agency says the goal of the workshop is to gather feedback about the feasibility, benefits, risks, current attitude, and impact on current standard of care of potential self-collection of cervical cancer screening samples, as well as regulatory and validation considerations.

> *"The implications of the public workshop potentially go well beyond the field of cervical screening."*
>
> — Jeffry Gibbs, Hyman, Phelps & McNamara

Regular screening and early detection of human papillomavirus (HPV), especially high-risk strains HPV16 and 18, can prevent cervical cancer. Routine Pap testing has been heralded as a success in decreasing the incidence of cervical cancer. Yet, screening gaps exist. Known barriers to cervical cancer screening include embarrassment, limited access to testing due to geography (e.g., rural areas), and socioeconomic or insurance status.

While some surveys have shown women are interested in home-based testing, the FDA says unanswered questions remain including: how such devices should be dispensed to end users for self-collection, proper use of the device, the collection of adequate samples for testing, and the use of these test results in patient care.

The announcement is a significant development for the diagnostics industry, as adoption of self-collection tests could drive up the volume of HPV testing and Pap testing and it creates a new potential market opportunity for companies that can make the self-collection devices.

"The implications of the public workshop potentially go well beyond the field of cervical screening," writes Jeffry Gibbs, from Hyman, Phelps & McNamara, in a Sept. 21 *FDA Law Blog* post. "Many companies have wanted to pursue self-collection of diagnostic specimens by consumers for a variety of analytes and conditions. Obtaining FDA clearance for those products has not been easy. The upcoming workshop may shed some useful light on how companies can better position themselves to enter the market for self-collection devices for other diagnostic purposes."

Takeaway: The diagnostics industry should watch for suggestions coming out of the FDA workshop to understand the scientific and the regulatory considerations for potentially enabling self-collection of cervical cancer screening samples. Experts note that the comments could inform FDA action on self-collection strategies more broadly beyond just cervical cancer.

FDA Medical Device User Fees Rise as Part of Reauthorization

On Oct. 1, the new 2018 U.S. Food and Drug Administration (FDA) user fees go into effect. Diagnostics manufacturers will notice increased medical device user fees, including a doubling of 510(k) fees and the introduction of a new fee for de novo 510(k) applications. However, small diagnostics companies are eligible for some significant discounts.

The FDA Reauthorization Act of 2017 reauthorizes the user fees for five years—through fiscal year 2022. G2 assessed some of the significant features of the reauthorization including the fee increases and the FDA's new performance goals.

Rising User Fees

On Aug. 29, the FDA published the fee rates for fiscal year 2018 (effective Oct. 1, 2017). Increases were seen for all registration-related categories. The standard user fee for 510(k) applicants is $10,566; $310,764 for pre-

market approval (PMA) user fees; and $93,229 for the entirely new de novo classification request user fee.

For de novo classification requests, the reauthorization sets the new user fee at 30 percent of the PMA user fee set each year, which is significantly more than the a 510(k) premarket notification submission, which will be 3.4 percent of the PMA user fee (and was 2 percent of the PMA user fee in the 2012-2017 reauthorization). Some experts fear the de novo classification requests may slow efforts to bring innovations to market.

The reauthorization eliminates the FDA's ability to grant user fee waivers or fee reductions, even if it is in the interest of public health. The existing fee waiver for a small business (defined as gross sales of $30 million or less) submitting its first PMA remains. Small businesses (defined overall as having gross sales of less than $100 million) do see discounts for all registration-related categories, even if it is not their first submission. These discounts are substantial, but reduced from previous years.

Application Type	Standard Fee	Small Business Fee
510(k)	$10,566	$2,642
De Novo classification	$93,229	$23,307
PMA	$310,764	$77,691

There are, however, no waivers or reductions for small business establishment registration fee, which was announced to be $4,624.

Speedier Reviews

Along with the new user fee, FDA has committed to new performance goals for the review of de novo classification requests. Under the new performance goals, between 2018 and 2022 the FDA plans to increase the percent of decisions within 150 "FDA days" from 50 percent to 70 percent of requests. It has been reported that in practice, the FDA takes an average of 10 months to a year to issue a decision. The new de novo user fee should enable the FDA to commit additional resources to these reviews and significantly reduce the time to decision. However, the number of de novo classification requests is likely to increase over the next several years with the rise of new technologies potentially entering the marketplace.

Takeaway: The diagnostics industry will see increased medical device user fees starting Oct. 1 as part of the five-year reauthorization of the agency's fees.

Supreme Court May Take on Its First Health Care Data Breach Case

In a case to watch, CareFirst BlueCross BlueShield will ask the U.S. Supreme Court to consider its first health care data breach case. CareFirst is arguing that the case presents a "substantial question" about whether the prospect of future harm resulting from a data breach warrants legal action. CareFirst's attorneys argue that the court has yet to decide on the definition of an injury in relation to a data breach.

"The Supreme Court needs to address this area of the law to provide more guidance to federal district and appellate courts, especially given that federal courts have struggled to reach consensus as to when the prospect of future injury resulting from stolen information truly presents a 'substantial risk' of actual harm," the September CareFirst motion reads.

Data breaches are nothing new for the health care industry, which accounts for 30 percent of all U.S. data breaches.

The case stems from a 2015 cyberattack against CareFirst, which exposed protected health information, including names, email addresses, dates of birth, and subscriber ID numbers, for 1.1 million of members. The class action suit, Chantal Attias vs. Carefirst, Inc., was dismissed by a district court, but the U.S. District Court for the District of Columbia overturned the ruling and allowed the case to proceed, even though there was not a concrete injury to plaintiffs, according to *HIPAA Journal*.

