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New Trends, Applications, and IVD Industry Analysis

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FDA Continues Easing DTC, Home Use Test Regulations

In a continued reversal of its 2013 crackdown on direct-to-consumer (DTC) genetic tests, the U.S. Food and Drug Administration (FDA) unveiled loosened regulations in November that will effectively enable growth in the DTC genetic test market, as well as ease restrictions on bringing other CLIA-waived tests to market.

Enabling DTC Tests for Genetic Health Risks

The FDA has slowly been approving DTC tests on a case-by-case basis. But new proposed regulations unveiled in November will allow genetic carrier screening tests, taken by prospective parents, and other genetic health risk (GHR) tests to enter the market without prior review. The new regulatory approach doesn't apply to genetic tests that inform treatment decisions (e.g., hereditary cancer tests for BRCA1 and BRCA2 genes).

In its November notice, the FDA said GHR test developers will face a one-time FDA review, but can subsequently expand their GHR-mar-

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LDTs, FDA-Approved Companion Diagnostics Perform Similarly; Off-Label Use of Companion Diagnostic Kits Common

One of the arguments for U.S. Food and Drug Administration oversight over laboratory-developed tests (LDTs) involves the need for greater assurances regarding the quality and consistency of these tests. A brief report published Dec. 14 in *JAMA Oncology* may allay some of these concerns.

A study of close to 7,000 College of American Pathologists proficiency testing samples found that LDTs and FDA-approved companion diagnostics (FDA-CDs) had similarly high accuracy for detecting variants in three oncology-related genes—BRAF, EGFR, and KRAS. However, the researchers found that more than 60 percent of laboratories report modifying the intended use of FDA-CDs, essentially making them LDTs.

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keted tests without further review. The FDA acknowledged in a statement that consumers are increasingly embracing GHR tests to better understand their individual risk for developing diseases and possibly make lifestyle choices to counter these risks. However, the FDA cautioned, these tests can pose "their own risks" if they provide incorrect or misleading information to consumers in the absence of professional medical advice.

"The accelerated development of these innovative DTC genetic risk tests paired with the known safety considerations presents unique challenges to FDA regulation, as these technologies don't fit squarely into our traditional risk-based approach to device regulation," FDA Commissioner Scott Gottlieb, M.D., said in a statement. "In its consideration of GHR tests, the FDA seeks to strike a balance that provides for an efficient pathway to bring these tests to consumers, without sacrificing the assurances offered by FDA oversight."

Easing CLIA-Waiver Regulations

On Nov. 29, the agency issued two draft guidances proposing to reduce the burden of applying for CLIA waivers. The first draft guidance is in response to the Cures Act, which requires that FDA allow manufacturers of in vitro diagnostic devices submitting a CLIA waiver to demonstrate accuracy through comparable performance between a waived user and a moderately complex laboratory user, rather than based upon a gold standard. In addition to this statutory change, the draft guidance provides significant detail regarding demonstration of accuracy of a test for purposes of securing the "insignificant risk" waiver.

The second proposal would establish a dual submission pathway enabling test makers to use the same sets of studies to secure 510(k) approval and a CLIA waiver.

Takeaway: The FDA is sending strong signals it plans to continue to streamline regulations enabling easier market entry for innovative products, including DTC tests for GHR and CLIA-waived products.

FDA Warns About Biotin Interference With Lab Tests

In late November the U.S. Food and Drug Administration issued a safety communication warning that the supplement biotin (Vitamin B7) may interfere with laboratory testing results. The warning comes after Roche Diagnostics (Indianapolis, Indiana) published a study online Sept. 14 in the *International Journal of Pharmacokinetics* demonstrating that an eight-hour wait time or washout period is necessary for accurate test results when using streptavidin–biotin immunoassays following high doses of biotin (more than 5 mg/day).

