G2 INTELLIGENCE
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# DIAGNOSTIC TESTING & Emerging Technologies

New Trends, Applications, and IVD Industry Analysis

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## 23andMe's Return Signals Expected Growth in DTC Market

In what is being hailed as "a milestone for consumer genetics," personal genomics company 23andMe (Mountain View, Calif.) received U.S. Food and Drug Administration (FDA) approval to launch a revamped direct-to-consumer genetic test that includes reports on 60 carrier status, wellness, trait, and ancestry findings.

The late October launch of its overhauled test comes nearly two years after the FDA ordered the company to stop providing its health risk assessment test and just a week after the company raised $115 million in new funding. The revamped test costs $199 for 35 carrier status reports for autosomal recessive conditions including cystic fibrosis, sickle cell anemia, and hered-

*Continued on page 2*

## Labs Need to Focus on Providing Data-Driven Value for the System, Lab Institute Experts Say

Laboratory leaders are well aware of the unprecedented number of evolutionary forces exerting pressure on the industry and are heavily focused on regulatory and reimbursement uncertainties. But, according to multiple presenters at G2 Intelligence's recent Lab Institute conference (Washington, DC; Oct. 14-16), laboratories also need to utilize their resources to demonstrate their value to the health system.

While accurate test results are obviously needed to inform care decisions, laboratories hold valuable data that can be utilized for the benefit of the entire health care system. Sharing this data for the larger good ensures the laboratory is a valued partner and plays a role in designing the evolving configuration of health care delivery. The most immediate value laboratories can add is in the inpatient setting, given the rapid adoption of bundled payments for those services; however, forward-thinking laboratories will adapt these strategies for outpatient services as payment reform will permeate that setting as well, with increasing participation in accountable care organizations and risk-sharing models. Two case studies presented at Lab Institute demonstrate laboratories' ability to help manage test utilization and improve patient care.

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## 23andMe's Return Signals Expected Growth in DTC Market, *Continued from top of p.1*

itary hearing loss; four wellness reports including assessments related to caffeine consumption, lactose intolerance, alcohol flush reaction, and muscle composition; and more than 19 trait reports on hair, facial features, and taste and smell preferences. Notably, the new product lacks disease risk testing and pharmacogenomic evaluation.

"They are still a long way away from getting back to where they were, returning results about people's relative lifetime risks of developing various deleterious health conditions," Michelle Meyer, a bioethicist and legal scholar at the Icahn School of Medicine at Mount Sinai in New York, told *Nature*, although 23andMe says it will keep pressing to offer more health testing to consumers.

In the Oct. 27 *Federal Register*, the FDA issued a final order explaining how labs can legally commercialize carrier screening tests that are 510(k) exempt. The agency classifies an autosomal recessive carrier screening gene mutation detection system as a class II medical device with special controls. The device is assigned the generic name "autosomal recessive carrier screening gene mutation detection system." The FDA defines this over-the-counter test as "qualitative in vitro molecular diagnostic system used for genotyping of clinically relevant variants in genomic DNA" and says they are not intended for copy number variation, or cytogenetic or biochemical testing.

FDA special controls require, among other things, that the device manufacturer provide information about how to obtain access to a board-certified clinical molecular geneticist or equivalent to assist in pre-and post-test counseling; specific labeling about the gene and associated variants tested along with evidence of "scientifically established clinical validity;" and the manufacturer must conduct a study that assesses user comprehension of the device's labeling and test process, with a minimum of a 90 percent or greater overall comprehension rate. Additionally, the manufacturer must provide warnings recommending consultation with a health care provider, particularly for positive results.

***Takeaway: 23andMe's return to the direct-to-consumer genetic testing market signals the beginning of a regulatory path forward that could enable considerable growth to the market that has been stalled since the FDA's warning letter to the company nearly two years ago.*** G2

### Teens Have High Interest in Genetic Test Results

The majority of adolescents in grades 7 to 12 want to know the results of incidental findings found in whole exome sequencing, even if the findings are not medically actionable until adulthood, according to survey data presented at the American Society of Human Genetics Annual Meeting (Oct. 6-10; Baltimore, Md.). While evidence in teens' preferences is limited, these results may indicate future acceptability of personal genetic testing.

