September 2019

CLN Clinical Laboratory News

An AACC Publication | Volume 45, Number 7

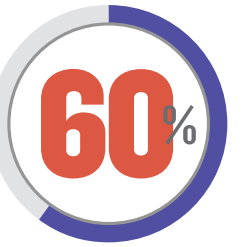
KIDNEY TRANSPLANT RISK

WEIGHING UNIVERSAL *APO-L1* TESTING

Facing the Opioid Epidemic

A Strategy for Primary Hyperaldosteronism

MACHINE LEARNING FOR PANCREATIC CYSTS



Rate of benign cysts identified vs. 18.9% for standard pathology.

PAGE 10

AACC Better health through laboratory medicine.

HOLOGIC®

New Aptima® assays are evolving the standard in vaginitis testing.

Vaginitis is the number one reason women visit their Ob-Gyns each year[1]. Traditional, subjective tests can miss co-infections, often leading to inadequate treatment.[2,3] The Aptima® vaginitis assays are evolving the standard, offering:

- **OBJECTIVE** detection of the three most common causes of infectious vaginitis: bacterial vaginosis, candida vaginitis, and trichomoniasis[2,3]
- **COMPREHENSIVE** testing using one simple swab[2,3]
- **ACCURATE** results using nucleic acid amplification test (NAAT) technology to deliver excellent sensitivity and specificity[2,3]

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References: 1. Kent HL. Epidemiology of vaginitis. Am J Obstet Gynecol. 1991 Oct;165(4 Pt 2):1168-76. **2.** Aptima BV Assay [package insert] #AW-18811, San Diego, CA; Hologic, Inc., 2019. **3.** Aptima CV/TV Assay [package insert] #AW-18812, San Diego, CA; Hologic, Inc., 2019.

HOLOGIC®

FDA Clearance of Aptima® Vaginitis Molecular Assays Ushers in a New Era of Comprehensive and Objective Diagnostic Testing for Vaginitis

The FDA granted clearance for two new molecular assays from Hologic's Aptima BV and Aptima CT/TV assay, which provide an accurate and objective method for diagnosing vaginitis, a very common and complex health issue affecting millions of women each year.

About 90% of vaginitis is caused by bacterial vaginosis (BV), vulvovaginal candidiasis (*Candida vaginitis*, CV, also commonly known as yeast infections), or *Trichomonas vaginalis* (TV) infections, either individually or in combination.[1,2] In fact, BV is the most common vaginal infection in the United States, affecting an estimated 21 million women between the ages of 14 to 49.[3] Diagnosis can be especially complicated due to the prevalence of co-infections, as approximately 20% to 30% of women with BV are co-infected with *Candida* species.[1] Mixed infections may require different treatment pathways and the Aptima assays provide comprehensive and clear answers for addressing these infections.

Traditional methods for diagnosing vaginitis (including microscopy, pH determination and Nugent scoring) are highly subjective, often leading to misdiagnosis and ineffective treatment.[1,2] When diagnosed using traditional methods and treated based on those subjective results, more than 50% of women with vaginitis experience recurring symptoms.[1]

"Vaginitis is one of the most common reasons women visit a healthcare provider and Hologic's new molecular assays have the potential to transform how these infections are diagnosed in that very first appointment," said Dr. Edward Evantash, an OB-GYN who serves as Medical Director and Vice President of Medical Affairs at Hologic. "The improved sensitivity and specificity of Hologic's molecular assays over traditional methods in determining the underlying cause of vaginitis not only means identifying the right infection, but enabling the right treatment and, in turn, reducing the potential for recurrent or persistent infections."

Hologic provides testing for cervical cancer and the detection of most STIs, including chlamydia, gonorrhea, *Mycoplasma genitalium*, trichomoniasis, HIV, HPV and Hepatitis B and C. All these assays run on the fully automated Panther® system. In addition, the Aptima® Multitest Swab Specimen Collection Kit, enables healthcare providers to test up to 7 disease states and infections, including BV, *Candida species*, *Candida glabrata*, trichomoniasis, chlamydia, gonorrhea and *Mycoplasma genitalium*. The Aptima "orange vial" and Aptima assays are run on the Panther system. Hologic's Panther and Panther Fusion® systems now offer 16 FDA-cleared assays that detect more than 20 pathogens.

For more information on Aptima assays and the Panther system, visit www.hologic.com.