The FDA says it has received a report that one patient taking high levels of biotin died following falsely low troponin results on a test for heart attacks known to have biotin interference. There have been previous case reports of

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FDA Recommendations for Laboratories

In order to cut the risk of adverse events associated with biotin interference with laboratory tests the FDA is recommending that laboratory personnel

- Be aware that biotin levels higher than the recommended daily allowance may cause significant interference with affected lab tests
- Communicate with health care providers and patients regarding use of assays with biotin technology
- At draw centers, ask patients if they are taking biotin
- Educate health care providers about biotin interference with specific tests
- Communicate with the lab test manufacturer if you have questions about biotin interference

biotin interference leading to incorrect diagnoses in both adults and children, particularly for cardiovascular diagnostic tests and hormone tests. However, there is increasing use of over-the-counter (OTC) biotin supplements that purportedly strengthen hair, skin, and nails. These products range in biotin doses from 50 µg in multivitamin to as high as 10 mg in some biotin-only products. The FDA notes these high-dose OTC products may contain biotin levels up to 650 times the recommended daily intake of biotin (30 µg/day). Additionally, physicians recommend extremely high doses for treatment of neuropathy and multiple sclerosis. Thus, there is increasing evidence that the risk of biotin interference with laboratory testing is also increasing.

High-sensitivity immunoassays made by companies like Abbott, Beckman Coulter, Ortho Clinical Diagnostics, Roche Diagnostics, and Siemens Healthcare Diagnostics are all susceptible to biotin interference. Excess biotin in patient samples can result in falsely high test results with competitive assay design and falsely low results with sandwich assay design. The study in the International Journal of Pharmacokinetics found that manufacturers provide a "spectrum of guidance" in package inserts ranging from no mention or vague generic warnings of biotin interference to comprehensive specification on serum biotin concentrations.

The Roche study sought to characterize the pharmacokinetic properties of biotin and establish a model simulating the effective half-life of biotin and biotin metabolites with different high-dose regimens (1 mg daily to 300 mg). Participants were divided into three different dosing groups (5, 10 or 20 mg taken orally once a day) for five days. Participants were required to fast for 8 hours prior to and 1 hour after biotin intake and blood samples were collected prior to biotin intake on days 1, 2, and 7, and at 1, 3, 6, 8 and 12 hours postdose on days 3 and 7. Samples were analyzed using the cobas e 411 analyzer (Roche Diagnostics) using an in-house competitive Elecsys research assay. The researchers identified the necessary washout periods for biotin concentrations to reach thresholds ranging from 10 to 100 ng/mL.

"It is important for clinicians and pathologists to be aware of which immunoassays are streptavidin-biotin-based and therefore when an abnormal result may be the result of interference and require repeat analysis before a diagnosis is made," write the authors led by Paul Grimsey, from Roche Innovation Center in the United Kingdom. "It is important to understand the time taken for the serum biotin concentration to fall below a specific threshold, to allow calculation of the washout period required before collection of serum samples for assessment using biotin-streptavidin based assays."

The researchers found that biotin has linear pharmacokinetics over the range of doses studied, is rapidly absorbed with a maximum serum concentration of less than 1 hour, and has an effective serum half-life of 15 hours.

- For biotin doses up to daily doses of 1 mg (e.g., in a multivitamin) serum biotin levels fall below an in vitro threshold of 10 ng/ml (one of the lowest recommended biotin interference thresholds) after 2 hours.
- For doses of biotin of up to 10 mg/day, an in vitro serum biotin threshold of 30 ng/ml could be consistently reached after 8 hours of washout.
- For extremely high doses of biotin (more than 20 mg), the residual biotin serum concentration did not drop to 30 ng/ml until 31 hours after last intake and took 73 hours to drop to 10 ng/ml, indicating an extended washout periods would be needed for immunoassays with a low in vitro interference threshold (less than 30 ng/ml) and following extremely high doses of biotin.

The authors caution that the study is not able to give information as to the size of any potential effect of biotin interference on test results or the proportion of laboratory values that are potentially vulnerable to interference.

Takeaway: The potential for supplementary biotin consumption to interfere with test results is a real concern and is something that laboratories need to work with providers on to ensure accurate diagnosis.