"The bottom line is that disclosure of secondary findings to adolescents is a complex issue that should involve the stakeholder (the teen) as well as their parents or guardians," said lead author Sophia Bous Hufnagel, M.D., in a statement. "While these decisions should probably be made on a case-by-case basis, it is important to have adolescents' input when shaping the policies and guidelines that affect them."

Clinical guidelines urge counseling of adult patients when secondary findings, if any are found. However, for minors the consensus has been to discourage disclosure in most cases.

The researchers from Cincinnati Children's Hospital Medical Center administered a survey to 282 students (aged 12 to 18 years) attending three area public schools. The students listened to a short presentation on genetic testing and answered multiple-choice questions about their preferences for disclosure and the reasons behind them. The survey found that 83 percent of respondents said they would prefer to know about non-actionable results. The primary reasons for wanting to know were related to planning their education, career choice, relationships, and reproductive choices. For those who did not want to know, the most common reason was concern for introducing stress into their family. Just over half of respondents (53 percent) would want to make this decision jointly with their parents, while 19 percent felt they could make the decision on their own.

The authors note that interestingly, adolescents' disclosure preferences were consistent between boys and girls, across race and ethnicity groups, and across socioeconomic groups. Younger participants, those 12 years of age, reported less frequently wanting to receive non-actionable genetic information (55 percent), compared to students aged 13 to 18 years (87 percent). Future research will evaluate this age-based finding and whether understanding of the test, the choice, and its ramifications, play a role.

■ Labs Need to Focus on Providing Data-Driven Value for the System, *Continued from bottom of p.1*

## Strategies to Improve Test Utilization

In a bundled payment environment, managing test utilization reduces unnecessary testing and preserves the financial incentive for providing effective, yet efficient care. This is one of the greatest opportunities for laboratories to improve clients' financial performance, while enhancing patient care.

*"We are identifying opportunities for our clients to reduce unnecessary testing from several hundred thousand to over a million dollars per year for inpatient testing alone. Since this unnecessary testing is not reimbursed by DRG payments, it represents an immediate improvement to the health system's bottom line."*

—Thomas Joseph, CEO, Visiun

But in his presentation "Managing Test Utilization for Better Patient Care and Improved Financial Performance" Thomas Joseph, CEO of laboratory analytics company Visiun (Ann Arbor, Mich.), told attendees that improving test management is not just focused on the problem of overutilization or unnecessary testing (estimated to occur in approximately 21 percent of all testing based on meta-analysis results). In fact, laboratories need to improve underutilization of needed tests. The same 2013 meta-analysis published in *PLOS One* found that underutilization of testing is even more common and can occur 45 percent of the time and can have "significant" clinical implications for patient care. Visiun data, for instance, shows that HbA1c is not reordered up to 30 percent of the time and similarly, elevated creatinine results are not followed up on within 90 days at rates approaching 40 percent in the outreach testing environment.

It's not just about educating doctors to order or not order tests, it's about teaching them to order the right tests. Joseph offered some strategies laboratories can employ to affect improved test ordering.

"A combination of approaches is necessary," Joseph warns, "as no one approach will be sufficient."

- Stop offering obsolete tests, which Joseph estimates account for 9 percent of all unnecessary testing;
- Redesign test requisitions to minimize bundled testing and esoteric testing availability;
- Use computerized physician order entry to enable hard stops (like requiring a genetic counselor consult for genetic tests) and popups with guideline-driven ordering reminders; and
- Employ audits, which Joseph calls a "key element."

"We are identifying opportunities for our clients to reduce unnecessary testing from several hundred thousand to over a million dollars per year for inpatient testing alone," says Joseph. "Since this unnecessary testing is not reimbursed by DRG payments, it represents an immediate improvement to the health system's bottom line."

Visiun's Performance Insight suite of tools provides laboratory directors and managers with business intelligence and analytics to help monitor key performance surrounding operational performance, efficiency and quality, including turnaround time, productivity, quality, financial management, and utilization.

The system allows queries against a network of peer comparisons that is built upon test ordering data from 300 laboratories, including academic medical centers, community hospitals, Lean labs, and specialty labs. Visiun's graphical report cards call out heavy test users and outliers.

