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23andMe's Approval Marks 'Baby Step' in DTC

While personal genetics company 23andMe (Mountain View, Calif.) was granted authority by the U.S. Food and Drug Administration (FDA) in late February to market the first direct-to-consumer (DTC) genetic test, experts say this does not mark a return to business-as-usual for the company. Rather, this approval marks a "baby step" in establishing a pathway for DTC testing to receive a regulatory nod and is notable for the FDA's classification of carrier status testing as a class II device with low to moderate risk, exempting them from premarket review.

The approval of the carrier test for Bloom Syndrome, a rare, autosomal recessive disorder, comes just 15 months after 23andMe received an FDA warning letter calling for discontinuation of marketing of the company's Personal Genome Service (PGS) due to a lack of submitted evidence of the service's safety and evidence. Unlike PGS, a comprehensive DTC genetic assessment of 254 diseases and conditions, the Bloom Syndrome Carrier Status test is very limited in scope and results are very clear-cut.

"These DTC panels have not been very predictive for common diseases," explains A. Cecile Janssens, Ph.D., Emory University (Atlanta). "The problem is in genes like BRCA 1/2, where thousands of mutations have been documented, but only a few are tested for. Compared to complex etiologies, like breast cancer, Bloom is a clear syndrome with a 'simple' genetic etiology. There is only one gene for the disease."

Continued on page 2

Routine Mass Spec Urine Drug Testing Gaining Traction

More than half of urine samples from addiction treatment patients tested using mass spectrometry-based techniques show some level of unexpected drug use, according to a study published in the January/February issue of the *Journal of Opioid Management.* These results, the authors say, demonstrate the high number of cases of ongoing drug use or relapse missed by immunoassay urine drug testing (UDT).

Immunoassay testing (IA) had its roots in point-of-care testing for forensic applications but was adopted in addiction treatment practice due to its quick, cheap nature. The tests are also limited due to their targeting of specific drug

Continued on page 3

23andMe's Bloom Test Approval Marks 'Baby Step' in DTC Testing, *Continued from top of p.1*

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>
> *—Kathy Hibbs, 23andMe*

While 23andMe founder and CEO Anne Wojcicki called the approval a "major milestone," 23andMe said in a statement that the company would not immediately begin offering the Bloom Syndrome Carrier Status test "or other health results," until it completes the regulatory process for additional tests and can offer "a more comprehensive product."

Proponents of DTC hail this approval as affirmation of the right of consumers to understand their own genetic information. But industry watchers say the FDA's approval was notable for establishing autosomal recessive carrier screening tests as class II devices with the intention to exempt such carrier tests from FDA premarket review due to their low to moderate risk. While the Bloom test went through the de novo process due to a lack of applicable predicate device, it may now be used as a predicate for future 510(k) submissions. In addition to demonstrating accuracy of the test, as a first-of-its kind DTC test, 23andMe showed evidence that consumers could understand the test instructions and collect an adequate saliva sample, as well as understand the results. Additionally, the FDA is not limiting who should or should not use these tests.

"This regulatory process helped establish the parameters for consumer genetics. We are pleased with the Agency's decision and its affirmation that consumers can understand and benefit from direct access to genetic information," said Kathy Hibbs, 23andMe's chief regulatory and legal officer, in a statement.

Janssens tells *DTET* that the future market for DTC testing remains uncertain. Of all genetic tests currently offered as DTC, expanded carrier screenings seem most straightforward. However, they are likely to permeate standard pre-conception care. While a DTC market for carrier testing may emerge, for $99 it will not be feasible for DTC companies to do the pre-counseling typically advised for sequencing-based mutational analysis. The challenge for DTC will be in receiving regulatory approval for DTC assessment of common diseases, an area where genetic testing has so far been challenged to produce highly predictive results.

"There are only a handful of conditions like macular degeneration and Alzheimer's disease that while not perfectly predictive, enough people may want to know," says Janssens. "For common diseases DTC genetic testing will likely end because it is simply not predictive enough. Too many other risk factors are involved in causing diseases like asthma and type 2 diabetes to use genetics to predict."