Pediatric Offices Fail to Act on 1 in 10 Abnormal Test Results

Diagnostic errors (DEs) and missed opportunity for diagnosis (MOD), including the failure to act on abnormal laboratory test results in a timely manner, commonly occur in pediatric primary care offices, according to a study published online Aug. 10 in *Academic Pediatrics*. Approximately one in 10 abnormal laboratory results in pediatric primary care offices are not acted on appropriately or in a timely manner

"While studies on reducing ambulatory diagnostic breakdowns in adults have emerged, little progress has been made in understanding or reducing ambulatory pediatric DEs," write the authors led by Michael Rinke, M.D., Ph.D., from Children's Hospital at Montefiore in the Bronx, N.Y. "Knowing that these DEs and MODs lead to long-term morbidity, it is crucial to pursue strategies to reduce their incidence."

Twenty-five primary care pediatric practices, participating in a national quality improvement collaborative (RedDE: Reducing Diagnostic Errors in Pediatric Primary Care), were randomized to collect five months of retrospective data (February through June 2015) on DEs or MODs regarding abnormal laboratory values, as well as elevated blood pressure and adolescent depression evaluation.

Specifically, five "subacute" laboratory tests were selected—abnormal hemoglobin and mean corpuscular volume (microcytic anemia), lead, or thyroid-stimulating hormone results, or a positive sexually transmitted

"Practices that enrolled onto a quality improvement project to reduce DEs are likely not representative of all practices, given their expressed interest in DE improvement and their baseline characteristics."

— Michael Rinke, M.D., Ph.D.

infection (gonorrhea, chlamydia, syphilis, or HIV) or group A Streptococcus throat culture. These tests were chosen because they are frequently ordered in primary care pediatric practices and can lead to long-term harm if left unrecognized or untreated. Chart reviews assessed the number of patients who did not have an appropriate action documented after receiving any of these abnormal laboratory results, or patients who had an appropriate action documented but with an excessive delay.

The researchers found that for 33 children there was no timely chart documentation there was an abnormal laboratory value. For 11 percent of the 381 patients with abnormal laboratory values there was not an appropriate follow-up action in response to the abnormal test result documented in a timely manner. This rate was much lower than DEs associated with elevated blood pressure (54 percent) or MODs for evaluating adolescents with depression (62 percent).

The authors warn, though, that the extent of Des and MODs in pediatric practices, may actually be underestimated in their study.

"Practices that enrolled onto a quality improvement project to reduce DEs are likely not representative of all practices, given their expressed interest in DE improvement and their baseline characteristics," write Rinke and colleagues. "Almost 70 percent of our practices were university affiliated, and 40 percent had already worked 'a lot' on one of these errors."

Takeaway: Failure to act upon abnormal laboratory results is a common occurrence in pediatric, primary care practices.

Foster Kids' Standard Screenings Tests May Be of Low Value

Routine laboratory screening for children entering foster care may be costly given the low diagnostic yield, according to a study published in the December issue of *Pediatrics*. The authors suggest that targeted, rather than routine, laboratory screening may be a more clinically meaningful approach to manage children entering foster care.

It is estimated that more than 400,000 children are in the custody of U.S. child welfare agencies. To address concerns related to "uncoordinated or discontinuous" medical care, most states mandate children receive a physical upon entering the foster care system. In 2005, the American Academy of Pediatrics issued expert opinion-based guidance in its *Healthy Foster Care America* report recommending certain disease screenings through laboratory testing as part of this examination.

In order to assess the utility of laboratory screenings for children entering foster care, clinical and laboratory data was examined for 1,977 children seen at a consultation foster care clinic over a three-year period in a single county in Ohio. Standard laboratory screening included testing for infectious diseases (HIV, hepatitis B and C, syphilis, and tuberculosis), and hemoglobin and lead levels.

The researchers found that over the study period 16,754 laboratory screening tests were performed, with 60 percent of children having at least 1 laboratory abnormality. The prevalence was less than 1 percent for hepatitis B, hepatitis C, syphilis, and tuberculosis. There were no cases of HIV and a positive chlamydia test occurred among 7 percent of teenagers. Just over 4 percent of kids were anemic and 2.7 percent had high lead levels. The most common screening abnormality was a negative hepatitis B surface antibody test (54 percent), which indicates an absence immunity to the hepatitis B virus.

