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FDA Workshops and Stakeholder Engagement Culminate in Draft Guidance on NGS-Based Testing

Promoting flexibility and efficiency, the U.S. Food and Drug Administration (FDA) issued two draft guidance documents in early July, addressing oversight of next generation sequencing (NGS)-based tests and the databases that support clinical claims for these tests.

Acknowledging input from genomics experts, providers, patients and other industry stakeholders via public workshops and other efforts, Jeffrey Shuren, M.D., J.D., director of the FDA's Center for Devices and Radiological Health said in a statement that the agency believes the guidance documents "will encourage innovation and advance the goal of precision medicine: to speed the right individualized treatments to patients sooner."

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Reimbursement for Molecular Testing Faces Cuts in CMS' Proposed Gapfill Prices

The Centers for Medicare & Medicaid Services (CMS) published interim gapfill prices last month for new CPT codes for molecular tests introduced earlier this year. Although the pricing was for a fairly narrow range of specialty molecular tests—just 16 CPT codes in all—they still caused some consternation among some of the esoteric molecular testing firms, several of which had codes designated specifically for their leading assays.

Most of the tests wound up having their preliminary prices cut, compared to their prior regionalized prices—in some cases as much as 85 percent. That's even if the regional prices had been in place for a significant period of time.

The prices would be placed on the 2017 Clinical Laboratory Fee Schedule if CMS grants final approval later this year, although labs and other parties will have a period to submit comments.

Not surprisingly, some laboratories and lobbying groups are up in arms. The Coalition for 21st Century Medicine, an organization that represents many molecular labs, suggested that the proposed prices were out of sync with the guidelines established by the Protecting Access to Medicare Act of 2014 (PAMA), whose rules were recently finalized by CMS.

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FDA Workshops and Stakeholder Engagement Culminates in Draft Guidance, *from page 1*

Public Input

The FDA explained that "current regulatory approaches are appropriate for conventional diagnostics that measure a limited number of substances associated with a disease or condition," but a more "flexible approach to oversight" is needed for sequencing technologies that "examine millions of DNA variants at a time."

> *"When the guidances are finalized, adherence to them will offer appropriate flexible and adaptive regulatory oversight of these tests, while allowing for variations in development and validation and accommodating the rapid evolution of NGS technologies."*
>
> — FDA

That need for flexibility was emphasized by participants in a February 2015 FDA workshop addressing potential NGS standards (See *National Intelligence Report*, March 9, 2015, p. 1). At that workshop when asked whether standards for NGS tests were feasible and, if so, who should develop them, who should implement them, and how could compliance be verified, panelists recommended the FDA involve multiple stakeholders in crafting any standards and advised that given the rapidly developing nature of the technology, the standards' flexibility was critical. Two more workshops held in November 2015 addressed NGS standards and use of databases to establish clinical relevance of genetic variants. The FDA at the time said it sought "sufficiently flexible assay performance standards that can accommodate innovation, including test modifications, while assuring NGS test safety and effectiveness."

The draft guidance documents just released are intended to provide that flexibility. The FDA explained in its announcement of the documents' release: "When the guidances are finalized, adherence to them will offer appropriate flexible and adaptive regulatory oversight of these tests, while allowing for variations in development and validation and accommodating the rapid evolution of NGS technologies."

NGS Test Guidance

"Use of Standards in FDA Regulatory Oversight of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Used for Diagnosing Germline Diseases"—provides the FDA's proposed recommendations for "designing, developing, and validating NGS-based tests for germline diseases, and also discusses possible use of FDA-recognized standards for regulatory oversight of these tests." The guidance informs test developers how they can get their NGS tests for germline diseases classified as class II devices and potentially exempt from premarket notification. NGS tests have not been classified by the FDA so they would normally fall into Class III device category under existing law. That means the developer would need to submit an application for premarket approval rather than premarket notification under Section 510k, because there are no similar predicate devices already approved by the FDA.

The guidance is limited to targeted and whole exome sequencing NGS-based tests that diagnose germline diseases or other conditions. It doesn't apply to NGS tests for "stand-alone diagnostic purposes" or for "screening, microbial genome testing, risk prediction, cell-free DNA testing, fetal testing, pre-implantation embryo testing, tumor genome sequencing, RNA sequencing, or use as companion diagnostics," which could have different analytical characteristics not addressed by the guidance. The guidance sets forth test design considerations, test performance characteristics, test run quality metrics and general recommendations for performance evaluation studies.