Vivek Wadhwa, director of research at Center for Entrepreneurship and Research Commercialization at Duke University (Durham, N.C.) believes the cat may already be out of the bag. He tells *DTET* that while the FDA is trying to manage DTC genetic testing in a "sensible way," he predicts that genomic interpretation will be an "unstoppable force" and part of the "app economy" in 10 to 20 years, with entrepreneurs (including overseas developers) disrupting the medical industry.

Takeaway: The FDA's recent approval of 23andMe's Bloom Syndrome carrier test marks a first step towards future regulation of DTC tests. While additional carrier tests will likely be the next DTC tests approved, the viability of a commercial market for future, comprehensive personal genomics tests remains unclear.

Routine Mass Spec Urine Drug Testing Gaining Traction, *Continued from bottom of p.1*

classes (i.e., amphetamines, barbiturates, benzodiazepines, and opiates). So, confirmatory testing with mass spectrometry-based tests are often necessary to verify the accuracy of IA results. Clinicians are increasingly recognizing the need for comprehensive, yet specific UDT, which is driving testing towards mass spectrometry (MS).

"Confirmation of negatives has not historically been part of the quasiforensic use of UDT in addiction treatment and this seems to be in need of change."

—Steven Passik, Ph.D.

Researchers from Millennium Research Institute (San Diego) analyzed 4,299 samples from the company's laboratory database (Q1 2013) sent in from addiction treatment and recovery practices that consistently report medication lists to the laboratory. Samples all underwent liquid chromatography tandem MS (LC-MS).

The vast majority of LC-MS results (92.6 percent) were positive for one or more substances. Less than half (48.5 percent) of the results were categorized as in full agreement with practice reports. The remaining 51.5 percent of samples fell into one of seven categories of unexpected results, with the most frequent being detection of an unreported prescription medication (n = 1,097; most often an amphetamine, tramadol, or an opiate) or detection of an unreported nonprescription medication (n = 1,097; most often cannabinoids and alcohol).

Comparison IA and LC-MS results yielded the "most striking" results, the authors report. IA had a "high rate" of missing drug abuse, which the authors call "profound." Specifically, the most actual positive results missed by IA were for amphetamines (43.9 percent, n = 112) followed by a 40 percent miss for barbiturates and cocaine (n = 34 and n = 38, respectively). False positive IA results were highest for phencyclidine (PCP; 100 percent of the 32 actual cases), 3,4-methylenedioxy-N-methylamphetamine (99.5 percent; n = 182) and tricyclic antidepressants (76.2 percent; n = 144).

"Addiction treatment providers have borrowed not only a methodology of testing reflective of UDT's forensic roots, but also a mindset. In forensic testing, only positive results are typically sent to the lab for confirmation," writes co-author Steven D. Passik, Ph.D., explaining that confirmation is necessary because of the potential legal consequences. "Our results show that this confirmation of positives with LC-MS is often merited due to the limitations of IA methods. However, the confirmation of negatives has not historically been part of the quasiforensic use of UDT in addiction treatment and this seems to be in need of change."

The Future of MS-Based Testing in Addiction Practice

The authors acknowledge that the cost of IA and LC-MS testing can vary by 10-fold, which raises questions regarding the financial impact of incorporating routine, nonconfirmatory MS testing into addiction treatment practice. The answer to this question, Passik says, requires a staged approach which will utilize more frequent testing to those who are newly sober ("to ritualize adherence" with a regimen that aids accountability) and less frequent testing in those demonstrating long-term sobriety. The American Society of Addiction Medicine December 2013 white paper recognized that drug testing technology "can and should" play a larger role in helping to deter unhealthy drug use, but the paper stopped short of making recommendations regarding testing frequency or strategy. Now, a consensus group of addiction professionals are drafting a forthcoming set of recommendations that are anticipated to address frequency of testing by suggesting a schedule of early IA sobriety testing three times a week, with one sample randomly sent to the laboratory for definitive (not

confirmatory) LS-MS testing. Passik says these recommendations could represent a "pretty big" shift in testing once engrained in routine addiction treatment practice.