"High-impact screening may include lead levels for children less than 6 years old, hemoglobin screens, sexually transmitted infection testing in children 12 years and older, and HBV testing if determining potential failure to seroconvert is needed," write the authors led by Mary Greiner, M.D., from Cincinnati Children's Hospital Medical Center in Ohio. "Targeted infection screening should take local prevalence rates and other clinical indications into account."

Takeaway: It may be more cost effective to conduct targeted screenings for children entering the foster care system, while keeping certain high-impact screening tests, like those for lead, anemia, and some sexually transmitted infections, as routine.

Testing Guidelines at a Glance

AMP Issues Consensus Guidelines for NGS Bioinformatics Pipelines

The Association for Molecular Pathology (AMP) published 17 consensus recommendations for the validation of clinical next-generation sequencing bioinformatics pipelines. The report, "Standards and Guidelines for Validating Next Generation Sequencing Bioinformatics Pipelines: A Joint Recommendation of the Association for Molecular Pathology and College of American Pathologists," is published in the January 2018 issue of the *Journal of Molecular Diagnostics*.

AMP convened a multidisciplinary expert working group, including representatives of the College of American Pathologists and the American Medical Informatics Association to summarize current knowledge, expose challenges, and provide guidance on how to develop, implement, and validate high-quality, bioinformatics pipelines. The report emphasizes the critical role of the properly trained molecular laboratory professional and recommends practical advice for the development of bioinformatics pipelines. Some of the recommendations include:

- Clinical laboratories offering NGS testing should perform bioinformatics pipeline validation, but only after completion of design, development, and optimization of the bioinformatics pipeline and all of its components.
- Supplemental validation is required whenever a significant change is made to any component of the bioinformatics pipeline.
- A qualified medical professional with appropriate training in NGS interpretation should oversee the validation process.
- The pipeline should ensure the security of identifiable patient information.
- The identity of the sample should be preserved throughout each step of the NGS bioinformatics pipeline, with a minimum of four unique identifiers.
- The bioinformatics pipeline is part of the test procedure, and its components and processes must be documented according to laboratory accreditation standards and regulations.
- Validation of the bioinformatics pipeline should include confirmation of a representative set of variants with high-quality independent data.
- Methods used to alter or filter sequence reads at any point in the pipeline should be validated to ensure that the data presented for interpretation accurately and reproducibly represents the sequence in the specimen. All methods should be fully documented.

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FDA's Two Big Moves on NGS-Based Tumor Panels May Offer Clues for Alternative Pathways for LDT Approval

In late November the U.S. Food and Drug Administration (FDA) authorized Memorial Sloan Kettering Cancer Center's Integrated Mutation Profiling of Actionable Cancer Targets tumor profiling test assay (MSK-IMPACT) and approved FoundationOne CDx (F1CDx), Foundation Medicine's comprehensive, next-generation sequencing- (NGS-) based companion diagnostic (CDx) test for solid tumors. While personalized medicine advocates can certainly hail these regulatory wins as progress towards greater adoption and reimbursement of comprehensive molecular panels in routine cancer care, the FDA's actions may also offer some more subtle clues for potential innovative regulatory pathways the agency may be exploring for laboratory-developed tests (LDTs).

Unlike previous FDA CDx approvals that match one test to one drug, Foundation Medicine's F1CDx enables matching of patients with five different tumor types to 15 different approved, targeted treatments

In the case of MSK-IMPACT, the FDA not only authorized the panel, but it also established a lighter regulatory pathway for the review of subsequent NGS-based tumor profiling assays, including the appointment of a third-party reviewer for such tests. In approving F1CDx through the Parallel Review Program in concert with the Centers for Medicare & Medicaid Services, the FDA is furthering regulatory mechanisms that enable faster reimbursement and adoption of emerging, innovative technologies.

The Two Panels

MSK-IMPACT is a 468-gene panel intended to detect genetic mutations in both rare and common cancers. The test uses formalin-fixed, paraffin-embedded tumor tissue matched with normal patient specimens. MSK (New York) says the test intends to provide information on somatic mutations (point mutations, as well as small insertions and deletions) and microsatellite instability (MSI).