## Lab Insights Save the System Money

Laboratory data can be used to reduce readmissions, control costs, and improve patient safety, according to Ran Whitehead, president of PeaceHealth Laboratories (Portland, Oregon). These were some of the motivations behind PeaceHealth's development of its RxAdhere medication safety panel that improves the process of prescription reconciliation.

It is estimated that 75 percent of Americans may not take medications as directed and this contributes to nearly $200 billion in avoidable costs annually to the health care system.

RxAdhere can determine both non-adherence to prescribed medications and intake of uncharted medications, which are both tied to costly adverse drug events. The traditional medication reconciliation process may not detect these discrepancies because of inaccurate patient self-reporting, incomplete pharmacy records, and non-interoperable medical records. The plasma-based RxAdhere test is based on tandem mass spectrometry and it confirms the presence or absence of 184 commonly prescribed medications used to treat common, chronic conditions (anticonvulsants; eight classes of anti-hypertensives; antiarrhythmics, analgesics; benzodiazepines; NSAIDs, anticoagulants/antiplatelets; antidepressants; antipsychotics; stimulants; and oral hypoglycemics).

Medication non-adherence is a significant and common problem, Grant Beardsley, a clinical toxicologist at PeaceHealth Laboratories, told attendees. He says it is estimated that 75 percent of Americans may not take medications as directed and this contributes to nearly $200 billion in avoidable costs annually to the health care system.

By administering medications in the hospital, based on what the patient is actually taking—not what prescriptions are in the medical record—Beardsley says more appropriate dosing can occur, cutting the likelihood of a life-threatening reaction to a high-maintenance dose. Relatedly, patients can continue taking all medications that they routinely use, instead of abruptly stopping. In either case, RxAdhere can reduce inpatient adverse drug events and resulting extended hospital stays with their associated expenses.

In an inpatient validation trial of RxAdhere at the PeaceHealth Sacred Heart Medical Center (Portland, Oregon) the test had 99 percent accuracy in detecting inpatient medications in 367 patients. There were no false positives and less than one percent for false negatives. In reconciling prescription data from medical records to 310 outpatient samples (collected in the emergency room) 41 percent of patients were non-adherent for at least one prescribed medication and 31 percent used at least one medication not in the medical record (mostly due to incomplete electronic data)

PeaceHealth has soft launched the test within the hospital and is working on establishing a standardized process to ensure ordering the test becomes the standard of care. In the outpatient setting, Beardsley sees a role for RxAdhere in reducing medication nonadherence, which can improve outcomes for common chronic conditions and medication treatment decisions—for example, it can help determine if the drug or dose is not working or the patient is not taking the medication.

***Takeaway: To remain competitive laboratories need to provide enhanced value to their partners throughout the health care system. Laboratory data must be utilized for the financial benefit of the health care system—whether to improve the appropriateness of test orders or prevent longer lengths of stays or adverse reactions.*** G2

# Inside The Diagnostics Industry

## ViveBio Enabling Ambient Temperature Storage of All Liquid Samples

Tim Murray,
President, ViveBio

Imagine completely eliminating the need for cold storage of samples. Imagine the dramatic reductions in transport costs with no sacrifice of the integrity of biological molecules in the specimen. ViveBio (Atlanta, Ga.) has a strategy to revolutionize the way sample transport and logistics systems are managed.

*DTET* recently spoke to Timothy Murray, ViveBio's president, about the advantages afforded by the company's dried sample transport and storage technologies, as well as the company's impending launch of its first laboratory developed test (LDT).

**How do the ViveST and the Vive Plasma Separation Card (PSC) technologies improve sample collection and transport?**

ViveST and VivePSC have applications both within molecular and outside of molecular testing. We are very excited. There is nothing like either of these products on the market. ViveST is generally used for high-volume sample transport and storage. It can accommodate up to 1.5 mL of liquid specimen—serum, plasma, urine, cerebrospinal fluid, you name it. It dries the specimen using our proprietary polymer chemistry and stabilizes the biological molecules in that specimen, whether it is DNA, RNA, or proteins.