Takeaway: There will be a noticeable shift in UDT towards MS-based tests for definitive, nonconfirmatory results. Use of this sensitive test will uncover lapses earlier in the addiction treatment process than IA. G2

Universal, Extensive MRSA Screening Too Expensive for Hospitals

Many policymakers have called for universal, hospital-based screening for methicillin-resistant Staphylococcus aureus (MRSA) as a means of potentially preventing hospital acquired infections. While some states have gone so far as to enact laws requiring MRSA screening upon admission, new research shows that such screening is too costly for hospitals.

"Screening for MRSA is becoming an accepted weapon against the spread of these antibiotic-resistant infections, but little thought has been given to how a hospital would actually implement such a program," said James McKinnell, M.D., from the Los Angeles Biomedical Research Institute, in a statement.

McKinnell and colleagues presented two abstracts at the ID Week conference (Oct. 7-12, 2014; Philadelphia). In the first study the researchers modeled the economic impact for a hospital to start universal MRSA screening for all inpatients and contact precautions for MRSA carriers. The models incorporated several screening strategies including the addition of non-nares MRSA screening and comparison of chromatogenic agar versus PCR-based screening.

The researchers found the cost of universal MRSA screening and contact precautions outweighed the projected benefits generated by preventing MRSA-related infections, resulting in a cost of $103,000 per 10,000 admissions. More MRSA-colonized patients were identified with non-nares screening and PCR-based testing. This averted more MRSA infections, but at an increased cost.

Relatedly, the researchers further modeled the economic impact of MRSA screening using three body sites (nares, pharynx, and inguinal folds) and presumptive isolation for high-risk admissions. The costs of screening and isolation exceeded savings generated by preventing MRSA infections. Nares screening and contact precautions prevented 0.6 infections per 1,000 high-risk admissions, with a net financial loss of $36,899. More extensive screening using three body-sites prevented 0.8 infections per 1,000 high-risk admissions, but at an even greater financial loss of $51,478. Three body-site surveillance, the researchers say, could be cost-neutral in targeted populations at risk for high-complexity infections (e.g., prosthetic joint infections or post-operative mediastinitis), when incorporating "optimistic estimates" for the efficacy of isolation for preventing new MRSA infections.

"Our results are surprising because we know that preventing MRSA infections is better for the health care system as a whole, but the rewards of this effort do not seem to come back to the hospital in a meaningful way," said McKinnell.

Takeaway: Employing universal MRSA screening is not a cost effective, infection control strategy. The cost of employing either universal screening or more extensive, three-site screening outweighs a hospital's savings from prevented cases. G2

Inside The Diagnostics Industry

More Comprehensive View of Laboratory Automation Unfolding

When you ask most in the laboratory industry about automation, robots come to mind. But this is increasingly too narrow a view of the trends occurring in laboratory automation. Labs of all sizes are recognizing that task-focused, automated equipment must be integrated and coupled with information technology (IT) solutions in order to create a comprehensive automated system.

Cost constraints fueling demand for greater efficiency, shortages of qualified laboratory personnel, and quality improvement pressures including for more seamless transmission of laboratory results are all driving interest in lab automation. While system design will vary by laboratory, the "right" solution can better workflow, speed turnaround time (TAT), improve standardization and test quality, while accommodating future growth.

Total laboratory automation solutions can be a daunting and expensive prospect. So smaller labs, with space and budgetary constraints, often instead implement a piecemeal strategy of modular automation with flexible benchtop or stand-alone solutions. Task-focused automation (like barcoding systems, spectrophotometric technologies for sample inspection, and robotic-assisted sorting, racking, centrifuging, and aliquoting) can reduce clinical laboratory errors associated with preanalytical and postanalytical processing of specimens. Such task-oriented automated solutions are most common in traditional chemistry and immunochemistry areas, but are expected to move into areas that have never seen widespread automation like microbiology and histology. But experts tell *DTET* that to really take advantage of automation solutions, implementation must extend beyond individual tasks and empower the entire testing process—from sample ascension to delivery of results.