Data submitted to the FDA demonstrated that the MSK-IMPACT assay is highly accurate (more than 99 percent) and capable of detecting a mutation at a frequency of approximately 5 percent (range, 2 percent to 5 percent). Additionally, the test could detect microsatellite instabilities 92 percent of the time across multiple cancer types in 175 cases, when compared to traditional detection methods. However, the FDA says the test is intended to provide information on cancer biomarkers, but its results are not conclusive for choosing a corresponding treatment, as a CDx would be. MSK says that more than 20,000 patients with advanced cancers have had their tumors sequenced using the test.

Unlike previous FDA CDx approvals that match one test to one drug, Foundation Medicine's F1CDx enables matching of patients with five different tumor types to 15 different approved, targeted treatments, including those for non-small cell lung cancer, melanoma, breast cancer, colorectal cancer, or ovarian

cancer. Foundation Medicine (Boston) estimates that the test could aid in the clinical management of one in three cancer patients.

F1CDx can detect genetic mutations in 324 genes and two genomic signatures in any solid tumor type. Data submitted to the FDA demonstrated the test's ability to detect select mutation types (substitutions, as well as short insertions and deletions) with 94.6 percent accuracy. The company says F1CDx results are delivered in an integrated report that identifies alterations matched to FDA-approved therapies; additional alterations in genes known to drive cancer growth; information about other genomic biomarkers, including microsatellite instabilities and tumor mutational burden; relevant clinical trial information, and s interpretive content on solid tumors developed in accordance with professional oncology guidelines.

Overview of MSK-IMPACT and F1CDx

	FDA Regulatory Pathway	Testing Procedure	Genes Assessed	Test Results
MSK-IMPACT	De novo premarket review	Single site assay conducted at MSK (New York)	468	Not conclusive for choosing targeted treatment
F1CDx	Breakthrough Device Program and Parallel Review Program	Single site assay conducted at Foundation Medicine (Boston)	324	Indicated as a CDx for

The Assays' Regulatory Pathways and Implications

MSK-IMPACT became the first comprehensive tumor-profiling LDT to receive FDA authorization through the de novo premarket review pathway. It had previously been approved by the New York State Department of Health as a laboratory-developed clinical test. The FDA authorized MSK-IMPACT as a Class II, moderate-risk device, which enables subsequent, similar types of tests to use the FDA's less onerous 510(k) clearance pathway.

Aside from the size of the panel, the authorization is noteworthy because it highlights a new, efficient pathway for authorization in the future. In addition to the Class II designation, the FDA also announced the recent accreditation of the New York State Department of Health as an FDA third-party reviewer of in vitro diagnostics, including for NGS-based tests similar to MSK-IMPACT test. The agency says that, moving forward, laboratories whose NGS-based tumor profiling tests have been approved by the New York State Department of Health do not need to submit a separate 510(k) application to the FDA. Instead, test developers can choose to forward their NYSDOH application, as well as the state's review memorandum and recommendation, to the FDA for possible 510(k) clearance.

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> *"This is really a clever sleight-of-hand in a way. It appears that the FDA is announcing a new, low-burden regulatory pathway for IVD devices, when it is really about a voluntary 'authorization' process for LDTs."*
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> — Carol Pratt, FDA regulatory attorney, Lee & Hayes PLLC

"The goal of allowing NGS-based tumor profiling tests to undergo review by accredited third parties is to reduce the burden on test developers and streamline the regulatory assessment of these types of innovative products. As this field advances, we are modernizing the FDA's approach to the efficient authorization of laboratory tests from developers that voluntarily seek 510(k) clearance," said FDA Commissioner Scott Gottlieb, M.D. in a statement. "This is another example of where the FDA is working to find creative and flexible approaches to regulation that spurs development and efficient delivery of innovative technology."

Private-sector regulatory experts believe the FDA's action may provide important insight for how the agency will handle LDTs in the future. They note that use of accredited third parties is in line with steps the FDA has taken to respond to rapidly evolving technologies, such as in digital health.