The PSC takes the place of a plasma separation tube and utilizes a fingerstick or a heel prick. Using three to five drops of blood it separates the solid components—the white cells, the red cells, and platelets—and then captures the purified plasma on a small plasma collection pad. Separating and stabilizing the whole blood sample at the point of collection offers a lot of advantages for testing. With standard dried blood samples on a Whatman card, cellular debris and content spills out and you have a breakdown of red blood cells spilling their hemoglobin, which can inhibit polymerase chain reaction testing. With our technology, by separating out the cellular piece and just leaving pure plasma, you have none of that.

With both of these technologies, once the specimen is dried those samples can then be shipped under World Health Organization standards for dried specimens. You no longer have to ship it as a diagnostic liquid specimen. You no longer need dry ice, or wet ice, or special packaging. You can imagine the simplification for the user and the cost reduction for shipping and shipping supplies.

**How do you see these products expanding testing access?**

We feel in industrialized nations, the PSC is ideal for home health type self-collection. At a macro-level, you have consumerization of health care and decentralization of laboratory testing throughout the system. Many laboratories, big and small, are already doing self collection, especially in the area of molecular genetics. Take cheek swabs, for example. We see that need growing significantly over the next three to five years. With a product like the PSC you have a simple user interface similar to blood glucose meter. You just prick your finger and put three to five drops on the card and are done. It's very simple. Just a few of the types of tests that can be done this way are non-invasive prenatal testing, which is performed using a plasma specimen, and any number of molecular virology tests like viral load and drug resistance testing for HIV.

# Inside The Diagnostics Industry

The other area we are very excited is taking the ViveST membrane technology and embedding it into kits of in vitro diagnostics (IVD) manufacturers to stabilize the positive controls included in their kits. For example, imagine a point of care molecular test for an infectious disease target. That CLIA-waived kit will be in a physician office or a drug store and it will be in a non-refrigerated format on the shelf. Over the last year and a half, we have been working with the major control and calibrator manufacturers as well as several point-of-care, CLIA-waived platform developers for them to put their controls on our ViveST technology. These kits are in development and looking to go into clinical trials before the end of year.

*"We can reduce shipping and logistics charges by 50 percent to 70 percent."*

—Timothy Murray

**Do you sell directly to laboratories? How much do these products list for?**

With the ViveST and VivePSC we sell both direct and through distribution to clinical diagnostic labs, clinical researchers, contract research organizations, and one of our bigger customers is the U.S. Department of Defense because they are shipping specimens all over the world.

PSC in resource-limited settings has to be competitive with the Whatman card, or have a slight premium as a result of the technology embedded (i.e., $2 to $3). In industrialized markets, the PSC is roughly a $4 to $6 device. The ViveST has a current $5 to $8 per unit price, in line with a single nucleic acid extraction, a small premium over existing technology. Pre-analytic products are pretty price sensitive.

**How do these products impact the workflow of the receiving laboratory?**

We have found these products change how clinical laboratories do accessioning and processing once the specimen shows up. What happens is that the ViveST membrane is placed inside the barrel of 3 mL syringe. It is compressed and then you pull up a volume of buffer or first pre-analytic liquid and let it rehydrate 30 seconds before you are ready to run the test. With the PSC it is a bit more simple. Newborn screening labs process an enormous number of dried blood cards and they usually hand punch out a couple of punches. Our PSC is laser-perforated around the collection disc. The technician takes the tip of their pipette and pops it into the tube. We don't sell an automated platform, yet. It is all done by hand, usually in a specialty-testing environment, not a super high-volume environment that would require automation, although we are looking at that for the future.

**What impact does the dried sample handling have on the lab's bottom line?**

We have done quite a bit of analysis of FedEx and UPS charges. It differs by institution as to who cares about shipping costs. It is not across the board, but 50 percent of the time it is the lab manager or a financial manager. We can reduce shipping and logistics charges by 50 percent to 70 percent.

To stabilize and freeze to minus 20 degrees a small iPhone-sized cardboard pack with 500 µL in five tubes you need five to six pounds of dry ice and that is about $125 to $145 in an overnight FedEx pack. The same sized box with standard overnight on ViveST costs $25 to $30. It's a big difference.