Aptima® BV Assay

Aptima® CV/TV Assay

References: 1. Aptima BV assay [package insert] AW-18811 Rev. 001. San Diego, CA; Hologic, Inc.; 2019. **2.** Aptima CV/TV assay [package insert] AW-18812 Rev. 001. San Diego, CA; Hologic, Inc.; 2019. **3.** Koumans EH, et al. The prevalence of bacterial vaginosis in the United States, 2001-2004; associations with symptoms, sexual behaviors, and reproductive health. Sex Transm Dis. 2007;34(11):864-9.

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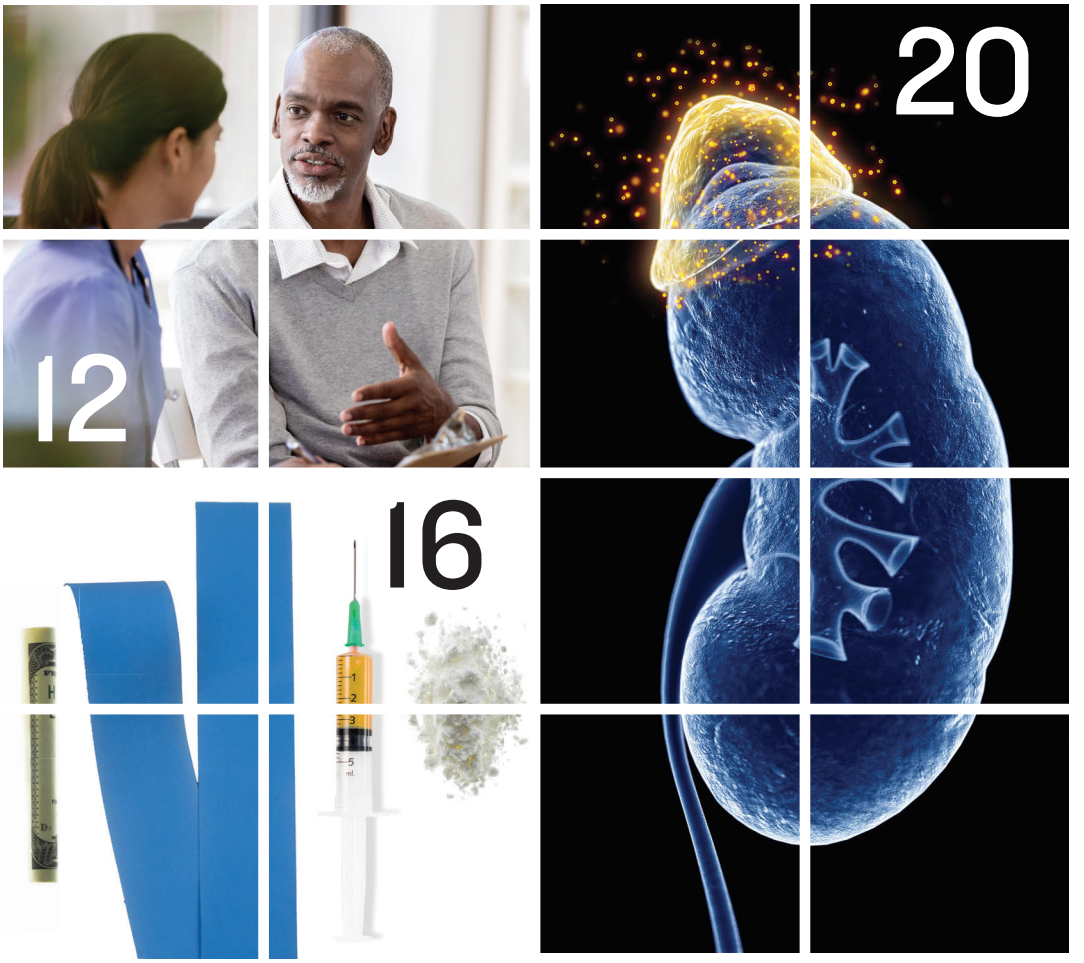
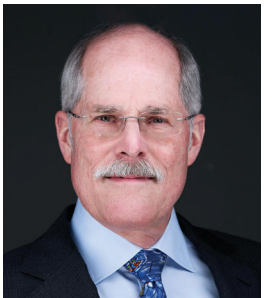


Departments



If you belong to a university department, you are likely to hear about quantitative measures of academic performance. By understanding the h-index, you are in a better position to evaluate its pros and cons as a yardstick for scientific achievement.
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Federal Insider

AACC Calls for Pediatric Reference Interval Funding

Aiming to scale up Centers for Disease Control and Prevention (CDC) resources to improve pediatric reference intervals, AACC is asking Congress to boost the agency's Environmental Health Laboratory budget by $10 million. Two dozen professional associations, laboratories, and medical centers have signed on to AACC's call for funding.

