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INSIDE THIS ISSUE

FDA Discussion Paper Synthesizes Stakeholder Feedback on LDT Regulation

Last December, the U.S. Food and Drug Administration announced that it would not finalize the guidance on agency oversight of laboratory developed tests (LDTs) that it proposed back in 2014—at least not yet. Instead, the FDA said it would work with the new administration and Congress "to get our approach right."

With that in mind, on Jan. 13, 2017, the agency issued a discussion paper summarizing the public feedback it has received on the 2014 draft guidance and outlining the key features of a possible alternative approach to FDA regulation of LDTs. Here is an overview of the key points from the new discussion paper.

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VA Final Rule Steps Back from Allowing APRNs to Perform Lab Tests

The laboratory sector has successfully fought a Department of Veterans Affairs (VA) rule that would have allowed advanced practice registered nurses (APRNs) to "perform and supervise" lab testing. Numerous organizations, including The American Society for Clinical Laboratory Science (ASCLS), American Association for Clinical Chemistry (AACC) and American Society for Clinical Pathology (ASCP) raised concerns about the rule's provision on lab testing. One objection is that the Clinical Laboratory Improvement Amendments (CLIA) regulations address titles and qualifications regarding who can perform lab tests and what tests they can perform.

Details of Proposal

A May 2016 proposed rule would have granted APRNs' full practice authority in four roles while serving as employees in the VA health system, which provides medical and hospital services to veterans. That would mean the APRNs could practice "to the full extent of their education, training and certification, without the clinical supervision or mandatory collaboration of physicians." Ultimately, the VA granted

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Analysis of the Feedback

As part of the feedback process, the FDA asked stakeholders to suggest how they think the agency should regulate LDTs. According to the discussion paper, the various proposals shared some similar features, including:

- Risk-based approach;
- Premarket review for some tests, with exemptions for certain categories;
- Test approval based on analytical and clinical validity;
- Adverse event reporting;
- Quality systems;
- "Grandfathering" for certain existing tests; and
- Transparency regarding test performance information.

"Based on the feedback received, a *prospective* oversight framework that focuses on new and significantly modified high and moderate risk LDTs would best serve the public health and advance laboratory medicine," the new discussion paper concludes.

The FDA Alternative Model

The FDA also sets out how its own thinking on LDT regulation has developed since 2014. Over the two years of "engagement," "positions of many groups, including the FDA, have evolved." The paper then sets out key features that may be incorporated in an alternative to the framework it proposed back in 2014, including:

- Phased-in oversight program over four years rather than the originally proposed nine years;
- Grandfathering for many LDTs already on the market;
- Broader definition of LDTs for unmet needs;
- Collaboration between FDA and third parties to use existing review standards and certification programs—such as the National Glycohemoglobin Standardization Program or the Cholesterol Reference Method Laboratory Network—for evidence standards;
- Potential use of existing review programs for third-party review, such as New York State's Clinical Laboratory Evaluation Program and independent CLIA accreditation programs;
- Clinical collaboration with stakeholders and health care professional organizations on standards for analytical and clinical validity;
- Public availability of evidence regarding analytical and clinical validity;
- Reliance on CLIA certification requirements plus three FDA quality systems requirements regarding test development processes—design controls, acceptance activities, and procedures for corrective and preventive action (CAPA); and
- Postmarket surveillance requiring labs report serious adverse events for tests except for traditional LDTs, LDTs for public health surveillance, specific transplantation related LDTs, and forensic-use LDTs.

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What It Means

The FDA expressly states that its discussion paper and the proposal it outlines is not a final version of the 2014 guidance and "does not represent the formal position of the FDA, nor is it enforceable. We hope to simply advance the public discussion by providing a possible approach to spur further dialogue."

Takeaway: LDTs remain very much a work in progress, one that has evolved since 2014, and you need to stay tuned for further developments.

ACA Still Intact for Now, But for How Long?

Now that President Donald Trump has taken office legislative efforts to "repeal and replace" the Affordable Care Act (ACA) have begun in earnest. Both the House of Representatives and the Senate voted—though not without controversy and much debate—to approve a budget resolution that is a first step towards repealing the ACA through a budget reconciliation measure. As we indicated in our November issue of *National Intelligence Report*, legislation to repeal the ACA would need 60 votes in the Senate to pass, unless it was part of budget reconciliation legislation, which only requires approval by a simple majority.