"This is really a clever sleight-of-hand in a way," Carol Pratt, an FDA regulatory attorney with Lee & Hayes PLLC in Portland, Ore., told *Bloomberg Law*. "It appears that the FDA is announcing a new, low-burden regulatory pathway for IVD devices, when it is really about a voluntary 'authorization' process for LDTs."

Pratt stresses that the word "voluntary" in Gottlieb's statement is "critical" because it acknowledges that 510(k)s aren't required for LDTs. While many see this action as providing a new pathway for developers wanting their tests cleared, clarification is still needed over if and how the agency will exert its authority over LDTs.

The FDA reviewed F1CDx under its Breakthrough Device Program. The FDA says this program enables the agency to provide "intensive interaction and guidance" to companies, assisting them with efficient device development and expedited evidence generation for devices that provide for more effective treatment or diagnosis for life-threatening conditions. F1CD qualified as it represents a significant advantage over the existing standard of care because F1CDx effectively consolidates multiple CDx into a single test.

The FDA and the Centers for Medicare & Medicaid Services (CMS) simultaneously reviewed F1CDx under their Parallel Review Program, enabling the test to receive approval and secure an immediate proposed Medicare coverage determination. The Parallel Review Program is open to certain premarket approval applications for new device technologies that fall within Medicare's Part A or Part B benefit categories. A final coverage decision is expected in the first quarter of 2018, at which time F1CDx will be made commercially available.

It is noteworthy that the draft coverage determination is not just for the F1CDx, but would also provide coverage for other FDA-approved companion diagnostic

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claims, as well as a pathway for additional coverage with evidence development as the company adds claims for other solid tumor types.

Analysts are optimistic that FDA approval and Medicare coverage could have a positive impact on future private reimbursement decisions. Foundation Medicine's CEO Troy Cox said that Medicare's coverage determination will represent a "significant expansion" of coverage for Medicare beneficiaries nationwide, as approximately 40 percent of the company's testing volume consists of Medicare and Medicare Advantage patients. Ultimately, though pricing will be determined under the Protecting Access to Medicare Act, company officials said.

Earlier this year, Foundation Medicine reported it had received its first payments for Medicare patients from Palmetto for its LDT FoundationOne test, at an allowable rate of $3,416. However, overall, payments for the LDT appear to have been significantly lower. In a November earnings call with investors the company said that the average revenue for each test in the third quarter was $2,600.

Takeaway: Recent FDA action related to two comprehensive NGS-based oncology panels may accelerate adoption and reimbursement for these types of tests. Additionally, these actions reveal emerging, alternative pathways for future approval of complex LDTs.

LDTs, FDA-Approved Companion Diagnostics Perform Similarly, *from page 1*

The researchers compared analytical validity and associated preanalytic practices for 6,897 proficiency testing responses. Combined, both LDTs and FDA-CDs exceeded 97 percent accuracy across all the samples.

- For BRAF mutations, LDTs outperformed FDA-CDs with a 96.6 percent acceptable rate while FDA-CDs results were significantly lower at 93.0 percent. The researchers attributed this difference primarily to analysis of the BRAF p.V600K mutation (88.0 percent for LDTs versus 66.1 percent acceptable rate for FDA-CDs).
- For EGFR, LDTs performed slightly, but significantly, less well than the FDA-CDs (97.6 percent acceptability for LDT versus 99.1 percent for FDA-CDs). This discrepancy was driven by detection of the EGFR p.L861Q mutation (91 percent for LDTs versus 100 percent for FDA-CDs).
- For KRAS, there was no significant difference between acceptability rates for LDTs and the FDA-CDs overall or by individual variants.

The researchers importantly found that more than 60 percent of participants using FDA-CDs report modifying the approved preanalytic methods to broaden clinical use. This off-label practice essentially turns the FDA-CDs into LDTs. Reported off-label practices include unapproved specimen types and tumor types, as well as accepting specimens with lower tumor content than are required for the approved assay and not quantifying DNA before performing the assay.