In a letter to Sens. Roy Blunt and Patty Murray, AACC noted that while reference intervals for adults are generally reliable, there are considerable inconsistencies and large gaps in the ranges provided for children. "Accurate and actionable reference intervals are particularly important for our youngest patients, who are often unable to verbally communicate their symptoms," the letter says. "Unfortunately, most laboratories are unable to obtain enough samples from healthy children to develop their own accurate pediatric reference intervals."

The letter stresses that when test results fall outside of a reference interval, pediatricians may order a medical intervention to address the condition. "If the diagnosis is mistaken for any reason, including a faulty reference interval, the result could be harmful for the young patient. Therefore, it is critical that reference intervals be correct," the letter states.

AACC also emphasizes that the CDC already has the infrastructure in place to take on this problem. The CDC Environmental Health Laboratory can generate the needed reference intervals with clinical samples obtained from its National Health and Nutrition Examination Survey.

LAB ACT AIMS TO FIX PAMA PROBLEMS

AACC is endorsing the Laboratory Access for Beneficiaries (LAB) Act, a bill intended to make sure laboratory tests are paid appropriately under the Centers for Medicare and Medicaid Services (CMS) clinical laboratory fee schedule. The Protecting Access to Medicare Act of 2014 (PAMA) introduced a market-based reimbursement system for laboratory testing, but AACC and other groups have voiced concern that the current methodology employed by CMS is flawed. The way CMS has collected data—focusing on large, national laboratories—has resulted in what many see as excessive cuts in laboratory reimbursement that may jeopardize patient access to laboratory services.

The LAB Act would delay by 1 year the next round of PAMA reporting requirements so that hospitals recently designated to submit payment data would have more time to comply with the mandate. It also would direct the National Academy of Medicine to study the methodology used by CMS and whether the data used to determine the new rates are representative of the laboratory market.

Currently, more than 90% of the private sector payment information CMS has used for making rates has come from independent commercial laboratories, with only 8% coming from physician office laboratories (POLs) and just 1% from hospital laboratories. In a letter to Rep. Scott Peters, a Democrat from California who sponsored the bill, AACC says that it believes modifying the current methodology to include more payment data from hospitals and POLs may improve the validity of the payment rates.

ACA INSURANCE ENROLLMENT DECLINES FOR THOSE WITHOUT SUBSIDIES

The Centers for Medicare and Medicaid Services (CMS) released a report showing that overall monthly enrollment in the Affordable Care Act health insurance exchanges remained steady in both 2018 and 2019—about 10 million people—while average 2019 premiums actually declined by a small amount—the first drop ever in premiums.

However, the report also found a precipitous drop in enrollment among those who do not qualify for government help in paying their premiums for plans offered under the exchange.

Between 2016 and 2018, 2.5 million people who did not qualify for subsidies left the market, a 40% drop. These enrollment declines among unsubsidized enrollees coincided with increases in average monthly premiums of 21% in 2017 and 26% in 2018.

CMS Administrator Seema Verma said that "people are fleeing the individual market" and that the "ongoing exodus of the unsubsidized population" proves premiums on the exchanges remain unaffordable.

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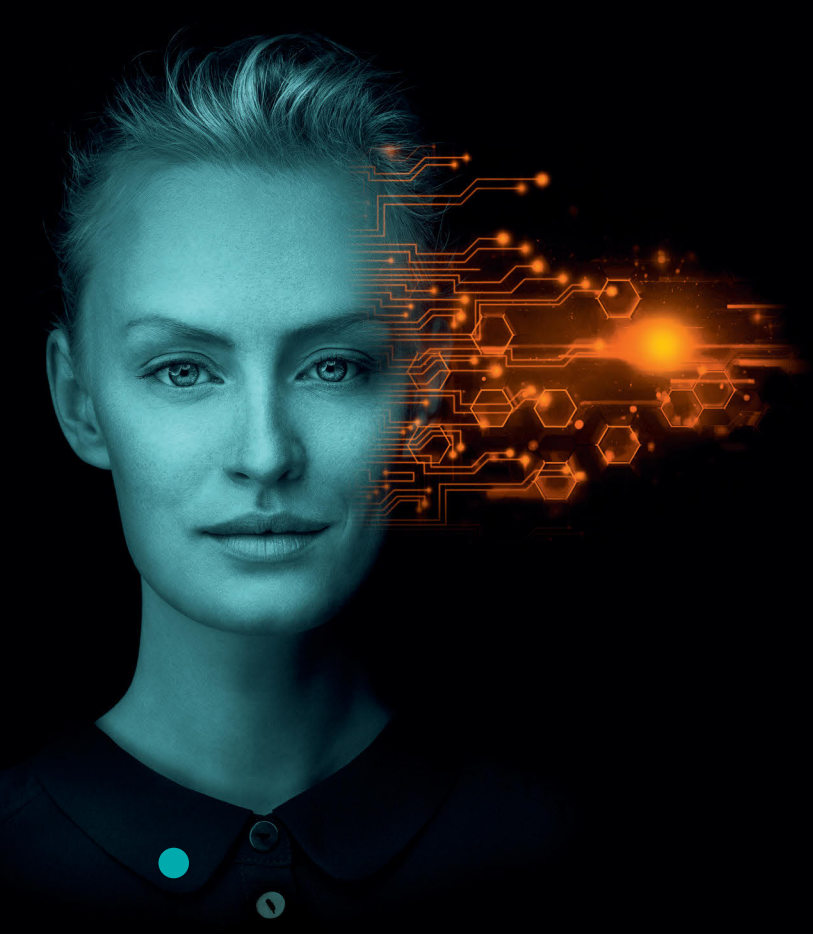

