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HIGHLIGHTS

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ACLA Pushing for Broadening of Coverage for Vitamin D Testing

The American Clinical Laboratory Association (ACLA) has asked regional fiscal intermediary Novitas—and by extension, much of the Medicare program—to reconsider its austere position on testing for some vitamin deficiencies. In particular, the ACLA has asked Novitas to reconsider its position regarding testing for vitamin D.

"Vitamin D deficiency is an important contributor to the development of osteoporosis; specific patient populations with specific diagnoses are at substantially increased risk for complications related to Vitamin D deficiency," said the comment letter the ACLA sent to the Pittsburgh-based Novitas and authored by ACLA Senior Vice President JoAnne Glisson.

Currently, Medicare does not reimburse for many forms of vitamin or micronutrient testing, considering such tests to be medically unnecessary. It makes a few exceptions for patients with specific diseases or medical conditions, but they are generally narrow.

Continued on page 7

As Theranos Tries to Fix Up California Lab, Reports Surface It May Have Performed Inaccurate Blood Clotting Tests

As startup laboratory Theranos continues to struggle through its regulatory and compliance growing pains, it appears to be using the fingers of one corporate hand to keep better tabs on its operations, while those on the other hand are plugging holes in a precariously porous dam.

As Theranos announced it had hired a new lab director to oversee its troubled facility in Northern California to address issues cited by federal regulators, the *Wall Street Journal* reported earlier this month that the company had distributed test results from assays it knew may have been suspect.

The Centers for Medicare & Medicaid Services (CMS) had announced in January that the operations of Theranos' laboratory were deficient in several areas and were placing the safety of patients in immediate jeopardy in the area of hematology. Theranos was given

Continued on page 2

Theranos May Have Performed Inaccurate Blood Clotting Tests, *from page 1*

10 days to fix the problems or potentially lose certification of its laboratory and the ability to participate in the Medicare and Medicaid programs. In the wake of CMS' letter, The New York Times reported that Walgreens announced it would not be sending samples for testing to Theranos' California lab.

The decision was a significant setback for the Palo Alto, Calif.-based Theranos, which is attempting to market a wide arrange of lab tests that can be performed with just a few drops of blood at a price point 50 percent below that of Medicare rates.

"As part of that comprehensive review and our review of CMS's survey findings, we made personnel changes in our Newark, California lab, adopted enhanced policies and procedures, and provided additional support to the lab, as we became aware of any potential issues during the survey," Theranos said in a statement.

Meanwhile, the *Wall Street Journal* reported that Theranos conducted 81 prothrombin time/international normalized ratio assays (PT/INR) even though the company was likely aware that the results it was receiving when performing that test were erratic. The test is used to determine the clotting ability of a patient's blood, and is often used in conjunction with prescribing the dosage of blood thinners such as warfarin, which can be hazardous if the dosage is too large or small.

Theranos appeared to believe the issue would make headlines; two days before the *Wall Street Journal* published its article, it stated that it had "investigated all PT/INR issues raised by CMS, notified any potentially affected patients, and has no reason to believe that these issues have affected patients' health. The PT/INR issues identified by CMS related to tests run on conventional equipment using venipuncture samples."

Theranos also announced the hiring a new lab director for the Newark facility. The company reached high: The new hire is Kingshuk Das, M.D., a pathologist who was educated at Case Western Reserve University School of Medicine and completed his residency at Los Angeles County-USC Medical Center near central Los Angeles.

"We have conducted assessments to identify any patients affected or having the potential to be affected by the issues identified by CMS, and we have no reason to believe that these issues have affected patients' health," Das said in a statement. "At its heart, the CMS report is about people and processes in one Theranos lab in the past, and does not reflect the current state of that lab."

Takeaway: Theranos is juggling the dual issues of fixing its laboratory operations while trying to convince the public that its testing platforms are safe. G2

CAP Issues New Guidelines for Reports on Bone Marrow Testing

The College of American Pathologists has released new practice guidelines for the reporting by laboratories of clinical findings from bone marrow samples. CAP's intent is to create a standardized format and template for the reporting of the results of bone marrow tests. Such testing can be used to diagnose leukemia, lymphoma, multiple myeloma and a variety of infections, as well as determine whether forms of cancer are metastasizing to the bone marrow or other parts of the body.

"Diseases emerging from bone marrow analyses—such as blood cancers—can be difficult to distinguish from a wide variety of noncancer causes, and often additional testing and data integration is required beyond morphologic evaluation of the bone marrow," said Cordelia E. Sever, M.D., a hematopathologist at Presbyterian Hospital in Albuquerque and one of the primary authors of the new guidelines, in a statement.