"The preanalytic questions highlight the fact that many FDA-CD laboratories conduct practices that are not in accord with their FDA-approved methods," write the authors led by Annette Kim, M.D., Ph.D., from Brigham and Women's Hospital in Boston, Mass. "Although this flexibility is advantageous for patient care, it is important to recognize that the use of specimens other than formalin-fixed paraffin-embedded samples of the specified tumor type for the FDA-CDs is off-label, resulting in reclassification of the assay as an LDT."

Several authors report financial ties to the diagnostics industry.

Takeaway: While it may be reassuring that LDTs and FDA-CDs perform with similar access for detection of oncology-related genetic mutations, it may concern regulators the extent to which FDA-approved in vitro diagnostic kits are being used off-label.

Teaching Hospitals Consistently Order More Lab Tests Per Patient

A new study validates the long-held assumption that intensity of care is consistently higher at teaching hospitals, compared to nonteaching hospitals. Patients in Texas admitted to major teaching hospitals with two common conditions receive significantly more laboratory tests per day, compared to similar patients at nonteaching hospitals even after controlling for illness severity, length of stay, and patient demographics, according to a study published Nov. 13 in *JAMA Internal Medicine*. In an environment with increased focus on value-based care and appropriate test utilization, the authors say that studying cultural factors in the training environments that may lead to increased use of laboratory tests is essential.

Findings Applied to A Single Case

The authors offer the following illustration:

Patient: A 42-year-old African American man with Medicaid insurance coverage presenting to the emergency department with community-acquired pneumonia.

Hospitalization: A 4-night hospital stay with an illness severity of 2.

Laboratory Testing: Based on the study results, if this patient were admitted to a nonteaching hospital, he would receive 10 laboratory tests per day during his hospitalization, for a total of 40 laboratory tests versus if he were admitted to a major teaching hospital he would receive 13 laboratory tests per day, for a total of 52 laboratory tests, representing a 30 percent increase in use of laboratory testing.

Using a large statewide all-payer database, the researchers identified hospitalizations with a primary diagnosis of bacterial pneumonia (n = 24,118) or cellulitis (n = 19,211; from Jan. 1, 2014, to June 30, 2015) across 11 major teaching hospitals, 12 minor teaching hospitals, and 73 nonteaching hospitals in Texas each with 100 or more hospitalizations for each condition. These diagnoses were selected in part due to the fact that specialized laboratory testing is generally not required for these conditions and that they are cause for admission at both teaching and nonteaching hospitals.

The researchers found that the mean number of laboratory tests per day varied significantly by hospital type and was highest for major teaching hospitals for both conditions (bacterial pneumonia: major teaching hospitals, 13.21 versus 8.92 at nonteaching hospitals; cellulitis: major teaching hospitals, 10.43 versus 7.29 at nonteaching hospitals). This association held for all levels of illness severity for both conditions, except for patients with cellulitis with

the highest illness severity level. The size of the effect amounted to approximately 3.6 additional laboratory tests per day for pneumonia and 2.6 additional laboratory tests per day for cellulitis. Hospitals that had more laboratory tests ordered for patients with pneumonia also had more laboratory tests ordered for patients with cellulitis.

Of the 11 major teaching hospitals, eight were above the mean number of laboratory tests performed across all hospitals for pneumonia and seven were above the mean number of laboratory tests performed across all hospitals for cellulitis.

"Our data also show that patients with pneumonia at major teaching hospitals are sicker, perhaps leading to learned behaviors by trainees of ordering more laboratory tests," write the authors led by Victoria Valencia, from University of Texas at Austin. "Perhaps higher rates of testing are justified for a substantial fraction of patients in teaching hospitals, but this behavior may then spill over to less acutely ill patients.... If this phenomenon exists it could complicate generalized efforts to reduce testing at academic medical centers and could even lead to harm if there is an overall nontargeted reduction in testing."

Takeaway: This study confirms a widespread pattern of increased laboratory test ordering in teaching hospitals, even for common conditions. In an environment with increased focus on value-based care, targeted test reduction interventions need to ensure sicker patients are receiving needed tests, but that less severely ill patients are not receiving unnecessary testing.