"Automation is an extremely narrow term for what we are doing," says Franz Walt, CEO of the Chemistry, Immunoassay, Automation, and Diagnostics IT business unit at Siemens Healthcare Diagnostics (Tarrytown, N.Y.). "It's an oversimplification. We are optimizing the entire laboratory workflow."

Beyond Equipment

At its simplest form, lab automation is task oriented. But, experts say the real success of automation and favorable return on investment occurs when laboratories think of automation from a systems perspective.

"Laboratory automation is a transformational process. The transformation is not just a matter of technology but also our ability to use it," explains Joe Liscouski, executive director at the Institute for Laboratory Automation. "We have to broaden our view of what laboratory automation is about. It is more than just dealing with liquid handling systems and robotics but also the ability to apply them."

Liscouski says that this shift in understanding automation requires acknowledgement that laboratory automation is a process. To embrace this shift from a task-level focus to a processes approach requires the recognition that software, robotics, and instrumentation are the tools needed to assist with tasks in order to achieve the ultimate goal of an automated system.

Inside The Diagnostics Industry

"A key issue is the need for integration, taking a comprehensive view of the entire process of data acquisition, data management and information delivery."

—Emerging Trends in Laboratory Process Management

"The ROI calculation is not just a matter of dollars and cents, but also includes human factors, safety, data integrity, streamlining operations across the organization," says Liscouski. "We have to take into account not just work that is done on the lab bench, but also how we work with the resulting data in lab wide applications such as laboratory information management systems, electronic laboratory notebooks, and the whole range of laboratory informatics."

Lab automation and IT can no longer be viewed separately. "Process management" has been defined as integrating process control with data management to provide accurate, actionable, and timely diagnostic information as the centerpiece of high-quality care.

The Impact of Siemens Automated Solutions

Siemens Healthcare Diagnostics (Tarrytown, N.Y.) is the current market leader in installations of automated laboratory systems. The company embraces the holistic view of automation in developing customized laboratory solutions, which leverage diagnostics IT to realize the comprehensive vision of every laboratory—to expeditiously and efficiently deliver highly accurate diagnostic information that impacts clinical care.

"A key issue is the need for integration, taking a comprehensive view of the entire process of data acquisition, data management and information delivery," according to the Siemens Healthcare Diagnostics white paper *Emerging Trends in Laboratory Process Management*. "It includes all the steps required to acquire diagnostic data—from patient specimen collection to sample accessioning, measurement, analysis and quality control—and then to deliver actionable information to clinicians. If we think about this as a continuum rather than discrete steps, then we can begin to tear down the walls between instrument analytics, middleware and LIS. By the same token, data acquisition, data management, quality control and process control should be viewed as an integrated process."

Siemens shared with *DTET* the implementation approaches of several recent laboratory automation clients to illustrate the impact of automated solutions on operations and to highlight lessons for laboratories considering future implementation.

In 2012, National Health Service Tayside (United Kingdom) became the first laboratory in northern Europe to deploy Siemen's Aptio Automation system. The Ninewells Hospital Laboratory consolidated four laboratory disciplines (chemistry, immunology, hematology, and hemostasis) on a single 75-foot track that features multiple input routes and centrifuges; automates decapping/recapping, aliquoting, and sealing/unsealing functions; and allows for refrigerated storage of 15,000 tubes—all centrally managed by the CentraLink Data Management System.

NHS Tayside serves a population of 480,000 through a network of 22 hospitals and infirmaries and 69 general-practice sites that rely on two laboratories. With the automated system in place, the laboratory can process as many as 7,000 tubes a day on the track (1,700 tubes an hour at peak times), which is a 20 percent increase in workload

Inside The Diagnostics Industry

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> *—Bill Bartlett, Ph.D.*

with no additional staff. TAT improved across the board with a median TAT of 41 minutes and 95 percent of work completed in 67 minutes.

These efficiencies have directly impacted the business case at Ninewells Hospital Laboratory. Increased capacity allowed Ninewells Hospital laboratory to take on 73 percent of the testing historically performed at the smaller Perth Royal Infirmary (PRI) laboratory, allowing PRI to focus exclusively on acute admissions and inpatient testing, while Ninewells now handles 100 percent of the general-practice testing in the entire region. Additionally, the increased capacity has enabled Tayside to introduce new testing protocols.