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1. Wen D, et al. Establishment and application of an autoverification system for chemistry and immunoassay tests. 69th AACC Annual Scientific Meeting Abstracts. 2017.
2. Columbus Regional Health leverages informatics and automation efficiency. Siemens Healthcare Diagnostics Inc. 30-19-13821-01-76. 2019 May.

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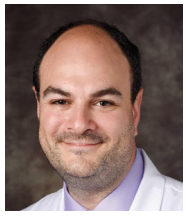
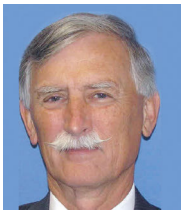
Bench Matters

Making a Choice We All Can Live With

How to engage staff and select an automated chemistry and immunochemistry platform



Matthew Feldhammer, PhD



Robert Ainslie, PhD

The timing for selecting new automated chemistry and immunochemistry analyzers usually relates more to necessity than desire. Instrument life spans, testing catalogue and volume changes as well as departmental or institutional capital budgets are much more likely than analytical or clinical needs to dictate when platform upgrades occur. Consequently, frontline technical staff frequently are more in tune with the daily shortcomings of current platforms and stand to have their work much more directly impacted by these decisions than lab medical directors, pathologists, or administrators. That is why staff input and expertise should factor prominently in the decision process.

In our recent experience selecting a new automation line we needed to consider many aspects of these platforms. Current systems offer many attractive features, from inventory management to clinical decision support and real-time remote system monitoring. These broad functionalities underscore the benefits of leveraging stakeholder expertise, both within and outside a lab, to make the best overall decision for an institution.

With that in mind, before contacting any vendors, we recommend defining a lab's current scope of practice: Who are the lab's primary users? What are their needs? When is the busiest time of day? Where will the equipment live, and are there space constraints? Why are we selecting new equipment/automation?

Armed with answers to these questions labs will be ready to determine which vendors best meet their needs. This may be a very short list with just one or two vendors. More than likely, however, there will be several choices. So labs will need to narrow the possibilities, which is where technical staff expertise becomes invaluable.

We highly encourage an open dialogue when soliciting proposals from vendors to get the most accurate and comprehensive solution for your lab's needs. Consider current workflows extensively and how a new Lean 5S laboratory could bring efficiencies. Most major vendors employ experts who will work with you and develop a plan to get the most out of a new platform.

BRINGING STAFF ON BOARD

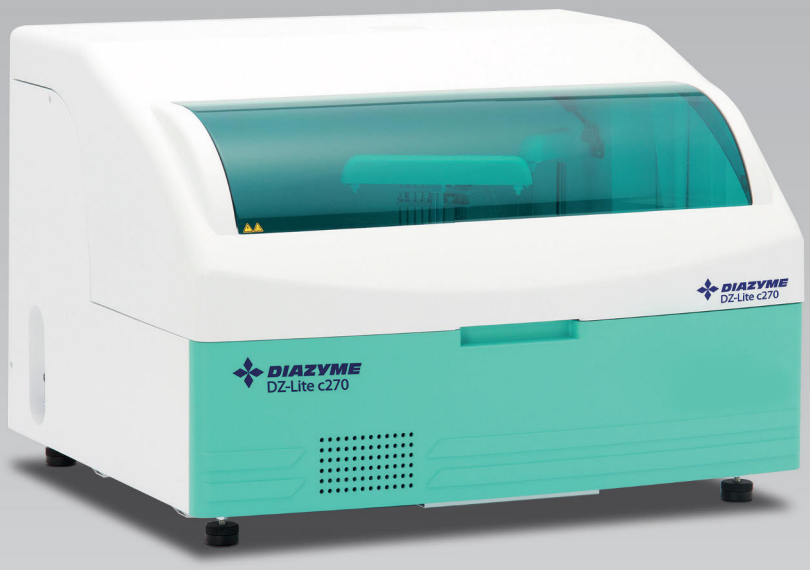
Eliciting staff input is not always straightforward and may require some out-of-the-box ideas to extract the most useful advice. We involved our team early on, encouraging participation in vendor presentations and on field trips to other facilities that recently upgraded instruments. Many vendors will truck in a scaled down version of a lab so that staff can interact with the instruments and pose questions.