Genetic Variant Databases Guidance

"Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing(NGS)-Based In Vitro Diagnostics—details the FDA's thinking on "how publicly accessible databases of human genetic variants can serve as sources of valid scientific evidence to support the clinical validity of genotype-phenotype relationships in FDA's regulatory review of NGS-based tests."

The guidance also indicates how publicly accessible databases can apply for FDA recognition and how the FDA will evaluate such databases.

One of the FDA's objectives for this guidance is to promote use of publicly accessible databases of genetic variant data to help determine clinical validity of NGS-based tests and thus advance precision medicine. So the guidance sets standards for determining "whether a genetic variant database is a source of valid scientific evidence" that could support the clinical validity of an NGS-based test in a premarket submission. The FDA addresses the quality of the data contributed as well as the privacy and security of information in the databases and transparency as to the sources of data in the databases. As to data quality, the guidance recommends genetic variant databases use consistent nomenclature "that is widely accepted by the genomics community for gene names and/or symbols, genomic coordinates, variants, described clinical and functional characteristics and classifications." The FDA also recommends that metadata accompany the variant data in the databases, demonstrating the number of independent laboratories and names of laboratories reporting variant classifications and the name of the test used to detect the variant, and when possible, technical characteristics of such tests.

The guidance also indicates how publicly accessible databases can apply for FDA recognition and how the FDA will evaluate such databases. The recognition process would be voluntary and similar to the standards recognition process under Section 514 of the Food, Drug and Cosmetic Act for standards assuring safety and effectiveness of medical devices. But, the FDA explains in a footnote, it won't be conducted under Section 514. Databases that receive recognition will be reviewed regularly to ensure they continue to meet the requirements of the guidance.

Next Steps

The two draft guidance documents have a 90-day comment period and were published in the July 8 Federal Register. Public comments can be submitted at any time for FDA guidance documents but to have comments considered before these draft guidance documents are finalized, comments must be submitted by Oct. 6, 2016 for each guidance.

The FDA is also hosting two webinars focusing on the guidance documents on July 27. The first webinar, from 12 noon to 1 p.m. EST, focuses on the technical and regulatory aspects of the guidance documents. The second webinar, 1:30 to 2:30 p.m. EST, will discuss the significance of the guidance documents for patients and health care providers. See www.fda.gov/CDRHwebinar for more information about the webinars. Transcripts of the webinars and the slide presentations will be available for review after the webinars for those who don't attend.

Takeaway: Workshops and stakeholder input yield results with draft FDA guidance on how to get FDA approval for NGS tests and the databases that support their clinical validity. G2

Democratic Committee Leaders and CMS Present Latest Challenges to Theranos

Both the Centers for Medicare & Medicaid Services (CMS) and some high ranking Democratic Committee members had some bad news for Theranos at the start of this month. The company itself issued a statement announcing "CMS has decided to impose all available sanctions regarding our lab business." Three members of the House Energy and Commerce Committee sent the company a letter expressing concern about the compliance issues and asking for a briefing on Theranos' plans to address the issues.

Theranos' had claimed that the tens of thousands of test results voided earlier this year represented "less than one percent of all blood test results."

Briefing Request from E&C Committee Leaders

Even before CMS announced that the company's latest corrective actions were insufficient, three Democratic Committee leaders sent Theranos a letter seeking more information about "how company policies permitted systematic violations of federal law and how Theranos is working with regulators to address these failures," as well as information about the "steps Theranos is taking to correct flawed test results sent to medical professionals and patients." The letter came from Energy and Commerce Committee Ranking Member Frank Pallone, Jr. (D-NJ), Health Subcommittee Ranking Member Gene Green (D-TX) and Oversight and Investigations Subcommittee Ranking Member Diana DeGette (D-CO).

Dated June 30, the letter referred to the CMS Nov. 15 inspection of Theranos' Newark, Calif., Laboratory and the subsequent letters from CMS on Jan. 25, 2016 and March 18, 2016 detailing failures to comply with Clinical Laboratory Improvement Amendments (CLIA) requirements. The January letter had documented results of the inspection and listed the condition-level and standard-level CLIA violations and the March 18 letter notified Theranos that CMS was considering imposing sanctions. The Committee members also expressed concern about news media reports, in the *Wall Street Journal* in particular, that raised questions about test results involving Warfarin. Additionally, they cited an independent assessment by the Icahn School of Medicine at Mount Sinai which questioned accuracy of Theranos testing, noting that study's inclusion of an example regarding cholesterol testing.