# Inside The Diagnostics Industry

**How do you see the pre-analytical sample collection market evolving over the next few years?**

In the next three years, you will see both additional dry transport and wet transport technologies designed to stabilize specific types of biological molecules. It really started with Becton Dickinson and Qiagen with their joint venture for PAXgene Tubes. They created that segment by optimizing chemistry to stabilize RNA. I think you are going to see continued specialization of stabilization technologies. This dovetails with the decentralization and home health collection in the marketplace.

**ViveBio recently announced it is entering the clinical testing market. What provoked the company's entry into clinical diagnostics?**

Strategically we knew we wanted to move upstream in the diagnostics value chain, up from the pre-analytics products, which have an average selling price $1 to $3 to $6, or $8, to diagnostic technology that can add more value to our company and to the health system. We were in a fortunate position to secure a great intellectual property (IP) portfolio that Renovar (Madison, Wisconsin) developed. We had been working with them and were able to come to terms for the worldwide exclusive license for all of their IP. Today that represents six patents and five patent applications. All the IP revolves around diagnostic methods and compositions for kidney disease and disorders.

**ViveBio By-the-Numbers**

**Company founded:** 2009

**Number of Employees:** 6

**Patents:** 7 issued; 10 pending

**Published posters/papers:** 37

**Shipping Savings With ViveST:** $125.53 to $155.17 per shipment

We have had tremendous feedback from clinicians, nephrologists, and transplant surgeons because there is quite a bit of pent up demand for kidney transplant rejection technology. The standard of care today is a serum creatinine blood test, which is terribly non-specific and on the other end of the spectrum, the gold standard is an invasive biopsy. There is nothing in between. This technology fits a nice noninvasive niche, where we can monitor a patient using two key markers during the first year, when the majority of rejections occur, and tip off the clinician that something is going wrong, so they can take the appropriate therapeutic intervention. There have been a number of clinical trials and published articles validating the two key markers of the technology CXCL9 & CXCL10 and we are negotiating with a couple clinical labs to launch the test as an LDT within the next six months.

**Is there an economic argument supporting the test?**

We are spending a lot of time on the health economics of using these predictive biomarkers to guide treatment and monitor patients. Transplants are extremely expensive—more than $250,000 just for the transplant—and the federal government pays for the majority of transplants. We are engaged in a health economic study and believe this test could be a strong candidate for value-based pricing. It is pretty clear if we were to monitor all patients or a subset of patients, the cost of this is $X and could save $Y, if you can avoid a rejection. A rejection can be very expensive too and ultimately results in removal of the kidney, which is another couple hundred thousand dollars and then the patient is back on dialysis, which is also expensive. The numbers add up quickly and the value proposition for a diagnostic test in a monitoring capacity in year one is extremely attractive.

# New Markers Aid Determination of IVF Success, Prenatal Maturity

Sequencing based testing is already making significant inroads into obstetric care with non-invasive prenatal testing. Now, two new studies show the potential for sequencing technology to further improve success rates in reproductive medicine and neonatal care of pre-term infants.

## Cell-Free RNA to Assess Fetal Maturity

Gene expression signatures in amniotic fluid (AF) can indicate organ-specific fetal maturity, according to a small study published Oct. 22 in *BMC Medical Genomics*. The current study identified both plausible genes associated with maturation of multiple organ systems as well as the different time points in pregnancy when the expression patterns could be utilized. The AF transcriptome may improve upon current methods to help clinicians assess potential neonatal morbidities and inform delivery planning for preterm births.

*"Taking a broader overview of fetal maturity than just focusing on the lung will better enable obstetricians to make delivery planning decisions for preterm births, and prepare pediatricians and neonatologists for the various neonatal morbidities these preterm infants may face."*

—Beena Kamath-Rayne, M.D.

There is ongoing debate about whether fetal lung maturity testing alone is sufficient to predict postnatal readiness prior to 39 week's gestation. Although amniocentesis is falling out of favor in light of the rapid adoption of non-invasive prenatal testing early in pregnancy, AF contains higher amounts of cell-free fetal RNA/DNA than maternal serum and researchers believe it holds clues about organ system development beyond that of lung maturity testing.

