Put it on the Board, 7/15

AMP puts a cost—and value—to sequencing procedures

July 2015—Amid excitement about the groundbreaking work of unlocking the human genome's secrets to speed diagnosis and target oncologic treatment comes the unpleasant reality that much of this labor now goes unpaid. Getting the American Medical Association's editorial panel to publish nearly two dozen new genomics-related CPT codes for molecular pathology was a vital step, as was having those codes accepted in the Medicare clinical laboratory fee schedule.

But when the Centers for Medicare and Medicaid Services determined that the payment basis for those codes would be gap-filled, that meant that pricing would not be determined until later this year and not take effect until 2016. With Medicaid and private payers following Medicare's lead—or lack thereof—laboratories find themselves with a raft of CPT codes to use when billing their genomic sequencing procedures but no price tag associated with them.

Genomic testing "is expanding in CLIA laboratories, and it's important that these codes get prices," Aaron D. Bossler, MD, PhD, said in a talk at this year's Executive War College. Dr. Bossler is director of the molecular pathology laboratory at the University of Iowa Carver College of Medicine. He also chairs the Association for Molecular Pathology's Economic Affairs Committee.

Setting the right price depends on understanding how much laboratories spend to develop, perform, and maintain a genomic test, as well as the value that assay delivers for patients and for payers, Dr. Bossler said. AMP has come up with a method to do just that, formulating a model to help laboratories calculate their genomic testing costs to the penny while demonstrating—in the sometimes obscure specifications of health economics—the financial merit of these innovative assays.

The association's Genomic Sequencing Procedures Pricing Project Oversight Committee gathered detailed protocols on 13 representative genomic tests from nine laboratories using the Illumina or Ion Torrent platforms. The committee examined the costs associated with each step of the process, such as consumables and supplies, equipment, bioinformatics and reporting, personnel time, and test validation and maintenance.

Dr. Bossler

Some assays, such as test code 81430—a genomic sequence analysis for hearing loss—showed relatively little variation, with the cost per test ranging between $1,899 and $1,949, Dr. Bossler said. Others showed a much broader array of costs. For example, code 81415—for exome sequence analysis—found laboratory expenses ranging from $1,639 to $3,142.

AMP also examined the value proposition of three genomic sequencing procedures, contrasting current pathways that leave genomic testing for last with new paradigms in which sequencing is done earlier in the patient's evaluation. In some areas, the proposed pathway would save payers money, Dr. Bossler said. If a targeted multiple gene sequencing test were done immediately after hearing loss was confirmed, the cost per diagnosis would add up to $4,106. That is less than a third of the current tally of $15,498 per diagnosis, says the AMP analysis.

"This really helps on this problem of the diagnostic odyssey, where it's not entirely clear what the diagnosis is for

the patient, and you end up spending a lot of money on single-gene tests, procedures, imaging studies, all those sorts of things that add to the cost of doing this," Dr. Bossler said.

In the case of an exome sequencing-first approach to undiagnosed neurodevelopmental disorders, AMP estimates the cost per diagnosis would be $9,484, less than half of what it costs under the current care pathway.

"Again, we are showing that using this very powerful technology is extremely helpful for these patients. And, hopefully, we'll be able to convince payers that that is the case," Dr. Bossler said.

The economic case for expanding genomic testing for patients with non-small cell lung cancer was not as strong. Compared with the current standard of doing *EGFR* and *ALK* mutational analysis, a new pathway expanded to look for a number of other markers that the National Comprehensive Cancer Network has tabbed as potentially useful in targeting NSCLC treatment would actually cost about $2,500 more. That is likely due in part to the fact that this alternative approach would boost—from six percent to 30 percent—the proportion of patients receiving targeted therapy. However, the new pathway would be expected to improve patient outcomes and dramatically reduce adverse events.

More information about AMP's genomics pricing model, including a step-by-step video tutorial for laboratories interested in using it, is available at http://j.mp/amp_pricing. At press time, the CMS was set to hold a July 16 meeting in Baltimore to accept public comments on payment for new test codes for 2016. The agency will post preliminary pricing determinations in September, to be followed by a 60-day comment period. The final pay rates for the new codes will be unveiled in November, along with the final fee schedule.

It may be an uphill battle for next-generation sequencing to get its due from payers, Dr. Bossler said.

"It will have to be a lot of folks speaking up, including the patients who will benefit from these things, before we're going to get a whole lot of traction."—*KBO'R*

Liquid biopsy seen as one disruptive technology

Forces potentially disruptive to mainstream clinical laboratory practice lie ahead, Gregory J. Tsongalis, PhD, director of molecular pathology and clinical genomics at Dartmouth's Geisel School of Medicine, said in a War College presentation in May.