A House Energy and Commerce Commission statement at the end of January announced that its subcommittee on health would be holding a hearing in early February regarding "four practical bills to give patients cost relief from Obamacare, tighten enrollment gaps, and protect taxpayers."

That resolution called for a plan to be proposed by Jan. 27 regarding repeal and replacement for Obamacare but that deadline passed as we went to press without any proposals formally put forward. President Trump has indicated several times his goal is for repeal and replacement to happen at the same time.

Before his term ended, President Barack Obama wrote an article published in the *New England Journal of Medicine,* which described any plan to repeal ACA without a replacement at the same time as "reckless." He did concede that there was further work to do even if ACA remained in place but cautioned that "health care reform requires an evidence-based, careful approach, driven by what is best for the American people." He defended the individual responsibility requirement of the ACA, saying that the pre-existing condition protection depends on it and together with financial assistance such responsibility "is the only proven way to provide affordable, private, individual insurance to every American."

Rep. Greg Walden, chair of the House Energy and Commerce Committee stated in an interview with CNN in late January that Republicans are committed to protecting coverage for pre-existing conditions and for allowing offspring to remain on parents' insurance through age 26. A House Energy and Commerce Commission statement at the end of January announced that its subcommittee on health would be holding a hearing in early February regarding "four practical bills to give patients cost relief from Obamacare, tighten enrollment gaps, and protect taxpayers."

Takeaway: Repeal and replacement of the ACA remain on the front burner for legislators but the proposals for achieving that objective have yet to be finalized.

VA Final Rule Steps Back from Allowing APRNs to Perform Lab Tests, *from page 1*

full practice authority in three roles: Certified Nurse Practitioner, Certified Nurse Specialist, and Certified Nurse Midwife. APRNs were not granted full practice authority in the role of Certified Registered Nurse Anesthetists at this time.

The language raising the laboratory sector's ire stated that a Certified Nurse Practitioner "may order, perform, or supervise laboratory studies." The VA acknowledged in the Dec. 14, 2016 final rule that commenters objected that such language fails to "'adequately appreciate the levels of complexity involved in laboratory testing,' and that there are rigid standards for laboratory tests that require rigorous academic and practical training, which are not part of the training for APRNs." Other comments suggested the rule needed to more carefully distinguish the duties of an APRN and a laboratory specialist.

"We have successfully convinced the VA to adjust the language to better protect patients while expanding access to care for our nation's veterans."

— ASCLS

Terms of Final Rule

The VA agreed, responding in the final rule—which was effective Jan. 13, 2017—"We agree with the commenter in that the proposed language might be construed as allowing CNPs the ability to perform laboratory studies. It is not VA's intent to have APRNs take over the role of laboratory specialists. These specialists perform a crucial role at VA medical facilities and are skillfully trained in performing the various testing techniques that allow health care professionals to properly treat a veteran's medical conditions." So the VA changed the proposed language to instead clarify that a CNP could order lab testing (or imaging) and "integrate the results into clinical decision making."

"We have successfully convinced the VA to adjust the language to better protect patients while expanding access to care for our nation's veterans," the ASCLS said in a statement. The ASCP similarly praised the change in the language and took the opportunity to highlight a similar issue relating to the Centers for Medicare and Medicaid Services' April internal memo that requires a bachelor's degree in nursing for performing high complexity testing and an associate's degree for moderate complexity testing. The ASCP had earlier objected to that memo arguing it "significantly lowers the qualifications necessary to perform high and moderate complexity testing and could have significant repercussions for test quality and patient safety." In praising the changes in the VA final rule, ASCP noted "Given the VA's position on laboratory testing by APRNs, ASCP plans to discuss with the Centers for Medicare & Medicaid [Services] its interpretation that a bachelor's degree in nursing is equivalent to a degree in biology."

Takeaway: Laboratory industry successfully argues for changes in proposed rule that would make APRNs eligible to order perform lab testing in VA facilities. Yet, concerns remain about a CMS memo that addresses the degrees needed to conduct moderate and high complexity testing.

FOCUS ON:

LCDs Demonstrate Evolving Coverage of Molecular Diagnostics

Advanced diagnostic tests are emerging faster than the clinicians can document their clinical utility. All of this creates an interesting dilemma for payors as far as coverage is concerned. Normally the most cautious of payors, Medicare has demonstrated an increasing willingness to cover newfangled tests—at least in certain circumstances—with the expectation that they do work and that the studies will eventually catch up.