Once our staff had a good grasp of the options each vendor was proposing, we surveyed team members via an online doodle poll to learn which features they felt were most important and why. This was eye-opening, as we found our technical staff valued things quite differently than our medical director or administrator. For example, they insisted that any instrument we chose had to allow reagent loading on the fly. We never would have considered that a critical feature but our team's knowledge of the intricacies of our daily workflow made clear that this was an essential feature.

IDENTIFYING KEY ATTRIBUTES

We selected three vendors based on test menus, throughput size, equipment footprint, our experience, and their presence in our region, the latter considered crucial in case we might need to share experiences with or borrow reagents from a local lab. We posted in staff areas side-by-side comparisons of all the vendors' features. We then elicited staff members' feedback via an online survey to identify the five most important features based on their daily operations experience and drawing upon their many years' interacting with different instruments at multiple employers (Figure 1). From this, eight attributes rose to the top, including: hands-on time for maintenance; field service availability and skills; ready-to-use calibrators; calibration frequency; user-friendly software; handling short samples; reliability; and automatic retrieval of add-ons.

CHEMISTRY ANALYZER



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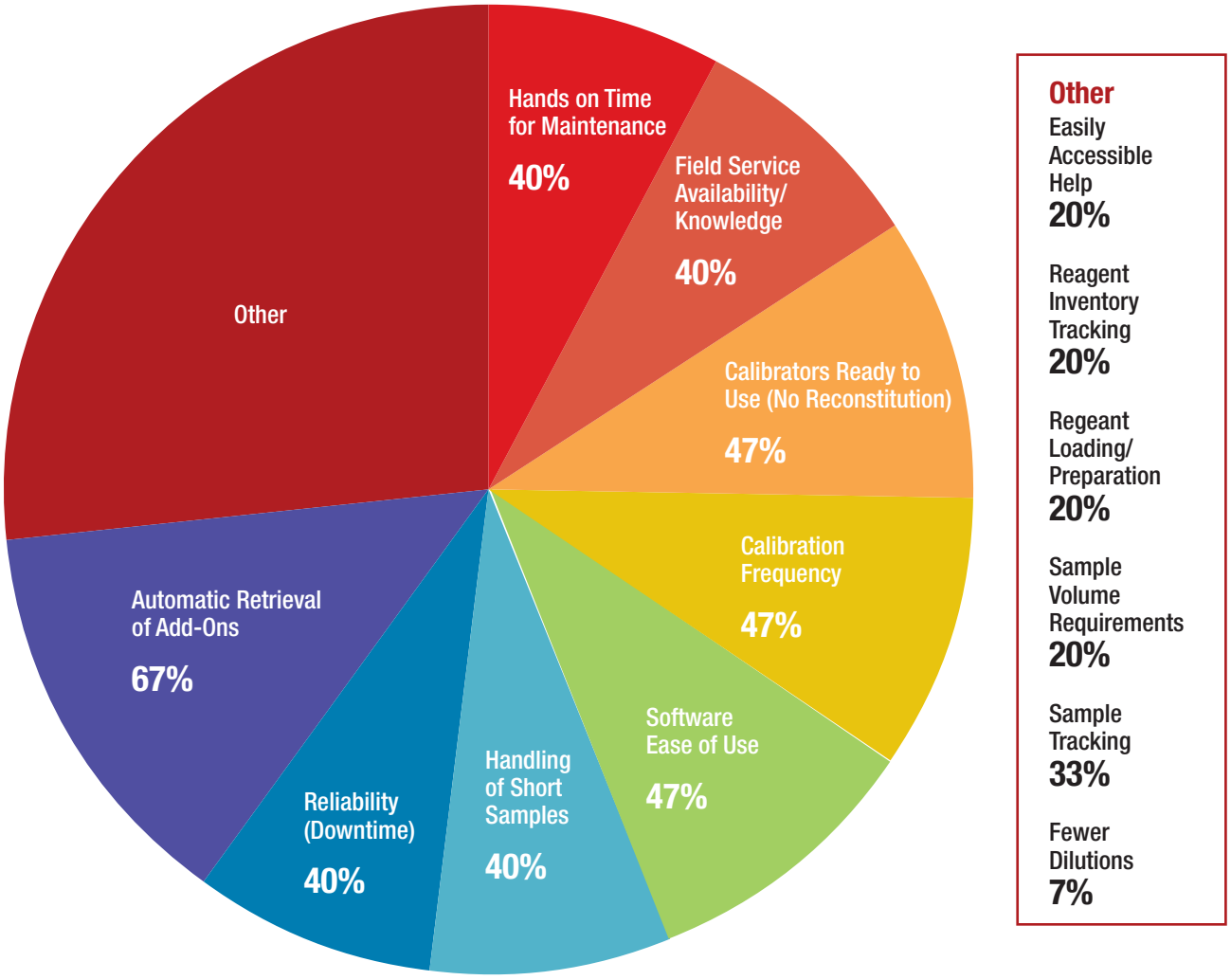
UF Health Lab Staff Survey

