Put It on the Board, 9/16

AMP lays out clinical utility standard for molecular Dx

The Association for Molecular Pathology has published a 14-page report its leaders hope will reset the conversation payers, policymakers, and medical guideline panels have when assessing the clinical utility of molecular diagnostics in oncology and inherited diseases. The key to AMP's approach is to broaden the standard for what is considered a clinically useful molecular diagnostic test.

"We tried to take an inclusive approach and look at patients, providers, and clinicians, and we tried to address clinical utility from all those standpoints," says Elaine Lyon, PhD, co-chair of the AMP Framework for the Evidence Needed to Demonstrate Clinical Utility Task Force. The panel met for two years to develop the document, "The Spectrum of Clinical Utilities in Molecular Pathology Testing Procedures for Inherited Conditions and Cancer: A Report of the Association for Molecular Pathology" (Joseph L, et al. *J Mol Diagn.* 2016;18[5]:605–619).

"In our discussions, it became apparent that this needed to be patient-centered," says Dr. Lyon, senior author of the report and medical director of genetics, genomics, and pharmacogenomics at ARUP Laboratories. "We've also tried to describe the many types of utilities that these tests can be used for.

So, rather than a therapeutic-only type of definition—if you give this drug, do patients fare better?—we have expanded that to say, 'Does this information give an accurate diagnosis, and can it detect what the disease course is likely to be?' There's more to this than simply finding the right drug at the right dose. That's an important definition, but it's too narrow."

The AMP report offers this more ambitious standard for clinical utility in molecular diagnostics: "the ability of a test result to provide information to the patient, physician, and payer related to the care of the patient and his/her family members to diagnose, monitor, prognosticate, or predict disease progression, and to inform treatment and reproductive decisions."

In the report, Dr. Lyon and her co-authors point to the example of microsatellite instability testing. A narrow standard of clinical utility would judge solely whether MSI testing led a treatment change that improved survival for patients with MSI-positive tumors compared with patients who have MSI-negative tumors.

"A different end point," the report's authors suggest, "may show that testing of a proband with an inherited mutation of the MSI pathway led to identification of relatives who are carriers of the mutation and that identified carriers fared better than unscreened relatives."

AMP's report (available in full at http://bit.ly/amp_clinicalutility) comes amid great scrutiny of payment for molecular testing procedures. The watchword of such explorations has been whether the results of molecular diagnostic testing are "clinically actionable." That modus operandi sells short the value of molecular diagnostics, argues Dr. Lyon, professor of pathology at the University of Utah School of Medicine.

“We need to recognize that everything centers around a correct diagnosis,” she tells CAP TODAY. “If the physician is only treating the symptoms of the disease without knowing what the disease is, that’s a problem. Even if, with the result, the physician can only say, ‘There’s nothing more we can do,’ that’s a medically important answer for the clinician and the patient.”

Along those lines, AMP’s report suggests ways to expand the CDC’s model for evaluating genetic tests (available at http://bit.ly/cdc_accemodel) to recognize that all “therapeutic options are interventions, even when they are not curative.” Examples provided include monitoring and patient management. Likewise, in judging the effectiveness of molecular diagnostics, clinician utility ought to be considered, Dr. Lyon and her co-authors argue. That should encompass “diagnostic, therapeutic, prognostic, and predictive management (even in the absence of therapy),” the report says.

The clinical utility of some molecular diagnostic tests are only revealed with time, Dr. Lyon adds.

“It becomes a circular argument that a particular test needs to demonstrate clinical utility, but until it does, it is poorly valued,” she says. “If it’s poorly valued, testing isn’t reimbursed and funding isn’t available for research, and then you can’t collect the information to demonstrate the full value.”

This report does not address cost-effectiveness, which was the subject of a previous AMP report (Sabatini LM, et al. *J Mol Diagn.* 2016;18[3]:319–328) and a presentation at last year’s Executive War College (see “AMP puts a cost—and value—to sequencing procedures,” CAP TODAY, July 2015, page 114).

If the status quo on judging molecular diagnostics’ clinical utility remains unchanged, then “the big picture is that the realization of precision medicine won’t happen,” Dr. Lyon says. “We need to put in place a structure where we can realize the benefits of precision medicine.”

In an accompanying commentary, Daniel H. Farkas, PhD, HCLD, writes that the AMP report’s authors “make the case that current requirements for a laboratory to demonstrate clinical validity and clinical utility for a genetic test or service are not only onerous but also limit the recognized value of genetic test results. Laboratories cannot sustain services if they continue to perform tests without sufficient payments, or they may resort to acting as gatekeepers, assessing the suitability of test requests. Physicians may oppose this interference in their delivery of medical care” (*J Mol Diagn.* 2016;18[5]:635–637).