"Combining the essential data elements will help pathologists and laboratories produce clear, complete, and consistent synoptic reports that address the most relevant diagnostic and prognostic information."

— Cordelia E. Sever, M.D.

CAP noted in a report recently published in the *Archives of Pathology & Laboratory Medicine* that a diagnosis of leukemia can range from a single sentence to paragraphs of analysis. "The significant variability in reporting of bone marrow specimens may result in incomplete information or misleading information that is ill-defined and difficult to find in the report," it said.

Altogether, CAP issued nine different guideline statements:

- Laboratories should adopt synoptic reporting as a component of bone marrow pathology reports for clearly defined neoplasia.
- When reporting on peripheral blood specimens for bone marrow synoptic reports, laboratories should report clinically and diagnostically pertinent elements.
- When reporting bone marrow aspirate results, laboratories should report clinically and diagnostically pertinent elements in the synoptic section. These may include the evidence-based parameters.
- When reporting bone marrow core biopsy results, laboratories should report clinically or diagnostically pertinent elements in the synoptic section. These key elements may include the evidence-based parameters.
- If relevant ancillary testing studies are performed on the primary sample, laboratories should report the results, general methodology, performance site, and interpretation site or have the data readily available.
- Laboratories should include in the synoptic section of the report data groups for diagnosis, supporting studies, and ancillary data that are critical for diagnosis. Key morphologic descriptors should be included and may be in the diagnosis line if critical or if a component of the disease classification. The diagnosis (or diagnosis group) should head the synoptic section when possible.
- Laboratories should consider the integrity of electronic data transmission for formatting and data presentation of synoptic reports.
- Laboratories should include clinical and laboratory data required for a definitive diagnosis in the synoptic section, along with its source(s), if applicable.
- No recommendation was made regarding the inclusion of coding terms in a synoptic report because coding terms are distinct from scientific terms and vary considerably among health authorities, payers, and different countries.

"Combining the essential data elements will help pathologists and laboratories produce clear, complete, and consistent synoptic reports that address the most relevant diagnostic and prognostic information," Sever said.

Takeaway: The College of American Pathologists has issued guidelines intended to clarify the reporting of bone marrow samples in order to better improve cancer diagnoses. G2

Inside The Lab Industry

With Foreign Deals and Offshore CLIA Certifications, the U.S. Lab Sector Globalizes

For the better part of a century, laboratories had been among the most local of health care providers. They were mom-and-pop operations, often located hard by the local hospital or medical offices.

Some examples of globalization are straightforward: Sonic Healthcare Laboratories, an affiliate of an Australian firm, has had significant operations in the U.S. for years, although for the most part keeps a very low profile here and it keeps testing within U.S. borders.

But in recent decades, that dynamic has taken a 180-degree turn. Quest Diagnostics and LabCorp have taken a lot of hospital and physician office testing business as they have grown nationally. And as the global economy has taken off, labs have not escaped its impact.

In the United States, that means two things: Large multinational corporations that own laboratories in other nations are buying American companies and acquiring either their labs or opening new domestic facilities. Alternatively, those multinational labs are melding their overseas and U.S. operations in unique ways.

If there is any facet of health care delivery in the U.S. that could be globalized in this manner, the laboratory sector is the likeliest candidate. Hospitals and individual physicians can't easily operate overseas; medical tourism is the most likely example of globalization to be seen in those forms of care delivery. But tissue samples and specimens can be shipped to virtually any place in the world overnight, while test results can be transmitted almost instantaneously via Internet portals.

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Instead, much of the evidence of the next wave of globalization is often buried deep in the quarterly and annual financial reports of the publicly traded labs. In a recent earnings call with analysts, Foundation Medicine Chief Operating Officer Steven Kafka said one of the company's goals in 2016 "is to commence commercialization activities outside of the United States with (pharmaceutical giant) Roche" and that the company's FoundationOne assay would likely be introduced through Roche in the near-term. More and companies are also noting the effect of foreign currency rates of exchange on their bottom lines.

And there have also been some straightforward deals that have given foreign labs a toehold in the U.S. market. In February, India-based MedGenome acquired LifeCode Health, a transaction that included LifeCode's 13,000 square-foot lab in

Inside The Lab Industry

Northern California. "The acquisition of this lab will allow us to grow our customer base even more aggressively in the U.S.," said MedGenome Chief Executive Officer Sam Santhosh in a statement. A MedGenome spokesperson did not respond to a request seeking comment. MedGenome received a $20 million investment from Sequoia Capital last year to help it expand in the U.S. market.