The recent local coverage determinations (LCDs) issued by Palmetto, GBA, one of Medicare's most important contractors, is an excellent illustration of where things seem to be evolving with regard to Medicare coverage of new molecular diagnostic tests.

Palmetto says there is conflicting evidence on Vectra DA's effectiveness, citing, among other things, a recent study suggesting that test scores yielded are unreliable and should not be used to guide treatment.

What's At Stake

First, a quick refresher on LCDs. Medicare covers only services that are "reasonable and necessary." Each Medicare contractor has discretion to decide which services meet those criteria. LCDs set out the particular contractor's coverage rules. So-called draft LCDs typically contain proposed revisions and updates to coverage rules and are open to comment for at least 45 days. Once the comment period ends, the contractor issues a final LCD.

The lab test LCDs discussed in this article are draft LCDs that Palmetto issued on Dec. 23. The comment period runs between Feb. 6 and March 23.

Let's go through the 8 key coverage changes.

1. Eliminate Coverage of Vectra DA for Rheumatoid Arthritis (DL37024)

Test: Vectra DA generates a test score based on 12 biomarkers associated with rheumatoid arthritis inflammation that is used to track disease activity and a patient's response to treatment.

Proposed Change: The draft LCD proposes to end Medicare coverage of Vectra DA.

Explanation: Palmetto says there is conflicting evidence on Vectra DA's effectiveness, citing, among other things, a recent study suggesting that test scores yielded are unreliable and should not be used to guide treatment. Palmetto also notes that 2015 American College of Rheumatology treatment guidelines recommend "functional status assessment using a standardized, validated measure" and do not even mention biomarker testing.

Financial Impact: Vectra DA is manufactured by Myriad Genetics' subsidiary Crescendo Biosciences. Myriad "strongly disagrees" with the proposal and claims the cited study is flawed. There is a lot on the line. Ending Medi-

FOCUS ON:

care coverage of Vectra DA could cut Myriad's revenues by $35 million to $40 million, according to one report by a Piper Jaffray analyst cited in GenomeWeb.

> Palmetto ... says that prospective studies supporting the [Prolaris's] effectiveness for identifying low-risk patients who can then avoid unnecessary invasive procedures is enough to justify coverage.

2. Coverage of Prolaris for Intermediate-Risk Prostate Cancer Patients (DL37043)

Test: Prolaris measures the aggressiveness of prostate cancer by analyzing 31 cell cycle progression genes.

Proposed Change: The LCD proposes to cover the test for men who have favorable intermediate risk of prostate cancer under National Comprehensive Cancer Network (NCCN) guidelines.

Explanation: Palmetto acknowledges the current lack of evidence supporting Prolaris's clinical utility among men at intermediate risk of prostate cancer but says that prospective studies supporting the test's effectiveness for identifying low-risk patients who can then avoid unnecessary invasive procedures is enough to justify coverage. Last year, Palmetto and another Medicare contractor Noridian issued a final LCD covering Prolaris for patients meeting NCCN criteria for low- and very-low-risk prostate cancer.

Financial Impact: Like Vectra DA, Prolaris is manufactured by Myriad Genetics. If approved, the draft LCD proposal would expand coverage for about 15 percent of men or roughly 30,000 per year, according to an official company statement. Prolaris coverage in intermediate-risk patients is a $65 million market, according to the aforementioned Piper Jaffray analyst.

3. Limited Coverage of Xpresys for Lung Cancer Screening (DL37031)

Test: Xpresys is a molecular blood test in which expression levels of two proteins are assessed against five clinical risk factors to identify which lung nodules are likely benign and which patients are eligible for surveillance via noninvasive CT scans rather than invasive surgical procedures.

Proposed Change: Palmetto would cover Xpresys Lung version 2 (XL2) but only in limited circumstances. Under the LCD, XL2 would be covered only:

- To assess lung nodules of between 8 and 30 mm in diameter;
- For patients over age 40 who have a pre-test cancer risk of 50 percent or less.

Explanation: In February 2015, CMS announced that Medicare would cover lung cancer screening. But while it can save lives and minimize the need for costly treatment, low-dose computed tomography screens also detect intermediate lesions that cannot be defined as benign or malignant without costly and sometimes dangerous additional testing.