Finally, the letter cites inconsistencies in the company's own claims regarding its testing. Theranos' had claimed that the tens of thousands of test results voided earlier this year represented "less than one percent of all blood test results." The letter questions whether that claim is consistent with statements about volume of patients tested using proprietary technology and whether the company has really identified all potentially affected patients. The leaders requested a briefing addressing the company's efforts to comply with not only the CMS inspection letters but also the FDA 483 inspection reports issued in August and September 2015. Specifically, the letter requests the briefing address changes to policies and procedures the company has made, efforts to investigate the "root cause" of compliance issues, how it identified affected patients, and how the company is helping affected providers and patients.

CMS Gives Notice of Impending CLIA Sanctions

CMS issued a letter to Theranos July 7 explaining why multiple submissions made by Theranos in response to CMS' January and March letters still do "not constitute

a credible allegation of compliance and acceptable evidence of correction" of the deficiencies found in the 2015 inspection.

For example, echoing the concerns of the Committee leaders detailed above, CMS found fault with the evidence provided regarding corrective actions taken for patients whose test results were "found to have been affected by the deficient practice." Flash drives purported to demonstrate corrective action were difficult to search said CMS and it wasn't clear that every identified specimen was addressed in the flash drives. As to quality assessments, CMS said the lab failed to demonstrate what changes were made to ensure there would be no recurrence of the deficiencies. In discussion of proficiency testing, CMS again indicates a concern expressed by the committee leaders about the impact on patients. CMS questioned how the lab arrived at its conclusion that no patients have suffered harm.

"We accept full responsibility for the issues at our laboratory in Newark, California, and have already worked to undertake comprehensive remedial actions."

— Elizabeth Holmes, CEO, Theranos

Therefore, CMS is proposing revocation of the lab's CLIA certificate, effective Sept. 5, 2016. Loss of CLIA certification brings with it a prohibition against Holmes owning, operating or directing a lab for two years. Other sanctions include:

- Effective July 15, 2016, limitation of the lab's CLIA certificate for hematology services (this takes effect even if appeal is filed)
- Effective July 12, 2016, an alternative sanction of $10,000 daily penalty until deficiencies resolved (if appeal is filed, the penalty won't be collected until after the appeal is decided)
- By July 12, 2016, Theranos was required to provide a list of names and addresses of all physicians and clients who used the lab's services since January 2014 (due date applied regardless of any appeal)
- Suspension of Medicare/Medicaid payment eligibility for hematology services effective July 15, 2016
- Cancellation of approval for Medicare/Medicaid pament for all laboratory services effective Sept. 5, 2016 (this takes effect regardless of any appeal filed)

Theranos Response

"We accept full responsibility for the issues at our laboratory in Newark, California, and have already worked to undertake comprehensive remedial actions," Theranos CEO Elizabeth Holmes said in a statement released July 7. "While we are disappointed by CMS' decision, we take these matters very seriously and are committed to fully resolving all outstanding issues with CMS and to demonstrating our dedication to the highest standards of quality and compliance."

Theranos got out in front of the news, not only announcing CMS' threatened sanctions in its own statement, but also attaching a copy of the entire CMS July 7 letter, and providing a Q/A addressing several questions concerning the sanctions and their impact on operations. The company said July 8 it is "considering all its options." The company's statement didn't indicate whether it would be filing an appeal but vowed to continue on with its mission, promising to work with CMS "non-stop to resolve the issues identified." It addressed the issue of patient safety, stating "Patient safety and quality are our top priorities. As of now, we have not been made aware—by CMS, physicians or patients—of any harm to patient health resulting from our tests."

Theranos' statement also highlighted that the company does more than just lab testing, including research and development of "many technologies that are not dependent on running a clinical laboratory." Promising to continuing building on its mission of accessible and affordable testing, the company explained: "Improving access through innovative technologies is a universal need, with growth opportunities in global and domestic vertical markets."

Takeaway: Theranos continues to face questions about its technology and compliance with CLIA and FDA requirements as threat of sanctions looms closer.