"There is a lot of global interaction. We have (testing) facilities in Germany, Japan and India and I have a lot of collaboration and communications with them."

— James Corne, Eurofin

Eurofins Scientific, the Luxembourg-based biotech firm, acquired Boston Heart Diagnostics last year. Its genomics division opened a 65,000 square-foot laboratory in Louisville, Ky. earlier this year.

"There is a lot of global interaction. We have (testing) facilities in Germany, Japan and India and I have a lot of collaboration and communications with them," said James Corne, Eurofins' head of marketing for genomics in the U.S.

Corne noted that having a lab in an overseas market provides a myriad of advantages, because each market has different demands and expectations. Providers in Japan expect each specimen to be hand-couriered to and from the lab. The German market also has very strict system as to how specimens should be handled.

Even the Centers for Medicare & Medicaid Services (CMS) has been getting into the globalization game. Posted in an obscure corner of its website is a document entitled "International Laboratory CLIA Certification Process" that provides a blueprint for labs operating outside of the United States to legally accept and process samples from the U.S.

At least one laboratory so far has taken the agency up on that offer.

Earlier this year, WuXi NextCODE, the Icelandic and Chinese laboratory concern, became one of the first companies to obtain a certification in China from CLIA, the College of American Pathologists and regulators in California for its laboratory in Shanghai. It will be used to perform molecular testing on specimens gathered in California.

"There was a very specific business rationale" behind the CLIA certification in China, said Hannes Smarason, WuXi NextCODE's chief operating officer. WuXi Pharmatech acquired NextCODE, previously known as deCode Genetics, in early 2015.

The biggest driver, according to Smarason, is to accommodate testing for the global pharmaceutical market. Having a CLIA certified lab outside of the U.S. met the quality expectations of pharma customers while making the logistics of performing testing for firms anywhere in the world more straightforward. The company also wanted the ability for the Shanghai lab to perform other clinical work as well. While U.S. regulators might be providing the flexibility for lab work to be

Inside The Lab Industry

performed overseas, Chinese law bars sending specimens abroad for testing, according to Smarason.

"It is all the question of having the maximum flexibility to work with as many clients as we can," he said. "And because of that, we want to be (CLIA) certified in as many places as we can."

WuXi NextCode currently performs some of its U.S. testing in Massachusetts through an agreement with Claritas Genomics, a strategic and operational partner, but it appears having lab operations in China offer some of the same advantages that having manufacturing operations in that country confer: Lower costs.

Genscript, which also has headquarters in Nanjing, raised more than $67 million through an initial public offering on the Hong Kong Stock Exchange earlier this year.

According to Corne, there is a wave of companies that might have U.S. operations but prefer to perform testing in China. "It gives them a big price advantage," he said. "We're cognizant of it now, and a little worried."

One specific example is the Beijing Genomics Institute, or BGI. The company has struck up a variety of testing deals with Chinese hospitals, but its sequencing platform business may hold the biggest promise for globalization. It developed a high-speed, high-volume sequencer in conjunction with Complete Genomics, its U.S. subsidiary based in California. That platform, known as Revolocity, was released last year and has landed significant customers in both Australia and Europe. It is considered a direct competitor—one of the very few—to Illumina's HiSeq platform, although it is priced about 20 percent higher than the Illumina platform.

Another company with operations both in the U.S. and China—Genscript Biotech—performs high-speed gene sequencing. Corne said the company has a huge lab in China that can provide sequencing tests at a fraction of the cost of similar services in the U.S. Genscript, which also has headquarters in Nanjing, raised more than $67 million through an initial public offering on the Hong Kong Stock Exchange earlier this year.

Globalization and the accompanying loss of jobs has been a big issue in the U.S. presidential campaign. Although the lab sector has not been as robust a creator of jobs as other areas of health care delivery, it remains to be seen if U.S. lab jobs could be vulnerable as the industry changes.

Smarason, the Icelandic lab exec with operational toes in two other countries and more to come, doesn't see it as a problem.

"Maybe at some point in the future. But not yet," he said.

Takeaway: Laboratories are not being left behind as the economy globalizes, creating opportunities for foreign operators both inside and outside the United States. G2

ACLA Pushing for Broadening of Coverage for Vitamin D Testing, *from page 1*

The draft local coverage determination released by Novitas mostly reiterates that position: "Vitamin or micronutrient testing may not be used for routine screening. Once a beneficiary has been shown to be vitamin deficient, further testing is medically necessary only to ensure adequate replacement has been accomplished. Thereafter, annual testing may be appropriate depending upon the indication and other mitigating factors."