Researchers from Cincinnati Children's Hospital Medical Center (Ohio) isolated AF RNA from 16 women at different time points in pregnancy: 18 to 24 weeks (prenatal; n=4), 34 to 36 weeks (late preterm; n=6), and 39 to 40 weeks (term; n=6). Samples were collected from patients undergoing amniocentesis for prenatal diagnosis purposes or during caesarian section delivery. RNA sequencing was performed on cell-free RNA.

Overall, the researchers found a strong correlation between cellular molecular markers in the intrauterine environment and fetal respiratory, digestive and external barrier tissues of the fetus. There were differences in RNA transcripts of 257 genes seen at different time points in pregnancy and these expression patterns were associated with distinct neonatal co-morbidities (underdeveloped lungs and immature feeding patterns), indicating fetal immaturity.

"Given the advantages of amniotic fluid being less complex than serum and containing higher amounts of cell-free RNA and DNA that more directly reflect fetal status, analysis of the amniotic fluid transcriptome is a practical first step towards the biomarker discovery that can later be translated to less invasive methods," write the authors led by Beena Kamath-Rayne, M.D. "Taking a broader overview of fetal maturity than just focusing on the lung will better enable obstetricians to make delivery planning decisions for preterm births, and prepare pediatricians and neonatologists for the various neonatal morbidities these preterm infants may face."

## Elevated Mitochondrial DNA Lessens Success of IVF

Elevated levels of mitochondrial DNA (mtDNA) in embryos leads to lower success rates for in vitro fertilization (IVF) procedures, according to a study published June 3 in *PLOS Genetics*. The researchers identified an mtDNA threshold above which

no viable pregnancies occur and they say that incorporating quantification of embryo mtDNA into pre-implantation testing can boost IVF success rates.

"There is an urgent need for new methods to improve the efficiency and success rates of IVF," said Elpida Fragouli, Ph.D., laboratory director of Reprogenetics UK and lead author of the study. "The discovery of a new biomarker of embryo viability, independent of standard assessments such as morphology, is a rare event and of great clinical potential."

This study assessed the clinical relevance of mtDNA quantification in 379 embryos (39 cleavage-stage and 340 blastocysts, which are five days post-fertilization). The embryos were examined using a combination of microarray comparative genomic hybridisation, quantitative polymerase chain reaction, and next-generation sequencing (which has the benefit of enabling evaluation of both chromosomal status and mtDNA quantification).

*"We propose that mtDNA content represents a novel biomarker with potential value for (IVF) treatment, revealing chromosomally normal blastocysts incapable of producing a viable pregnancy."*

—Elpida Fragouli, Ph.D.

The researchers found that the quantity of mtDNA was significantly higher in embryos from older women and in aneuploid embryos, independent of age. By linking clinical outcomes to embryo assessment data, the researchers determined that blastocysts that successfully implanted contained lower mtDNA quantities than those failing to implant. This led to the identification of an mtDNA quantity threshold, above which implantation was never observed.

The predictive value of this threshold was confirmed in an independent blinded prospective evaluation of 42 chromosomally normal blastocysts. Fifteen embryos had mtDNA levels above the .003 threshold (relative quantity of mtDNA) and none of these resulted in a viable pregnancy. Of the 27 embryos with mtDNA levels below .003, 16 ultimately established viable pregnancies. Overall, only 38 percent of the 42 embryos resulted in a viable pregnancy, but by including mtDNA data in the selection process, the percentage was raised to 59 percent. Additionally, the authors note that the mtDNA threshold does not appear to be altered by variation in the processes used by different fertility clinics.

Reprogenetics (Livingston, N.J.) already offers preimplantation genetic testing that screens embryos for chromosomal aneuploidy, a leading cause of IVF failure, and says it plans to add mtDNA testing to its aneuploidy test. It has been reported that the company's mtDNA Mitograde test will cost $500 as an add-on to the $2,000 preimplantation genetic screening test.