Lab Implicated in Long-Running Kickback Case Pleads Guilty, Forfeits Assets

Amidst the guilty pleas and sentencing of dozens of individuals, the laboratory company Biodiagnostic Laboratory Services LLC (BLS) entered a guilty plea the end of June in New Jersey federal court. The company was the subject of a long-running government investigation and enforcement effort surrounding allegations of kickbacks in exchange for lab test referrals.

The company pleaded guilty to one count of conspiracy to violate the Anti-Kickback Statute and the Federal Travel Act and one count of conspiracy to commit money laundering, the Department of Justice (DOJ) announced. U.S. District Judge Stanley R. Chesler then sentenced the company, requiring forfeiture of all its assets (operations have already ceased).

So far, the case has led to 41 guilty pleas including 27 from physicians. The latest guilty plea came from a New Jersey physician just days after the lab entered its plea. That physician admitted to receiving "consulting fees" in exchange for referrals of patient blood specimens to the lab for testing. The DOJ has said the case is "believed to be the largest number of medical professionals ever prosecuted in a bribery case" and it has "recovered more than $12 million through forfeiture." The government had alleged millions of dollars in bribes were paid to providers to influence test referrals to the laboratory which yielded more than $100 million for the lab in Medicare and private payor payments. One of the most recent physician sentences involved a 37-month jail sentence to a physician who had pleaded guilty to accepting bribes in violation of the Anti-Kickback Statute. Those bribes were said to include cash payments as well as meals and entertainment such as tickets to professional sporting events, Katy Perry and Justin Bieber concerts, and a Broadway show.

Takeaway: The lab at the center of purportedly the largest physician bribery case is finally sentenced.

FCA Penalties Nearly Double Under DOJ's Interim Final Rule

On June 30 the Department of Justice (DOJ) published an Interim Final Rule in the Federal Register that has significant ramifications for enforcement under the False Claims Act (FCA). Pursuant to the Bipartisan Budget Act of 2015 the DOJ adjusted for inflation the amount of civil monetary penalties that can be imposed for violations of laws enforced by the DOJ.

The new penalties for violations of the FCA were nearly doubled by this adjustment. The current penalty range for FCA violations is a minimum of $5,500 and maximum of $11,000. Under the adjustments, those rates will increase to $10,781 and $21,563, respectively.

The FCA provides that those who violate the Act can be liable for a penalty between $5,000 and $10,000 as adjusted by the Federal Civil penalties Inflation Adjustment Act plus three times the amount of damages the Government suffers due to the violation. The court does have the ability to reduce damages to "not less than 2 times the amount of damages" the Government suffers.

The interim final rule is effective Aug. 1, 2016, but written comments can be submitted until Aug. 29, 2016. The new penalty amounts can be imposed only for penalties assessed after the Aug. 1 effective date for violations that occurred after Nov. 2, 2015. Penalties for violations occurring on or before Nov. 2, 2015 are subject to the prior rates.

Takeaway: The cost of noncompliance just increased for labs and all health care providers.

Editor's Note: To learn about how your laboratory can avoid false claims liability, see G2 Intelligence's report, Lab Compliance Essentials 2017: Managing Medicare Fraud & Abuse Liability Risk, released July 2016. This report provides a practical, plain-language guide to protecting labs against false claims, Anti-Kickback and Stark Law violations and discusses the latest enforcement cases involving and affecting lab compliance.

Reimbursement for Molecular Testing Faces Cuts, *Continued from bottom of p.1*

"The proposed gapfill rates are inconsistent with rates established by commercial payers and the PAMA statute," the Coalition said in a statement. "Additionally, the PAMA statute sets a maximum of 10% reduction in payment for any test code in [2018] using the new market-based rate methodology."

For example, reimbursement for CareDx's AlloMap assay was proposed to be reduced 74 percent, to $732 from $2,821. That test helps predict the risk of acute cellular rejection in potential heart transplant patients. Another proposed cut would impact Genomic Health's Oncotype DX test for colon cancer. Such a test gives greater treatment options to patients who have been diagnosed with intermediate stage forms of the disease, along with evaluating their risk of recurrence. CMS proposed a price of $848.86. That's 73 percent lower than the price Genomic Health is receiving from local coverage determinations made by individual MACs.

