For precision medicine, next-generation mass spec

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February 2018—The modern analytical technologies of mass spectrometry continue to garner prominence and broader utility in clinical diagnostics. This was showcased at the 7th Annual American Association for Clinical Chemistry Conference on Mass Spectrometry and Separation Sciences for Laboratory Medicine, held last fall in Philadelphia. Representatives of academia, industry, and regulatory bodies came together to share information about the technology and best practices, the aim of which is to strengthen clinical diagnostics for the betterment of patient care. In opening remarks, then CAP president Richard Friedberg, MD, PhD, shared his hopes for the future of mass spectrometry in anatomic pathology.

Here are highlights of six of the 19 conference presentations.

Michael J. Bennett, PhD, then AACC president and a professor of pathology and laboratory medicine, University of Pennsylvania Perelman School of Medicine and Children's Hospital of Philadelphia, gave a plenary on newborn screening and metabolomics. His presentation served as a history on the metabolomic roots of clinical mass spectrometry and spotlighted newborn screening as its most successful assay. Outcome studies show great benefit from the early identification of some metabolic diseases, most notably medium-chain acyl-CoA dehydrogenase deficiency, which is the most commonly identified disorder in the U.S. newborn population. As the technology advances, Dr. Bennett said, the potential for early diagnosis of many more metabolic diseases by mass spectrometry is clearly possible. The CDC considers newborn screening for metabolic diseases one of the top 10 health achievements of recent decades.

Yusheng Zhu, PhD, professor of pathology, medical director of clinical chemistry/automated testing laboratory, and co-director of the pathology core reference laboratory at Penn State University Hershey Medical Center, discussed issues related to total, free, and bioavailable testosterone testing and how to appropriately use the tests in clinical practice. He highlighted applications of testosterone testing in various patient populations, including men, women, and children, as well as the pros and cons of different methods. LC-MS/MS has become an attractive method for testosterone testing owing to its higher sensitivity, specificity, and reproducibility than immunoassays. Hence, it has emerged as the method of choice for testosterone testing in women, children, and hypogonadal men. Dr. Zhu also highlighted the practice guidelines and position statements of several professional organizations. It is recommended that a reliable total testosterone assay be used for initial testing for men. If initial values are low, free or bioavailable testosterone should be used for confirmation.

Nigel J. Clarke, PhD, vice president for technology and solutions development at Quest Diagnostics, gave a keynote address on phenotyping for pharmacogenomics and precision medicine. He provided a look at the role of precision medicine as it relates to mass spectrometry and genetics, specifically the treatment of breast cancer with tamoxifen and its metabolites. Dr. Clarke defined pharmacokinetic/pharmacodynamic relationships and their role in the use of pro-drugs such as tamoxifen in the face of the various genetic mutations in the *CYP* family, and he discussed the use of individual patient phenotypic metabolite measurements. He presented data from the use of a CLIA validated assay using LC-MS/MS to measure tamoxifen, the main active metabolite endoxifen, and multiple other active metabolites, including the newly discovered norendoxifen. These data showed the inter-patient variance in production of the metabolites as well as blocks within the metabolic pathways that may lead to patients not receiving optimum exposure to endoxifen owing to their genetics, physiology, diet, and lifestyle. Furthermore, he presented data showing an increase in endoxifen levels with increasing tamoxifen dose in low metabolizers and that ultra-metabolizers could lower their dosage and still obtain sufficient coverage while reducing debilitating side effects.

Steven Wong, PhD, past AACC president and professor of pathology and director of clinical chemistry and

toxicology, and co-director of the Clinical and Translational Mass Spectrometry Center, Wake Forest School of Medicine, provided an update on the opioid epidemic and pain management. He reviewed the potential applications of adjunct pharmacogenomics and pharmacometabolomics for pain management and addiction. The number of opioid deaths was 22,598 in 2015; it exceeded 30,000 in 2016.

Clinical pathology colleagues have helped to combat the epidemic by offering drug screenings and confirmations with immunoassays and mass spectrometry. Translational (Donaldson K, et al. *Ann Clin Lab Sci.* 2017;47[4]:452–456) and selected postmortem investigations further established possible roles for pharmacogenomics and pharmacometabolomics. By determining variations of 16 genes/single nucleotide polymorphisms in a neuropathology panel, opioid addiction risk could be predicted by use of an algorithm. Postmortem methadone investigations suggested risk assessment by screening for *CYP2B6, CYP3A4*, and μ-opioid receptor gene variations. Dr. Wong demonstrated, for pain management, the combinational use of mass spectrometry and clinical chemistry analyzers in assessing 10 urinary metabolites with acceptable reproducibility. These findings pointed to the potential applications of combinational pharmacogenomics and pharmacometabolomic biomarkers for precision medicine for pain management and opioid addiction.

Robert A. Middleberg, PhD, senior VP of quality assurance and operations and laboratory director, NMS Labs, gave a plenary presentation further addressing laboratory and toxicological issues surrounding the opioid epidemic and novel psychoactive substances. He reviewed how both arose, their continuing burden on society, and how they are not fads but problems that are likely to be a new norm. He also described the difficulty in creating legislation that effectively controls these compounds. He addressed designer opioids, synthetic cannabinoids, new hallucinogens and dissociative agents, and novel benzodiazepines, including brief exploration of their pharmacology and toxicology. The landscape of these substances changes rapidly, which presents remarkable challenges for laboratories trying to keep up analytically. These challenges range from determining the proper processes to use to stay relevant, to detecting compounds and their metabolites using techniques that can capture many compounds at once (e.g. LC-TOF), to the availability of reference materials. He closed with a description of the contemporary proficiency testing challenge created by the CAP to facilitate quality-based laboratory assistance with these epidemics.

Judy Stone, PhD, of the toxicology/mass spectrometry laboratory, University of California San Diego Health Center for Advanced Laboratory Medicine, gave a talk on reducing variance in clinical LC-MS/MS assays based on cases from clinical practice. She reviewed instrument technical and theoretical knowledge, troubleshooting tools, process elements, and quality assurance monitoring. She provided practical knowledge on troubleshooting and noted that complexity is one of the major challenges in implementing and operating mass spectrometry in clinical laboratories. The complexity of LC-MS/MS instrument systems and laboratory-developed tests is typically characterized as negative, but Dr. Stone suggested an alternative view, which is to see such complexity as an opportunity. Laboratory-developed tests on open LC-MS/MS systems make possible improved sensitivity, selectivity, adaptability, and reproducibility at lower cost compared with simpler, closed FDA-approved devices. Instrument vendors have responded to customer concerns about the difficulty of operating LC-MS/MS systems such that software and hardware have become easier to use. Still, she said, obtaining the best value from these requires skilled clinical laboratory personnel, well vested in the finer aspects of maintenance and troubleshooting of modern analytical instrumentation.

The 8th annual conference will take place Oct. 4–5 in Philadelphia.
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