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Financial Impact: So the capacity to detect benign tumors noninvasively makes biomarker tests like Xpresys, which is manufactured by Seattle-based Integrated Diagnostics and has been on the market only since 2014, potentially valuable. By the same token, only a few of these tests are commercially available; and they have yet to be adopted for routine clinical use. Accordingly, Medicare has been wary about covering them, as reflected in the LCD.

DecisionDx-UM was developed by an ocular oncologist and exclusively licensed to Castle Biosciences in 2009. The test is "now used as a standard of care by over 95 percent of ocular oncologists in the U.S.," according to the company website.

4. Limited Coverage of DecisionDx-UM for Metastatic Cancer Risk (DL37033)

Test: DecisionDx-UM is a gene expression profile test assessing the expression levels of 15 messenger RNA transcripts to evaluate whether patients newly diagnosed with uveal melanoma (UM) are at risk for metastatic disease.

Proposed Change: Palmetto proposes limited coverage of DecisionDx-UM for patients diagnosed with UM when there is no evidence of distant metastatic disease at the time of diagnosis for purposes of determining whether the patient should be referred to a specialist for further surveillance. Physicians should not order the test unless they intend to act upon the results.

Explanation: Although there is enough clinical evidence to support clinical utility for now, the LCD stipulates that continued coverage will depend on publication and/or presentation of clinical utility evidence. This is in line with LCDs of other contractors, such as Noridian which began covering DecisionDx-UM last year.

Financial Impact: DecisionDx-UM was developed by an ocular oncologist and exclusively licensed to Castle Biosciences in 2009. The test is "now used as a standard of care by over 95 percent of ocular oncologists in the U.S.," according to the company website.

5. Coverage of Comprehensive Genomic Profiling (CGP) for Specific Cancers

Test: CGP cancer analysis is a single test that uses tissue from a tumor to detect genomic alterations and information that can guide diagnosis and individualized treatment.

Proposed Change: Palmetto issued LCDs covering CGP for patients with three different types of cancers: i. metastatic melanoma (DL37041); ii. metastatic colorectal cancer (DL37039); and iii. advanced primary peritoneal, fallopian tube and ovarian cancer (DL37045). All three of the LCDs include the same basic coverage conditions, including the requirement that:

- The patient be newly diagnosed with the cancer involved;

FOCUS ON:

The new CGP LCDs are significant for what they do *not* include, namely, the requirement that labs submit testing and patient data through registries, a burdensome obligation that has appeared in previous Palmetto CGP coverage policies.

- The patient has not received CGP or, in the case of metastatic melanoma, CGP or polymerase chain reaction (PCR) testing for genomic alterations;
- The test is capable of detecting all four types of DNA alterations associated with cancer; and
- The test meets Palmetto's Analytical Performance Specifications for CGP (APS).

Explanation: The new CGP LCDs are significant for what they do *not* include, namely, the requirement that labs submit testing and patient data through registries, a burdensome obligation that has appeared in previous Palmetto CGP coverage policies.

Financial Impact: As in the brand-specific LCDs, Palmetto acknowledges the current lack of evidence supporting the clinical utility of CGP for metastatic melanoma but states its belief that the test works and will be validated by forthcoming studies.

Takeaway: Palmetto is only one Medicare contractor. But far from being a blip on the radar screen, the new Palmetto LCDs are a reflection of how CMS and its other contractors are coming around on newly developed molecular diagnostic testing—despite the current lack of evidence supporting their clinical effectiveness. In other words, the Medicare payor community is moving ahead with coverage in the expectation that the justifying scientific studies will eventually catch up and not the other way around.

Coalition Promotes cfDNA-based Noninvasive Prenatal Testing

Five major players in genetic testing have joined forces to promote cell-free DNA (cfDNA)-based noninvasive prenatal testing (NIPT). A newly formed organization, Coalition for Access to Prenatal Screening (CAPS) will promote prenatal screening using cfDNA-based NIPT. The five founding companies are: Illumina, Inc.; Counsyl, Inc.; Progenity, Inc.; Natera, Inc.; and Integrated Genetics, a specialty laboratory of Laboratory Corporation of America Holdings.