"It's a common perception that laboratory automation is intended to reduce staff," says Bill Bartlett, Ph.D., joint clinical director of diagnostics at Tayside, in a statement. "Tayside's approach is different. We're redirecting knowledge and skills away from routine tasks and toward the value-added side of the business, toward quality and collaborative support of caregivers. We're delivering efficiencies in order to focus on effectiveness."

University Hospital Campus Bio-Medico (Italy) evaluated the positive impact that total laboratory automation had on TAT in the clinical pathology and microbiology lab. In a study published in the January issue of the *Journal of Laboratory Automation*, the laboratory reports automation had significant effects in reducing TAT and percentage of outlier tests. The laboratorians evaluated intra-laboratory TAT pre- and post- implementation of automation solutions (July 2012–May 2013 versus June 2013–June 2014).

The automation implementation included a modular system designed to automate preanalytical, analytical, and postanalytical processes. By combining multiple analysis tools into a single workstation, common management processes could be applied to tubes. This is achieved through an input/output module that loads and unloads tubes, identifies tube type, reads barcodes, and tracks operations in progress in the tubes; an automated centrifuge module; a decapper module; an aliquot module that can generate secondary tubes; a recapping module, for secondary aliquots; a sealer module for after the analytic process; and an automated storage module. Automation software enables staff to manage the workload orders from the hospital information system and monitor progression of operations of the associated analysis tools.

While there were significant reductions in all TAT, automation most strongly affected efficiency in the preanalytical phase including centrifugation of the sample, and thus TAT improvement was more evident for tests requiring a longer preanalytical process such as troponin I and PT.

PCL Alverno

PCL Alverno, a full service, community-based medical laboratory, unveiled in early March a fully automated laboratory solution at its Central laboratory facility in Hammond, Ind. The company says growth and expansion are "key priorities." They have

Inside The Diagnostics Industry

added seven new patient service center locations in the past 18 months, gaining 250 clients and significant volume. The lab turned to "state-of-the-art" laboratory technology and automation to accommodate this growth.

"We have not just overhauled our labs with new laboratory technology solutions; we have also worked very closely with Beckman Coulter to apply deep process advancements to ensure we are equipped to offer improved levels of service to patients and physician satisfaction," says Sam Terese, the company's CEO.

Alverno, a joint venture of Presence Health and Franciscan Alliance Catholic health care systems, provides laboratory services for 26 hospitals in Indiana and Illinois and has a large reference lab for outreach work. The lab menu consists of 750 tests in both clinical and anatomic pathology and it processes more than 23 million tests per year, making it the largest microbiology lab in the Midwest.

By adding automated solutions in the microbiology area (digital imaging and matrix-assisted laser desorption/ionization-time of flight), Terese tells *DTET* that the lab can identify a causative organism for sepsis 24 to 36 hours sooner than it could just six to eight months ago.

"The goals of being more efficient at a lower cost are really only part of it," Terese says. "In reality, automation is about a broader goal of quality, which is absolutely critical to improving care... In today's health care environment, hospitals and laboratories are persistently under demands to reduce costs. While we cannot make decisions outside of that consideration, I would caution that you can't let that be the only deciding factor either. The broader decision is how automation impacts the people we serve. How will it make a difference for the patients, clinicians, and hospital clients?"

Takeaway: The focus on task-oriented automated instruments is short-sighted in understanding current trends in laboratory automation. Laboratory automation requires a holistic, system-wide approach that encompasses all aspects of diagnostics from sample processing through delivery of results.

Siemens, Quest Partner for "Lab of the Future"

As part of what is being called the "most complex automation project undertaken," the first analyzer, an ADVIA Centaur XP immunoassay analyzer, successfully aspirated from the automation track being installed at Quest Diagnostics' new 200,000 square-foot clinical laboratory being built in Marlborough, Mass. This will be the first comprehensive automation solution—totally automated and traceable—that Quest Diagnostics (Madison, N.J.) has deployed in one of its regional mega-laboratories in the United States. This system is designed to achieve high efficiency and decrease testing TAT by optimizing the entire tube flow.