"Even the transfer of a morphologically 'perfect' embryo, which is additionally considered chromosomally normal following analysis of biopsied cells, cannot guarantee the initiation of a successful pregnancy (only about two thirds of such embryos actually produce a child)," the authors write in the study. "We propose that mtDNA content represents a novel biomarker with potential value for (IVF) treatment, revealing chromosomally normal blastocysts incapable of producing a viable pregnancy. "

***Takeaway: New applications of sequencing-based testing hold the potential for improving IVF success and refining measurements of fetal maturity.***

## Lipid Panels May Be Useful in Diagnosing Migraines

Migraines may be associated with irregularities in the metabolism of certain lipids and serum sphingolipid panels could play a role in the diagnosis of migraines, according to a study published in the Oct. 6 issue of *Neurology*.

*"Further research, validating the ceramide and sphingomyelin associations with migraine, as well as research examining mechanisms for these associations, may advance our understanding of migraine pathophysiology and open possibilities of the identification of novel migraine biomarkers and targeted drug therapies directed against sphingolipid pathways."*

—B. Lee Peterlin, D.O.

Sphingolipids (e.g., sphingomyelins, ceramides) are a group of bioactive lipids that are critical components of cell membranes. Recent research suggests that even subtle changes of sphingolipid balance may be tied to neurologic disorders and obesity and that sphingolipids may participate in neuronal functions and signaling pathways associated with pain.

In the current study, researchers obtained fasting serum samples from 52 pain-free women, 88 women with episodic migraine, and 36 controls. Forty sphingolipid species were quantified using high-performance liquid chromatography coupled with tandem mass spectrometry.

The researchers found that total ceramide and dihydroceramide (ceramide's precursor) were significantly decreased in women with episodic migraine, compared with controls. Using multivariate logistic regression, each standard deviation increase in total ceramide and total dihydroceramide levels was associated with more than 92 percent reduced odds of migraine. However, every standard deviation increase in sphingomyelin, was associated with a 2.5 times greater risk of migraine.

"Our findings suggest it is possible that migraine is a neurologic disorder of 'minor' sphingolipid dysmetabolism," write the authors led by B. Lee Peterlin, D.O., from Johns Hopkins University in Baltimore, Md. "Further research, validating the ceramide and sphingomyelin associations with migraine, as well as research examining mechanisms for these associations, may advance our understanding of migraine pathophysiology and open possibilities of the identification of novel migraine biomarkers and targeted drug therapies directed against sphingolipid pathways."

***Takeaway: With further validation, serum sphingolipid panels may be useful in diagnosing episodic migraines in women.*** G2

## Molecular Tests Should Not be Standalone Diagnostic for C. Diff

Exclusive reliance on molecular tests for Clostridium difficile (C. diff) infection diagnosis is likely to result in overdiagnosis, overtreatment, and increased health care costs, according to a study published in the November issue of *JAMA Internal Medicine*. Virtually all C. diff infection-related complications and deaths occur in patients with positive toxin immunoassay test results, not just positive molecular test results, indicating that treatment is likely unnecessary based solely on molecular testing.

"Molecular tests should not be used as a stand-alone diagnostic test for CDI and diagnostic recommendations should move back in the direction of defining clinical disease as a positive toxin result in patients with diarrhea," write the authors led by Christopher Polage, M.D., from University of California, Davis. "Two-step testing

with a screening test, such as polymerase chain reaction or glutamate dehydrogenase antigen detection, followed by a toxin test to confirm active infection is a reasonable diagnostic strategy."

Molecular tests are increasingly used to diagnose C diff infection, but many molecular test-positive patients lack toxins that historically defined diagnosis, leading to some confusion as to which patients need treatment for pathogenic C. diff infections and which ones may just have bacterial colonization. The number of institutions using molecular tests is growing rapidly, with 44 percent of hospitals adopting the molecular test (alone or in combination) in 2014. Previous research has shown that adoption of molecular C. diff testing has increased the rates of C. diff reporting by as much as 100 percent.

*"Our results offer compelling evidence that as many as half of the patients with positive C difficile PCR test results are likely to be overdiagnosed and exposed to unnecessary treatment at institutions using molecular tests."*

—Christopher Polage, M.D.