"NIPT represents a major advance in the screening for fetal chromosomal aneuploidies through the analysis of millions of cfDNA fragments in the blood of a pregnant woman," according to a statement announcing the coalition's formation. CAPS' website indicates the coalition "seeks to improve access to state-of-the-art prenatal screening using cell-free DNA (cfDNA)-based noninvasive prenatal testing (NIPT) that is easily accessible to all pregnant

"As leading providers of cfDNA-based NIPT, CAPS members are working together towards the common goal of ensuring that this innovative and highly accurate screening method is easily accessible to all pregnant women who choose to pursue aneuploidy screening, regardless of their risk factors, income, age or geographic location."

— Arnold W. Cohen, M.D.

women who choose to pursue aneuploidy screening, regardless of their risk factors, income, age or geographic location."

cfDNA-based NIPT provides a less invasive method for screening pregnant women for Trisomy 21/Down syndrome and other chromosomal aneuploidies. Diagnostic testing such as chorionic villus sampling or amniocentesis must still be used to confirm positive screening tests but cfDNA-based NIPT identifies "a higher proportion of pregnancies affected by chromosomal aneuploidies" than serum-based screening, according to the coalition. A 2011 recommendation of the American College of Obstetricians and Gynecologists (ACOG) stated that cfDNA testing should be used for high-risk women. A more recent committee opinion from ACOG and the Society for Maternal-Fetal Medicine, however, suggested NIPT using cfDNA offered "tremendous potential" to screen for fetal aneuploidy and any patient regardless of risk should be able to choose the screening—but it still did not recommend universal use of the NIPT with cfDNA as first line screening for pregnant women. See "Obstetric Groups Still Don't Endorse Universal Use of NIPT, But Expand Access," *Diagnostic Testing & Emerging Technologies*, Feb. 2, 2016).

The coalition's announcement explains that cfDNA-based NIPT has high sensitivity and specificity with low failure rate, and leads to fewer invasive testing procedures for women. The testing can also be performed as early as nine to 10 weeks into a pregnancy.

The coalition will:

- "promote public awareness about the value of cfDNA-based NIPT";
- "advocate for the highest standards of quality, service and education";
- support relevant legislative action; and
- seek reimbursement policies supportive of such testing.

A clinical advisory board—to be named in the first half of 2017—will provide the coalition with "an independent medical perspective."

"As leading providers of cfDNA-based NIPT, CAPS members are working together towards the common goal of ensuring that this innovative and highly accurate screening method is easily accessible to all pregnant women who choose to pursue aneuploidy screening, regardless of their risk factors, income, age or geographic location," said Arnold W. Cohen, M.D., Chairman of the CAPS Clinical Advisory Board, in a statement. Cohen is also Chairman Emeritus of the Department of Obstetrics and Gynecology at the Einstein Healthcare Network. "We recognize the importance of providing reliable and useful information about cfDNA-based NIPT to patients, healthcare providers, and public and private insurers."

Takeaway: Growing recognition for the value of noninvasive diagnostics leads a coalition to form promoting standards and reimbursement for cfDNA-based NIPT.

Breach Notification Violation Ends in $475,000 Settlement

Patient health information breaches—whether from hacking, glitches or just plain old carelessness—remain an all too common occurrence in labs and other health care institutions. Three years ago, a new HIPAA rule took effect requiring providers to furnish timely notification of such breaches. And on Jan. 3, a large Illinois health system named Presence Health became the first provider to settle allegations it violated those notification requirements.

The Rule

Under the HIPAA rule, providers must furnish notification of breaches to three sets of recipients:

1. The HHS Office of Civil Rights (OCR);
2. The individuals affected by the breach; and
3. The media (if the breach affects 500 or more individuals).

The deadline for notification: within 60 days of discovering the breach.

What Happened

On Oct. 22, 2013, Presence discovered that paper-based OR schedules for one of its surgery centers had been removed from the files. The missing records listed personal health information of 836 individuals, including names, birth dates, medical record numbers, dates and types of procedures received and anesthesia administered.

It was a breach requiring notification under the HIPAA rule. The good news is that Presence did send out all of the required notices. The bad news is that it did so only well after the 60-day deadline had expired:

Notice Recipient	Notice Due Date	Actual Notice Date	Days Late
OCR	Dec. 22, 2013	Jan. 31, 2014	41
836 individual patients	Dec. 22, 2013	Feb. 3, 2014	44
Media outlets	Dec. 22, 2013	Feb. 5, 2014	46

The Case

The OCR charged Presence with a separate HIPAA violation for each one of the notices that was late (as well as additional violations committed later on that were discovered during the investigation). Faced with potential liability in the millions, Presence decided to settle the claims. The price tag: $475,000 and the promise to adopt a Corrective Action Plan (CAP) implementing measures to prevent future violations.