Top 8 Most Important Features in a Chemistry Analyzer:



We included these in a second staff survey after the vendors made presentations and gave demonstrations. We asked staff to rate each vendor across all features and included open comment fields for each vendor. We also had many lab huddles on the vendors' relative merits so our team would know administrators took their insights seriously. We asked vendors follow-up questions that came from this process so we were confident we had a good comparison of their capabilities.

We also considered each vendor's ability to connect automation with third party platforms. Being able to add (even later) hematology and coagulation equipment to an automation line is essential to creating a truly centralized multidisciplinary core laboratory. In addition, we asked each vendor to propose installation in phases so we could see how daily operations would be disrupted along the way, as we have to continue serving our patients while placing a new line and new equipment.

As we roll out our implementation, we are confident that we thoroughly considered the key variables by capturing the best thinking from the people who will use our new automation line and all its associated equipment. Our staff members are excited about and engaged with the new lab project because they know they had a major influence over the decision-making process.

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Machine Learning-based Cyst Fluid Analysis Bests Standard-of-Care in Distinguishing Benign, High-risk Pancreatic Cysts

In a proof-of-concept study a test that uses machine learning and incorporates data from clinical, molecular, and imaging features of pancreatic cysts outperformed standard-of-care pathology analysis in identifying benign cysts that required no further follow-up, those that needed ongoing monitoring, and those that were high risk and needed surgical removal (Sci Transl Med 2019;11:eaav4772). The findings, if validated prospectively, could significantly reduce the number of unnecessary surgeries in patients with pancreatic cysts, according to the researchers.

As many as 8% of people older than age 70 develop pancreatic cysts, but only a fraction of cysts progress to cancer. Yet because current tests don't distinguish precancerous cysts very well from low-risk ones, "essentially all people diagnosed with a cyst are followed long-term," the researchers noted in a statement, and many may have surgery "that in hindsight may not have been necessary."

The study involved 16 centers worldwide and 862 patients with pancreatic cysts who had cyst fluid analysis and cyst removal surgery. Cyst fluid analysis from a training set of 436 patients revealed four types of molecular abnormalities, including: mutations in 11 genes associated with specific cyst types; loss of heterozygosity in chromosome regions containing tumor suppressor genes; aneuploidy; and the protein markers carcinoembryonic antigen and vascular endothelial growth factor A. From this data the researchers worked out molecular features associated with benign cysts, mucin-producing cysts that had malignant potential, and malignant cysts.

The researchers then used a machine learning algorithm to combine these molecular features with clinical and imaging data to test "millions of combinations of features to predict the correct treatment pathway with the highest sensitivity and specificity," according to the researchers.

Next, the investigators validated the test—dubbed CompCyst—in a set of data from 426 patients and compared its performance against standard pathology assessment in discerning the three categories of cysts. CompCyst outperformed standard pathology in identifying these cysts' types but it did so most strikingly with benign cysts, correctly identifying 60.4% of cases that did not need follow-up versus 18.9%. CompCyst identified 48.6% of cases that should have been monitored and 90.8% that needed surgery versus 34.3% and 88.8% identified by pathology assessments, respectively.

Had CompCyst been used prospectively in this cohort of patients, surgery would have been avoided in 60% of 193 who had unnecessary procedures to remove their cysts.