In an interview with CAP TODAY, Dr. Farkas says the AMP report is worthy of “applause” because it clarifies “the nebulousness and vagueness” that have circulated around payers’ definitions of clinical validity and utility.

“It’s a tug of war between those who are billing for their services and those who are expected to pay for the services,” adds Dr. Farkas, section head, molecular pathology, Cleveland Clinic. “If a test clearly makes a difference in the way a physician is going to manage his or her patient and there is no dispute in the clinical community that you need to do test X for a patient with condition Y, then presto—you get paid. But molecular diagnostics can do so many other things.”

Dr. Farkas says he fears AMP’s report, and even his own commentary, “may be preaching to the choir.” He says AMP’s clinical utility standard needs to be seen in the pages of high-impact journals and considered in health plan boardrooms. Dr. Lyon says the development of AMP’s report came in response to queries from other stakeholders who sought formal input from the molecular pathology community.

“We wanted to have something in print that we could take out and help get a new discussion started,” Dr. Lyon says. “We are engaging payers and CMS, and what we’ve realized is that we are learning from them too. We are educating them from our point of view. And we are learning what they need from us, and we are seeing if we can come to a path forward to collect the types of evidence that will give them the confidence about which tests are performing well, have clinical validity, and meet a reasonable-and-necessary standard. It is a conversation.” —Kevin B. O’Reilly

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Alere’s RSV test cleared

The FDA has given Alere 510(k) marketing clearance for its point-of-care test to detect respiratory syncytial virus infection in children and adults. The RSV test is the latest offering on the Alere i platform and is the first molecular test that can be used at the point of care to detect RSV in 13 minutes or less, the company said.

Alere said it will soon submit an application for CLIA waiver of its RSV test. Alere i testing applications for streptococcus A and influenza A and B are CLIA-waived.

Alere’s RSV test detects the virus in nasopharyngeal swab samples using the company’s isothermal nucleic acid amplification technology. Alere said the test is faster than conventional PCR tests. In clinical performance studies, the overall sensitivity and specificity of the i RSV using direct NP swab samples was 98.6 percent and 98 percent, respectively, versus PCR. With viral transport media samples, the sensitivity and specificity of the i RSV was 98.6 percent and 97.8 percent, respectively, versus PCR.

The Alere i RSV test will be available for use in hospitals in time for the 2016–2017 flu and respiratory illness season.
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HHS announces $15.5 million for rapid Zika tests

The Department of Health and Human Services in August announced separate funding agreements with OraSure Technologies, Chembio Diagnostic Systems, and DiaSorin Group aimed at speeding the development of Zika diagnostic tests.

Nearly half of the money, $7 million, will go to OraSure, of Bethlehem, Pa., to help the company develop a point-of-care test. The HHS will provide the funding over the next three years to support the product’s continued development, manufacturing preparations, and the clinical testing needed to apply for clearance from the FDA.

The agency has the option to fund additional work through 2022 for as much as $16.6 million total to OraSure. During development, the company also could request that the FDA issue an emergency use authorization for the lateral-flow serological test.

Chembio Diagnostics, of Medford, NY, also is developing a POC lateral-flow serological test and will get $5.9 million from the HHS over the next year. That contract could be extended for up to three years and a total of $13.2 million.

DiaSorin Group, based in Italy, will get $2.6 million for work on an automated laboratory test for its Liaison XL system. That platform can test up to 120 samples at a time and generate results within an hour.
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MammaPrint may help more women avoid chemo

Agendia announced the primary outcome results of the MINDACT clinical trial, which demonstrated that 46 percent of breast cancer patients with tumors classified as low risk by the MammaPrint 70-gene signature have excellent survival without chemotherapy and can thus be candidates to forgo it.

Of the 6,693 patients in the trial, 23.2 percent were deemed to have high clinical risk and low genomic risk. Among these patients, the ones who skipped chemotherapy had a five-year survival rate without distant metastasis that was 1.5 percentage points lower than that of similarly risk-stratified patients who did receive chemotherapy (Cardoso F, et al. *N Engl J Med.* 2016;375[8]:717–729).

In a NEJM editorial, Memorial Sloan Kettering oncologists Clifford Hudis, MD, and Maura Dickler, MD, commended

the MINDACT trial’s efficient research model but said the study’s result is “statistically underpowered.” The survival “difference does not precisely exclude a benefit that clinicians and patients might find meaningful,” they added.[hr]