Editor's Note: For compliance guidance to help your lab avoid similar violations, see the January 2017 issue of *G2 Compliance Advisor.*

Takeaway: Based on the settlement agreement, it appears that Presence understood and made earnest efforts to comply with its breach notification obligations. Unfortunately, it took too long to do so. Although it is not clear why the notices were late, what can be said with confidence is that implementing clear and specific rules and timetables for responding to and reporting data breaches is crucial to ensure compliance with HIPAA breach notification requirements.

Industry Leaders Recommend Standardized Interpretation and Reporting of Somatic Sequence Variants

A common refrain within the diagnostics industry is a need for standardization. Rapidly developing technology and testing methods, the call for interoperability, and the vast amount of data and information producible via molecular testing makes this even more important. The capabilities of next generation sequencing have provided both opportunities and challenges as clinical laboratories interpret and report results of cancer-related sequencing tests.

"Cancer genomics is a rapidly evolving field so the clinical significance of any variant in therapy, diagnosis, or prognosis should be reevaluated on an ongoing basis by all of the key stakeholders."

— Marina N. Nikiforova, MD, Professor of Pathology, University of Pittsburgh Medical Center

Now, the Association for Molecular Pathology (AMP) has released guidelines developed by an industry working group that recommend standard classification, annotation, interpretation and reporting for somatic sequence variants in cancer. The AMP was joined in this effort by the American College of Medical Genetics and Genomics (ACMG), American Society of Clinical Oncology (ASCO), and College of American Pathologists (CAP).

"Cancer genomics is a rapidly evolving field so the clinical significance of any variant in therapy, diagnosis, or prognosis should be reevaluated on an ongoing basis by all of the key stakeholders," said one working group member, Marina N. Nikiforova, MD, Professor of Pathology at University of Pittsburgh Medical Center, in a statement announcing the release of the guidelines. Nikiforova is also the 2016 AMP Clinical Practice Committee Chair and adds, "These new recommendations resulted from the successful ACMG, AMP and CAP efforts on germline variant interpretation and were additionally informed by the diverse perspectives expressed at the ASCO, AMP and CAP Genomic Roundtable stakeholder discussions." The Guidelines will be published in the January 2017 issue of *The Journal of Molecular Diagnostics* but were released online by AMP in December.

To gain insight into the real world operations of varying laboratories, the working group solicited surveys from AMP members. The surveys focused on technical issues and reporting issues. They received 67 responses on technical issues and 44 for reporting issues. Survey responses revealed variation among NGS techniques used and the annotation and reporting of variants.

The U.S. Food and Drug Administration has similarly led industry-wide discussion of standards for NGS interpretation and reporting. Recognizing the vast amount of information that can be yielded from NGS, the difficulty in interpreting results of NGS testing and lack of evidence in some cases linking genetic variants to specific diseases a recent FDA workshop discussed how best to make use of the results of NGS testing—based on patient and provider preferences. The goal, the notice of the workshop announced, is "to learn, when results are generated in a CLIA-compliant laboratory, which results are of importance to patients and providers, how these results should be returned and how much and what types of evidence supporting interpretation of those results is necessary."

Tiered classification system

The Guidelines share several recommendations for laboratories involved in such NGS variant testing for cancer. To categorize variants, the guidelines recommend using a tiered system that categorizes somatic variants according to their impact on clinical care—using "currently available evidence."

- **Tier I** would be variants with strong clinical significance based on evidence regarding FDA approved therapy and "well-powered studies with consensus from experts in the field."
- **Tier II** covers variants of potential clinical significance based on evidence from FDA approved treatments but for different tumor types or investigational therapies, small published studies having some consensus, and preclinical trials or case reports without consensus.
- **Tier III** includes variants of unknown clinical significance when there is no "convincing published evidence of cancer association" and the variant isn't "observed at a significant allele frequency in the general or specific subpopulation databases, or pan-cancer or tumor-specific variant databases."
- **Tier IV** is for benign or likely benign variants when there is a lack of published evidence of cancer association and the variant is "observed at significant allele frequency in the general or specific subpopulation databases."

For further discussion of the guidelines see the December 2016 issue of *Diagnostic Testing & Emerging Technologies.*