The automated solution will be able to process several thousand blood samples every hour. The technology-driven, 200-meter track combines automated technology and software from sample feed through to storage. Highlights of the "lab of the future" include automated processing of unsorted test tubes (blood, urine, or serum) using bar code labels, while robotic arms place the samples on multi-lane conveyor belts that transport them to the appropriate diagnostic stations (Prioritization of samples is possible with a "passing lane" to the front of the line). At the analysis stations, pipettes draw the volume of sample required at each analysis station, eliminating the need to split a sample between several test tubes. Each sample's current position and all results can be called up at any time. Storage is also fully automated and can accommodate several hundred thousand refrigerated samples. The comprehensive automation system is being designed and installed by Siemens Healthcare Diagnostics and Inpeco.

"With our new 'lab of the future' in Marlborough, Quest Diagnostics will set a new standard in diagnostics services—not just for our company, but for our industry," said Quest's CEO Steve Rusckowski, in a statement. "These technologies will enhance quality and efficiencies so we can provide diagnostic services of the highest quality but at a low relative cost."

Wearable Technology Noninvasively Samples, Analyzes Sweat Markers

While sweat-based testing dates back more than 50 years as a screening tool for cystic fibrosis, sweat has never gained significant momentum as a non-invasive alternative to blood, largely due to the limitations of fluid collection. But with technological advances in microfluidics, nanotechnology, miniaturized electronics, and cloud-based computing, Eccrine Systems (Cincinnati, Ohio) believes sweat holds great promise as the best noninvasive bodily fluid for the real-time assessment of robust biomarker data.

"We recognize there are many well-known companies vying for the attention of broad consumer markets for wearable devices," says Eccrine cofounder Robert Beech in a press release, regarding the company's strategic position. "In direct contrast, our efforts are aimed at specialized and regulated medical and business markets that expect proof of data accuracy and chronological assurance, plus credible scientific studies related to physiological and economic outcomes."

The company was formed in 2013, but work on the sweat analysis platform began five years ago in conjunction with the U.S. Air Force Research Laboratory, at Wright-Patterson Air Force Base, in Ohio. The project was undertaken to identify a convenient way to monitor an airmen's alertness, stress, and other physical changes including dehydration during long flight missions.

The disposable electronic patch-sensor system is a light, Band-Aid-like wearable that relies on paper microfluidics for biomarker assessment. Eccrine cofounder Jason Heikenfeld, Ph.D., also from University of Cincinnati, reports in an *IEE Spectrum* article in October 2014, that the technology can analyze many biomarkers: electrolytes (sodium, chloride, potassium, and calcium), metabolites (lactate, creatinine, glucose, and uric acid), proteins (interleukins, tumor necrosis factor, and neuropeptides), and small molecules (amino acids and cortisol).

The paper in the patch wicks sweat in a "tree-root pattern" to maximize the collection area with minimum paper volume. The challenge, Beech says, is capturing the sweat quickly, getting it to the sensors, and then removing it, so that continuous assessment is possible. The microfluidic channels direct the sweat to a superabsorbent hydrogel (like the filler used in diapers), which pulls the sweat out of the paper and stores it. Heikenfeld reports that the patch can pull sweat along for several hours with the hydrogel swelling only 2 to 3 millimeters. Heikenfeld also notes that the patch performed as well as the benchtop electrolyte-sensing systems used by doctors to test for cystic fibrosis and that the patch can stay on for as long as a week.

In late February Eccrine announced it had raised $1.5 million in seed funding. The company is pursing a "platform business model" that relies on "exclusive relationships with downstream partners across multiple market segments." Beech says he sees large opportunities in areas such as medication adherence, clinical trials management, industrial safety, as well as medical diagnostics.

Takeaway: Advances in technology are allowing researchers to reexamine the utility of sweat for biomarker assessment for continuous monitoring of physiological changes, including drug levels associated with medication adherence.