In the *JAMA* study, an academic medical center tested 1,416 hospitalized adults (Dec. 2010 through Oct. 20, 2012) with suspected CDI with U.S. Food and Drug Administration-approved polymerase chain reaction (PCR) molecular tests (Xpert C. difficile/Ep [Cepheid]; and illumigene C. difficile [Meridian Biosciences]), while maintaining existing toxin testing for clinical diagnosis (C difficile Premier toxins A and B; Meridian Biosciences). Clinical outcome and treatment data were also evaluated. Patients were grouped by both toxin and PCR tests results: Tox+/PCR+, Tox–/PCR+, or Tox–/PCR–.

The researchers found that more than half (55.3 percent) of 293 PCR+ patients lacked the toxin on the clinical toxin immunoassay test. These Tox-/PCR+ patients had clinical outcomes that were comparable to patients with no C difficile detected. At baseline, Tox–/PCR+ patients had significantly lower C diff bacterial load, as well as less antibiotic exposure and diarrhea than Tox+/PCR+ patients. The vast majority of C. diff infection-related complications, including deaths, occurred in Tox+/PCR+ patients. In total, 58.7 percent of the 162 Tox-/PCR+ patients were never retested, and only 13.0 percent received a full course of treatment.

"Our results offer compelling evidence that as many as half of the patients with positive C difficile PCR test results are likely to be overdiagnosed and exposed to unnecessary treatment at institutions using molecular tests," write the authors. "The number of patients potentially affected by this issue is massive."

The authors urge laboratories to realize that rejection of formed stool samples is "not sufficient" to ensure that all positive molecular C. diff results represent disease. The authors also cite the need to educate physicians to recognize that molecular tests are not specific for C. diff infection and that even in the presence of symptoms patients with positive PCR results do not necessarily need treatment. Lastly, the authors say new diagnostic development should focus on quantification of C. diff DNA, toxins, or host response to distinguish patients with active C. diff infections from those with colonization.

***Takeaway: Despite growing adoption of molecular-based C. diff tests, these tests should not be employed alone as they likely result in overdiagnosis of C. diff infection in a sizable portion of those tested, who will recover without treatment.*** G2

G2 INSIDER

## Urinalysis Overuse in ER Has Repercussions

Urinalysis is overused in the emergency department, with most patients who are tested lacking an appropriate clinical indication, according to a study published in the October issue of *JAMA Internal Medicine*. This overuse contributes to the overdiagnosis of urinary tract infections and resultantly, excessive use of antibiotics.

While urinalysis has excellent negative predictive value for ruling out a urinary tract infection, a positive result is nonspecific and has been estimated to occur in as many as 90 percent of asymptomatic elderly patients.

The researchers studied 403 consecutive adult patients (median age, 79 years; 52.6 percent women) to assess the appropriateness of urinalysis orders on admission to the general medical service of a large tertiary care center. Assessment took place for four consecutive weeks in September and October 2014, as well as three consecutive weeks in January 2015. Evaluation included assessment of indications for urinalysis (symptoms of urinary tract infection or acute kidney injury), as well as the frequency of empirical therapy for urinary tract infection, orders for urine culture, and antimicrobial prescriptions based on urine culture results.

In total, roughly six in ten patients (62.0 percent) underwent urinalysis at the time of admission at the discretion of either the emergency department or general medicine physicians. Of these 250 patients tested, the vast majority (79.2 percent) lacked symptoms of either urinary tract infection or acute kidney injury. Only the presence of multiple comorbidities was significantly associated with urinalysis orders without a clinical indication.

As might be expected, positive urinalysis results were significantly associated with increased likelihood of urine culture orders, as well as antibiotic prescription among asymptomatic patients. In symptomatic patients, the researchers say that "appropriate urinalysis orders" were used "effectively" to exclude urinary tract infections and withhold unnecessary antimicrobial therapy.

"These findings highlight the harms of urinalysis overuse in this patient population because positive urinalysis results can introduce cognitive biases in favor of a urinary tract infection diagnosis even when patients lack accepted guideline-based criteria," write the authors led by Penny Yin, M.D., from University of Toronto in Canada. "Limiting indiscriminate urinalysis ordering has the potential to improve urine culture and antimicrobial prescribing practices among general medicine patients."

## *Company References*

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