Experts say that district and appellate courts have struggled to reach consensus about when the prospect of future injury resulting from a data breach constitutes a substantial risk of actual harm. Given the continuing quantity of annual data breaches, health-related entities experience annually, this is a case to watch.

Data breaches are nothing new for the health care industry, which accounts for 30 percent of all U.S. data breaches. Hospitals, insurers, and private provider offices have all been hit. Breach Barometer Report: Mid-Year Review, published by Protenus, tallied 233 breach incidents reported to the Department of Health and Human Services January to June 2017. This pace is expected to exceed the 2016 total of 450 breaches. In the first half of the year, 3.1 million patient records were affected in 2017.

The laboratory industry is not immune from data breaches. Back in December 2016, Quest Diagnostics announced client data had been compromised through an "unauthorized third party" accessing the MyQuest Internet application. Protected health information (including name, date of birth, lab results, and some telephone numbers) was compromised for approximately 34,000 individuals.

Takeaway: Laboratories, like the rest of the health care industry, are watching to see whether the Supreme Court will hear a case that could define an injury, as it relates to a data breach. In the meantime, health care entities are urged to protect protected health care information from cyberattack.

New Evidence Shows Genotype-Guided Warfarin Dosing Beneficial

Genotype-guided warfarin dosing reduced a combination of adverse events, compared to clinically guided dosing among older patients treated with warfarin before elective hip or knee arthroplasty, according to a study published Sept. 26 in the *Journal of the American Medical Association (JAMA)*. While single clinical outcomes, like major bleeding events, were

not statistically improved with genotype-guided dosing, the study provides evidence of the overall reduction in adverse events from a genotype-guided dosing regimen at initiation of warfarin that may inform future coverage decisions, the authors say.

"Compared with previous studies, this trial was larger, used genotype-guided dosing for a longer duration, and incorporated more genes into the dosing algorithm."

— Brian F. Gage, M.D.

Previous studies show that warfarin accounts for more medication-related emergency department visits among older patients than any other drug. While the product label for warfarin encourages genotype-guided dosing, evidence has been mixed as to whether or not genotype-guided dosing meaningfully improves the safety of warfarin initiation. In addition to concerns about clinical utility, adoption of clinical pharmacogenomic testing has been hampered by lack of payer coverage and logistical constraints in returning results fast enough to impact decision making in non-elective situations.

The present study, the Genetic Informatics Trial (GIFT) of Warfarin to Prevent Deep Vein Thrombosis, included 1,650 patients (mean age, 72.1 years; 63.6 percent women) initiating warfarin before elective hip or knee arthroplasty at six U.S. medical centers from April 2011 through October 2016. Patients were genotyped (for VKORC1-1639G>A, CYP2C9*2, CYP2C9*3, and CYP4F2 V433M polymorphisms) and randomized to genotype-guided (n = 831) or clinically guided (n = 819) dosing on days 1 through 11 of therapy and to a target international normalized ratio (INR) of either 1.8 or 2.5. Dosing was guided by a web application (WarfarinDosing.org) that incorporated clinical variables for all patients and variant information for patients randomized to genotype-guided dosing algorithms.

The researchers found that significantly fewer patients in the genotype-guided group had one of the adverse effects (a composite of major bleeding, INR of 4 or more, venous thromboembolism, or death), compared to the clinically guided warfarin dosing group (10.8 percent versus 14.7 percent). For major bleeding or non-major clinically relevant the groups were similar, but trended towards a benefit for genotype-guided dosing. The authors say the benefit of genotype-guided dosing was consistent across the subgroups, including those at high-risk, black race, or having the CYP2C9 genotype.

"Compared with previous studies, this trial was larger, used genotype-guided dosing for a longer duration, and incorporated more genes into the dosing algorithm," write the authors led by Brian F. Gage, M.D., from Washington University in St. Louis, Mo. Additionally, the authors say the large size enabled the effect of genotype-guided dosing to be quantified for clinical outcomes rather than for percentage of time in the therapeutic range alone.

Cost Effectiveness Still Debated

Yet, other factors, aside from clinical utility, will dictate the adoption of genotype-guided dosing, including reimbursement, practice recommendations, and logistics. The authors say that the Centers for Medicare & Medicaid Services used its Coverage with Evidence Development program to fund genotyping in this trial and the center will review the results to determine future coverage.

"There are remaining questions about the cost-effectiveness of this strategy," writes Jon Emery, M.B.B.Ch., from the Centre for Cancer Research in Australia, in an accompanying JAMA editorial. "Based on the GIFT trial composite primary outcome, 26 patients would need to be genotyped to prevent one 'event' (most commonly an INR ≥4). Although the cost of genotyping continues to decline, health insurers and publically funded health systems have not yet been convinced that genotype-guided warfarin prescribing is a cost-effective strategy worthy of investment."

Emery also highlights that the logistical constraints of implementing genotyping before prescribing warfarin were removed in the GIFT trial because of the "elective nature" of arthroplasty.

"A single pharmacogenomic test covering many common variants relevant to multiple different prescribing decisions over time is far more likely to be cost-effective; however, the evidence for this proposition is lacking," Emery explains. "Ideally an updated meta-analysis of trial data should be applied to cost-effectiveness modeling to inform new policy."

Takeaway: New evidence builds the case that genome-guided warfarin dosing improves safety following drug initiation for elective procedures. However, the cost-effectiveness of the strategy remains to be seen.