New, More Sensitive Tests May Indicate Severity of Peanut Allergies

It is estimated that three million people in the United States have nut allergies, yet there are notorious shortcomings in current peanut allergy (PA) tests. Positive test results do not always equate with a clinical allergy because of cross reactivity among protein targets and even in the case of a true allergy, test results are not informative about the severity of an individual's allergic reaction.

In vitro serum tests and skin prick testing (SPT) indicate sensitization to an allergy trigger based on either a local response or measurement of immunoglobulin E (IgE) antibodies specific for a particular allergen. Serologic testing will retain a prominent role in the near-term future of allergy testing, but several more specific approaches to allergy testing are emerging. These new tests are showing promise in providing more relevant allergen information. Among these strategies are basophil activation testing (BAT), which examines allergic responses at a cellular level and component testing, which offers more sensitive testing of individual peptide and even carbohydrate epitopes that bind to the IgE.

"An objective biomarker that could accurately reflect the likelihood of experiencing severe allergic reactions for individual patients would be useful to help define indications for the prescription of an epinephrine autoinjector and help with risk assessment in patients who have to undergo an oral food challenge (OFC) for diagnostic purposes," write U.K.-based researchers, led by Alexandra Santos, M.D., in the *Journal of Allergy and Clinical Immunology (JACI)*.

Cellular Assessment of Allergies With BAT

BAT is an in vitro assay where the activation of basophils (immune cells that play a role in anaphylaxis) are measured using flow cytometry following exposure to various IgE-challenging molecules. Recent studies are showing that basophil reactivity and sensitivity are tied to severity of allergic reactions and their associated threshold. The hope, Santos and colleagues say, is that BAT can eventually be used as a surrogate for OFCs to estimate allergy severity and threshold.

In the January *JACI* study, the researchers conducted SPT, serum measurements of specific IgE to peanut and its components, and BATs to peanut, in addition to an OFC in 124 children. Serum specific IgE levels were measured with an immunoenzymatic assay. Fifty-two patients (of 124) showed any clinical symptoms, with severe reactions occurring in 41 percent of cases. More than half of patients (57 percent) reacted to 0.1 g or less of peanut protein.

Patients with CD63 peanut/anti-IgE levels of 1.3 or greater had more than a 3-times increased risk of severe reactions. The percentage of CD63+ basophils at 100 ng/mL PE was the best discriminator of the patients who had severe reactions requiring the administration of intramuscular epinephrine. Basophil sensitivity value (as measured by CD-sens concentration at which basophil activation is half of the maximum activation) was independently associated with the threshold of allergic reactions to peanut during OFCs. Patients with a CD-sens value of 84 or greater had nearly a 2-fold increased risk of reacting to 0.1 g or less of peanut protein.

"One of the advantages of the BAT is that it is a functional assay that takes into account all these factors, including levels, specificity, diversity, and affinity of allergen-specific IgE, and even possible interference by other allergen-specific an-

tibodies," writes Santos, from King's College London. "Therefore, the BAT has a greater potential to reflect the allergic reaction as it happens in vivo than methods that test these IgE parameters separately."

One of the technical challenges with BAT, Vijaya Knight, M.D., Ph.D., who is separately involved in BAT research at National Jewish Health Advanced Diagnostic Laboratories (Denver), tells *DTET*, is that basophils are fragile and that testing currently must be performed within four hours of the sample draw. This instability will limit its adoption to laboratories in close proximity to allergy clinics, likely in academic and hospital laboratories. But, the test can be performed on small samples (250 µL to 1mL) and with a one-hour turnaround time.

While the OFC will likely remain the gold standard for the foreseeable future, BAT can play a "complimentary role" in that, regardless of SPT or serum IgE results, the cellular response measured in BAT correlates to whether or not a patient can pass an OFC in that if a negative BAT could give the parents/clinicians reassurance a child can pass an OFC.