However, the aging U.S. population has seen an uptick in the cases of osteoporosis, a weakening of bone density that can lead to serious fractures often requiring hip replacements and other expensive orthopedic surgical procedures. Cases of osteopenia—a precursor to osteoporosis—have also risen in recent years. According to data from the National Osteoporosis Foundation, as many as 54 million Americans over the age of 50 either suffer from osteoporosis or relatively low levels of bone mass that put them at risk for developing the disease later in life. That's about 60 percent of that particular age demographic in the U.S.

The ACLA noted that vitamin D deficiency can be linked to individuals undergoing bariatric surgery to address severe obesity. Such procedures rose nearly 15 percent between 2011 and 2013, with 179,000 such procedures performed in the latter year, according to statistics from the American Society for Metabolic and Bariatric Surgery.

Vitamin D deficiencies have also been linked to patients suffering chronic renal disease, as well as those taking steroids and cholesterol-lowering medications over the long-term.

According to data from the National Osteoporosis Foundation, as many as 54 million Americans over the age of 50 either suffer from osteoporosis or relatively low levels of bone mass that put them at risk for developing the disease later in life.

Although the draft LCD currently provides testing coverage for Medicare enrollees diagnosed with rickets, osteomalacia, osteoporosis, chronic kidney disease and some digestive disorders such as irritable bowel syndrome and Crohn's disease, the ACLA wants coverage to include other patients as well.

The organization is asking for coverage of patients who have been diagnosed with cystic fibrosis, undergone bariatric surgery or suffered from radiation enteritis—an inflammation of the digestive system due to radiation treatments for cancer. It is also asking for coverage for patients diagnosed with several forms of lymphoma and histoplasmosis.

ACLA is also requesting some clarity regarding coverage for patients who are taking certain drugs. "We note ... that many times clinicians will report the condition for which those drugs are used rather than the chronic drug use codes," Glisson wrote. "For some of these medications (e.g., HIV therapy, anticonvulsants) there would be a very clear map to the condition for which those drugs are prescribed. We would recommend, therefore, incorporating those conditions into the LCD."

Although vitamin testing is a relatively low-cost assay, if it's adopted as part of routine preventive care, tens of millions of such procedures could be performed in the U.S. and eventually be extensively covered by the Medicare program and Medicare Advantage payers.

Takeaway: The ACLA and other laboratory lobbies are pushing to try to get a longstanding Medicare coverage ban on vitamin testing to be lifted. G2

INDUSTRY BUZZ

Study Suggests Genomic Health Test Could Cut Down Use of Chemotherapy for Breast Cancer Patients

California-based molecular laboratory Genomic Health has released a new European study suggesting that precision medicine for breast cancer patients could significantly improve long-term survival rates for those diagnosed with more virulent strains of the disease.

"A low recurrence score result identifies patients who can be safely spared chemotherapy without compromising outcomes."

— Nadia Harbeck, MD, PhD

The study, which was conducted in Germany and recently published in the *Journal of Clinical Oncology*, focused on the use of Genomic Health's OncoType DX assay, which analyzes tumors and suggests a treatment pathway based on their genetic structure. The study was conducted at more than 90 cancer treatment clinics in Germany and involved nearly 3,200 patients diagnosed with estrogen-receptor positive, HER2-negative, early-stage breast cancer. The median age of the study group was 56. About 41 percent had the cancer spread into their lymph nodes; about one-third had stage three breast cancer.

About 15 percent of the patients in the study with a low score for risk of recurrence of the disease underwent hormone therapy alone, a diversion from the standard of care for most breast cancer patients. The three-year survival rate for that cohort was 98 percent. That was unchanged compared to the cohort of patients with a moderate risk of recurrence who underwent both hormone therapy and chemotherapy. Those patients with a higher risk of recurrence had only a slightly lower three-year survival rate of 92 percent.

"A low recurrence score result identifies patients who can be safely spared chemotherapy without compromising outcomes," said Nadia Harbeck, MD, PhD, head of the breast cancer unit at the University of Munich and one of the study's co-authors.

Over five years, the survival rates without a recurrence of cancer in both the low and moderate risk groups was 94 percent; it was 84 percent among those with a high risk for recurrence.

"The compelling suite of new global prospective outcomes data generated in the last six months proves that tens of thousands of patients worldwide can forgo chemotherapy and its harmful side effects based on a low recurrence score," said Steven Shak, M.D., Genomic Health's chief scientific officer.

Takeaway: Genomic Health's European breast cancer study strongly suggests that many patients being treated for the disease do not need to undergo chemotherapy. G2

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