In a statement issued to G2 Intelligence's *Laboratory Industry Report*, Genomic Health said that it believed the proposed rate "is based upon a flawed methodology that includes misinformed rates by local Medicare administrative contractors who do not process Genomic Health's claims."

"In addition, the methodology does not take into account the factors set forth in Medicare law to establish payment amounts, such as market rates and resources. These factors were considered when the local MAC originally established the payment rate for the Oncotype DX colon cancer test in 2011, which has been revalidated on multiple occasions by numerous MACs paying Oncotype DX claims over the past five years."

CareDx noted that MACs Palmetto GBA and Noridian had supported its original higher price but that input from other MACs led to the cut.

Another big hit came to Veracyte for its Afirma gene expression classifier test for thyroid cancer. The test can help patients and physicians decide whether a cancerous node requires total thyroid removal. Although the Afirma test received the highest-price among the assays on the list at $2,240.16, that remains far below the price Medicare has been paying based on local determinations: $3,200. The proposed pricing represents a cut of roughly 30 percent.

One test that went all but untouched: Myriad Genetics' Vectra DA assay to help predict the progression of rheumatoid arthritis and the threat of joint damage. Its pricing remained essentially the same at $587.

In a recent report, William Blair & Co. analyst Amanda Murphy noted that PAMA would likely provide some needed clarity to the issue. "While PAMA has caused angst around potential cuts to CPT codes, the perhaps under-appreciated positive from the legislation is that it will transition pricing power away from CMS and the MACs and provide much needed visibility into pricing," she observed.

Meanwhile, Genomic Health, CareDx and Veracyte said they would push to have CMS reconsider the proposed rates.

Takeaway: Many esoteric laboratories are unhappy with the current proposed 2017 gapfill pricing proposed by the Centers for Medicare & Medicaid Services, and plan to persuade the agency to change its position.

AMP Seeks to Impact Genomic Sequencing Reimbursement with Cost Study

At a time when payments for molecular testing are under increasing debate, the Association for Molecular Pathology (AMP) has commissioned a unique study breaking down the costs for genomic sequencing. The study focuses on the labor and consumable costs for four specific tests: A tumor panel of up to 50 genes (CPT code 81445); a panel of more than 50 genes (CPT code 81455); an XLID panel (CPT code 81470); and a hearing loss panel (CPT code 81430).

"It is very important that molecular laboratories continue to publish data on the health economic value, as well as the effectiveness and utility of molecular procedures to demonstrate value to payers."

— Samuel K. Caughron, M.D.

The AMP broke down the costs in five separate categories, including the cost of preanalytic consumables (to conduct DNA extraction and sequencing); preanalytic equipment use; labor costs; reporting costs; and costs of maintenance and overhead. Data from the Centers for Medicare & Medicaid Services (CMS) was used in most instances to calculate the costs. The overall costs of the tests ranged from $578 for the 5-50 gene panel (five different protocols were examined for the study); to $1,949 for the hearing loss panel (three different protocols were used for that test, among them including it in a consolidated genetic panel, where the cost was just $1,048). The purpose of the study, officials say, is to ensure that CMS and other payers bear in mind what it actually costs for labs to perform such tests and that they are reimbursed accordingly.

"It is very important that molecular laboratories continue to publish data on the health economic value, as well as the effectiveness and utility of molecular procedures to demonstrate value to payers," said Samuel K. Caughron, M.D., Laboratory Medical Director for Shawnee Mission Medical Center in Mission, Kansas and chair of the AMP's economic affairs committee.

Caughron observed that last year's gapfill process "resulted in many of the MACs not recommending prices for genomic sequencing panel, and the ones that were priced were either at or lower than the microcost analysis developed by AMP." He noted that the final payment determined for CPT code 81445 was $597.31, even as AMP's study found costs ranging from $577.99 to $907.82 for this procedure. According to Caughron, publishing such costs could encourage greater transparency among the Medicare Administrative Contractors (MACs), which set reimbursement for various parts of the country.

"AMP believes the gapfill process as originally intended to work could be an effective process to price new molecular tests," he said. "However, AMP strongly favors greater transparency and definition to the process, with accountability for all MACs to appropriately engage in the process."

Takeaway: The Association for Molecular Pathology is trying to preserve reimbursement for its members for often pricey and difficult to perform genomic tests.

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