Component Testing to Play Larger Role

Santos and colleagues also found that having a greater number of peanut major allergens as determined by patients' IgE results, was significantly associated with severe reactions. These results illustrate growing interest in identification of component parts that can inform the severity of allergies. Knight predicts that serological tests will remain the "mainstay" of allergy testing, but predicts that component testing will play a bigger role going forward.

Immunoarray for IgEs utilizing both peptide and carbohydrate epitopes are a promising strategy to improve diagnostic specificity of allergy testing. Researchers have developed a surface plasmon resonance imaging microarray that incorporates both peptide and carbohydrate allergen binding epitopes for peanut allergen IgE antibodies, according to a study published Sept. 16 in the *Analyst*. While the role of carbohydrate residues in allergen response remains controversial, the authors say that the assay is many times more sensitive than current PA testing.

The University of Connecticut (Storrs, Conn.) chemists tested a patient's allergic reaction to three components (a protein peptide, a carbohydrate residue, and a positive control) using just a few drops of serum. They incorporated magnetic beads that "greatly enhance" binding specificity, with detection of IgE concentrations of antibodies as low as 0.5 pg per milliliter. The test results correlated with the patients' known allergy levels from other standard tests.

"Using five different peptides and carbohydrate samples and seeing how these IgEs bind to them could determine a clear fingerprint of a patient's susceptibility to a specific allergen," says co-author James Rusling, Ph.D. "In the future we hope to develop a test that can determine if antibodies to peanuts are present in the blood and can also identify a pattern of antibodies used to predict the severity of response to the allergens in real time."

Takeaway: New tests are showing promise in providing information predicting the severity of peanut allergies. While serological testing is expected to continue to be a mainstay of allergy testing, BAT and component testing will play a larger role in the next few years.

G2 INSIDER

Some Common Diagnostic Tests for CKD Unnecessary

Several reflexively ordered tests for evaluation and management of chronic kidney disease (CKD) may be unnecessary, according to a research letter published online March 2 in *JAMA Internal Medicine*. Specifically, the researchers found that serum protein electrophoresis and screening for antinuclear antibody, C3, C4, hepatitis C, hepatitis B, and antineutrophil cytoplasmic antibody were commonly ordered, but test results failed to inform CKD diagnosis or management.

The researchers retrospectively reviewed the electronic medical records of 1,487 patients referred for initial evaluation of CKD at nephrology clinics affiliated with Brigham and Women's Hospital and Massachusetts General Hospital (Boston) from 2010 to 2013. Nephrology progress notes were assessed to ascertain whether a test (regardless of positive or negative results) affected diagnosis and/or management of CKD.

The most frequent tests included measurement of calcium (94.8 percent), hemoglobin (84.0 percent), phosphate (83.5 percent), urine sediment (74.8 percent), and parathyroid hormone (74.1 percent) levels; urine dipstick for blood (69.9 percent) and protein (69.7 percent); serum protein electrophoresis (68.1 percent); and renal ultrasonography (67.7 percent).

Tests with relatively high diagnostic yields included: hemoglobinA_{1c} level (15.4 percent), urine total protein to creatinine ratio (14.1 percent), and urine microalbumin to creatinine ratio (13.0 percent). Those three tests also had relatively high yields affecting patient management in 10.1 percent, 13.7 percent, and 13.3 percent, respectively. While commonly performed, serum protein electrophoresis and renal ultrasonography had much lower yields, affecting diagnosis in 1.4 percent and 5.9 percent of cases and management in 1.7 percent and 3.3 percent of the patients, respectively. Tests for antineutrophil cytoplasmic antibody and antiglomerular basement membrane antibody did not affect the diagnosis or management of any patients. Screening for antinuclear antibody (for complement proteins C3, C4) occurred in nearly one-quarter of patients, yet affected diagnosis in just over 1 percent of cases.

"Further investigation incorporating community-based patients and identifying subgroups benefiting from more extensive evaluation is needed. However, this study suggests that reflexively ordering several tests for CKD evaluation and management may be unnecessary," write the authors led by Mallika Mendu, M.D., from Harvard Medical School in Boston. "An evidence-based, targeted approach based on pretest probabilities of disease for diagnosis and management may be more efficient and reduce costs." G2

Company References

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