SUBSTANTIAL, PERSISTENT QUALITY GAPS FOUND IN CHRONIC KIDNEY DISEASE CARE

Patients with diagnosed chronic kidney disease (CKD) experienced "substantial and persistent gaps in quality of care" according to an analysis of a national cross-sectional study of outpatient visits (Clin J Am Soc Nephrol 2019; doi.org/10.2215/CJN.00060119). The findings from National Ambulatory Medical Care Surveys in 2006-2008 and 2012-2014 of 7,099 unweighted visits weighted to represent national estimates point to an "urgent need for CKD-specific quality measures and implementation of quality improvement interventions," according to the authors.

The investigators found that nearly half of individuals with a diagnosis of CKD (46%) in the 2006-2008 survey had uncontrolled hypertension with blood pressure >130/80 mmHg. This percentage

Mehau Kulyk/Science Photo Library

had barely moved in the 2012-2014 survey, when 48% had blood pressure >140/90 mmHg.

Figures for other quality measures the researchers considered also were low and showed little-to-no improvement between the two survey periods. Less than one-third of participants at least age 50 were taking statins (29% in 2006-2008; 31% in 2012-2014); and less than half were on angiotensin receptor blocker or angiotensin-converting enzyme inhibitor therapy (45% in 2006-2008; 36% in 2012-2014). HbA1c test results were only available in the 2012-2014 survey but 40% of individuals had values >7%.

In addition to the lack of dedicated CKD-specific quality metrics, the authors cited other potential causes of suboptimal care in individuals living with CKD, including low rates of referral to nephrologists and lack of information about the quality of care in nephrology clinics.

AACC has endorsed the National Kidney Foundation's laboratory engagement plan, aimed at better diagnosing CKD through use of the Kidney Profile Test, among other initiatives. A recent Q&A addressed optimal use of biomarkers for CKD (Clin Chem 2019; doi:10.1373/clinchem.2018.29907).

IMMUNE MARKER CHANGES SIGNAL PROGRESSION OF MGUS TO MULTIPLE MYELOMA

A prospective study investigating alterations in serum immune markers in patients with stable versus progressive monoclonal gammopathy of undetermined significance (MGUS) found that majorities of high-risk MGUS (53%) and low- or intermediate-risk MGUS (70%) converted to multiple myeloma (MM) within 5 years (JAMA Oncol 2019; doi:10.1001/jamaoncol.2019.1568). This finding suggests that the risk of MGUS progression is more complex and fluid than the 0.5% to 1.0% annual risk of progression generally ascribed to these populations and supports annual blood testing and risk assessment for patients with MGUS or light-chain MGUS, according to the authors.

This cohort study from the Prostate, Lung, Colorectal, and Cancer Screening Trial included 187 participants diagnosed with progressing MGUS and 498 with stable MGUS. The authors analyzed baseline and all serial samples obtained before participants' disease progressed.

Risk factors most associated with progressive MGUS included: skewed (<0.1 or >10) serum free light chains (FLC) ratio, ≥15 g/L monoclonal spike, severe immunoparesis with ≥2 suppressed uninvolved immunoglobulins (Ig), and IgA isotype, with adjusted odds ratios (ORs) of 46.4, 23.5, 19.1, and 1.80, respectively. Risk factors associated with progressive light-chain MGUS included severe immunoparesis and skewed serum FLC ratio, with adjusted ORs of 48.6, and 44.0, respectively.

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The Testing Debate

Transplant community explores whether preop workups in African American kidney donors should assess for risk-conferring variants

BY HEATHER LINDSEY

Physicians have long known that African Americans have higher progressive nondiabetic rates of chronic kidney disease and end-stage renal disease than whites. Evidence shows that much of this increased risk is associated with two variants in the *Apolipoprotein L1* gene (*APO-L1*). Emerging data suggest that patients who receive kidneys from deceased or living donors with these risk variants have worse outcomes. Some living donors with *APO-L1* variants also experience functional declines in their remaining kidney.

Consequently, transplant surgeons, nephrologists, ethicists, and other providers are weighing the benefits and drawbacks of universal testing for *APO-L1* risk variants in African American living kidney donors, and many are eagerly awaiting data from the *APO-L1* Long-Term Kidney Transplantation Outcomes Network (APOLLO) study to inform discussions about genotyping with their patients.

APO-L1 in Kidney Disease

In 2010, researchers discovered that two *APO-L1* risk variants cause kidney disease, said Barry Freedman, MD, a nephrologist at Wake Forest Baptist Health in Winston-Salem, North Carolina and principal investigator of APOLLO. About 13% of African Americans carry the high-risk alleles (Am J Kidney Dis 2018;72:S8-16).

APO-L1 proteins made in the kidney can damage the organ, explained Freedman. The protein attaches to cell and organelle membranes and "seems to punch holes in the mitochondrial membrane, and this process kills kidney cells," he said. These same proteins damage the lysosomal membrane of the parasite *trypanosome*, which causes African trypanosomiasis and are likely why some people of African ancestry have *APO-L1* risk variants.