"I want to share with you a couple of things that are going to change everything," Dr. Tsongalis said. The first is the vast potential of the humble blood test made possible by what is being dubbed the liquid biopsy.

"This whole idea that is now catching on pretty quickly is the idea of cell-free DNA in the plasma. We've already seen it work very nicely for noninvasive prenatal testing, and now people are starting to look at it for other types of variants in the genes. In your plasma, there's DNA floating around outside of a cell that represents some tissue or some cell population in your body. In cancer patients, we know that the cell-free DNA reflects the tumor, and that we can find the same mutations in the cell-free DNA that are in the patient's tumor . . . and that will be used to monitor patients," he said.

"This is really a game-changing type of technology for the way we assess cancer patients," Dr. Tsongalis said.

The second trend on the rise—and one that may be even more difficult for laboratories to reckon with, he said—is the emergence of wearable and implantable diagnostics and technology that can make a diagnosis based on breath.

"Just like we can identify different compounds by mass spectrometry, in your breath there are different compounds that can mimic, or reflect, or correlate back to a particular disease process you might be experiencing," Dr. Tsongalis said. "We have data in the laboratory now with mice . . . where we put a little cone over the mouse's nose and they breathe into this little bag for about a minute. Then we inject that breath into a mass spectrometer and we get profiles of those different compounds . . . that allow us to determine what the bacteria is that's

infecting the mouse's lung within three minutes."

Moreover, chips implanted under the skin could allow for ongoing blood monitoring.

"What happens if we put probes on these chips—which we know we can do—and put those probes in and inject it, and it monitors the cell-free DNA in your plasma?" he asked. "Those are the types of things that I think will be really disruptive."

Wearable and implantable diagnostic devices paired with smartphone technology could threaten the laboratory's traditional role within the health care encounter, Dr. Tsongalis added.

Dr. Tsongalis

"What's happened is that we've come an enormous way, and things have gotten much, much smaller, much quicker and much better. But I think the role we play in the clinical laboratory—in how things get paid for, how things get assessed, and how patients get managed—is going to change even more dramatically as our role changes from somebody that's a keeper of specimens to somebody that's really a keeper of data."

On that note, Dr. Tsongalis said he and his laboratory colleagues at Dartmouth are moving into a new, 11,000-square-foot laboratory space and that 25 percent of the footprint is dedicated to data analysis.

"It looks like Central Command," he said.—*KBO'R*

OPKO to buy Bio-Reference

OPKO Health and Bio-Reference Laboratories have signed a definitive merger agreement under which OPKO will acquire BRLI. Under the terms of the deal, already approved by the two companies' boards of directors, holders of BRLI common stock will receive 2.75 shares of OPKO common stock for each share of BRLI common stock. Based on a closing price of $19.12 per share of OPKO common stock on June 3, 2015, the transaction was valued at about $1.47 billion, or $52.58 per share of BRLI common stock. The companies expect the transaction to be completed during the second half of 2015.

OPKO intends to leverage the national marketing, sales, and distribution resources of BRLI to enhance sales of its 4Kscore test—a blood test that provides a patient's specific, personalized risk score for aggressive prostate cancer—as well as other OPKO diagnostic products under development. Through GeneDx and GenPath Diagnostics, BRLI has accumulated genetic and genomics data that OPKO plans to make available to industry and academic scientists to enhance their drug discovery and clinical trial programs.

OPKO intends to allow BRLI's laboratory operations to continue seamlessly, but with enhancement from its pipeline of diagnostic products. The diagnostic services of OPKO will be merged with BRLI operations.

Ventana gets OK for crizotinib IHC companion Dx

Ventana Medical Systems announced the FDA's approval of the Ventana ALK (D5F3) CDx Assay as a companion diagnostic to help identify patients for crizotinib, marketed as Xalkori by Pfizer. The Ventana ALK Assay was approved as a CE-IVD in Europe in 2012 and by the Chinese Food and Drug Administration in 2013. With this U.S. FDA class III approval, ALK IHC testing is accessible on Ventana BenchMark immunohistochemistry instruments worldwide, can be integrated into standard lab workflow, and offers fast test results with a binary, straightforward scoring method.

“The test provides physicians and patients a fast and accurate method to identify ALK protein expression, and clinicians can be confident knowing that our FDA approval is based on data resulting from collaboration between Ventana and Pfizer,” Mary Padilla, MD, senior director of pathology and medical director for Ventana Companion Diagnostics, said in a statement. “Ventana used the Ventana ALK (D5F3) CDx Assay and scoring method to retrospectively test patient samples from Pfizer-sponsored clinical trials and demonstrated that the test is effective in identifying patients with *ALK*-positive NSCLC who may benefit from treatment with Xalkori.” Ventana is a member of the Roche Group.