Case reports show that transplant recipients of kidneys from African American living donors with two *APO-L1* risk variants can develop focal segmental glomerulosclerosis disease, leading to graft failure. In addition, "the healthy donor can develop kidney failure," said Freedman. Mechanisms that cause kidney disease in African American living donors may be the same mechanisms that lead to kidney disease in the recipients of those kidneys.

Additional data published in 2018 indicate that African American living kidney donors with the high-risk genotype have an increased risk of complications (J Am Soc Nephrol 2018; 29:1309-16). Researchers evaluated 136 African American living kidney donors, 19 of whom had two *APO-L1* risk variants. Two of these donors were on dialysis at a median 12 years' follow-up compared with no one in the low-risk group. High-risk living kidney donors also had a greater decline in post-donation kidney function.

While these data are concerning, "we also have to remember that the majority of people who don't donate a kidney and who have two *APO-L1* variants have normal kidneys their whole lives," said Kenneth A. Newell, MD, PhD, professor of surgery at Emory University School of Medicine in Atlanta. This may mean a second genetic hit potentiates the risk inferred by the *APO-L1* variance. "Until we really know what that second hit is, it's difficult to know how important, in any given person, *APO-L1* variants are," he stressed.

Whether a person with two *APO-L1* variants who donates a kidney has a higher risk of complications than someone with the variants who does not donate a kidney isn't yet known, said Vasishta Tatapudi, MD, a nephrologist and assistant professor of medicine at NYU Langone's Transplant Institute in New York City. "From the data we have, I can't clearly say that donating heightens the risk any further," he said.

While Testing Isn't Universal, a Discussion Should Be

In 2017, a panel convened by the American Transplant Society on which Newell served published a guidance against universal screening for *APO-L1* as part of living donor evaluations of African Americans (Am J Transplant 2017;17:901-11). However, the guidance encourages physicians to have a comprehensive and informed discussion with patients about *APO-L1* genetic testing. At this point, there are no plans to update the guidance, according to Newell.

While doctors tend to agree that a discussion about APO-L1 should occur with African Americans who want to donate a kidney, the transplant community is still uncertain about what to do with test results indicating that a patient has a high-risk genotype, noted Newell. Generally, test results and risk should be discussed in the context of each patient's individual risk profile. Specifically, *APO-L1* variants likely need to be assessed alongside baseline fasting glucose, *estimated glomerular filtration rate*, obesity, smoking, and family and personal history of diabetes and hypertension, said Newell. "When you begin moving up the risk spectrum, I think that's where a discussion about testing is really useful," he said.

The donor's age is another important risk factor. "We can't say what will happen to the kidney function in younger donors with the high-risk genotype 20 and 30 years down the road," said Tatapudi. "It may be wise to not donate."

In clinical practice *APO-L1* testing appears to be limited, although interest in it seems to be growing. In 2018, a survey of 383 transplant surgeons and nephrologists found that 87% supported *APO-L1* testing, but just 14% actually offered it. However, 63% said they planned on using *APO-L1* testing in the next year.

"These findings and communication with members of the transplant community suggest that more clinicians are using *APO-L1* testing," said study author Elisa J. Gordon, PhD, MPH, a medical ethicist and professor of surgery at Northwestern University Feinberg School of Medicine in Chicago.

At NYU Langone Transplant Institute, all African American living donors are offered *APO-L1* genotyping as part of predonation testing, said Tatapudi. At Wake Forest Baptist Health, the transplant team discusses *APO-L1* testing with people with African ancestry who pass the initial donor screening process. "We don't mandate testing, but we encourage a discussion about testing because we think it helps stratify risk," Freedman said. Meanwhile, Newell discusses genotyping and risk with potential donors but *APO-L1* testing at Emory University School of Medicine is not standard.

THIS IS ONE EXAMPLE OF WHERE WE'RE ABLE TO LEVERAGE OUR KNOWLEDGE OF GENOMICS TO, VERY LIKELY, CHANGE TESTING POLICY.

—ANTHONY GREGG, MD

Ethical Considerations

Testing has numerous ethical considerations that doctors need to contend with, said Gordon. For one, physicians are obligated to prevent unnecessary harm in living donors, who are considering a surgical procedure that provides them no medical benefit.

Living kidney donors who find out they have two *APO-L1* gene variants might decide not to donate, which is well within their ethical prerogative, said Gordon. However, not donating may magnify the already existing disparities in African Americans' access to living kidney transplantation.

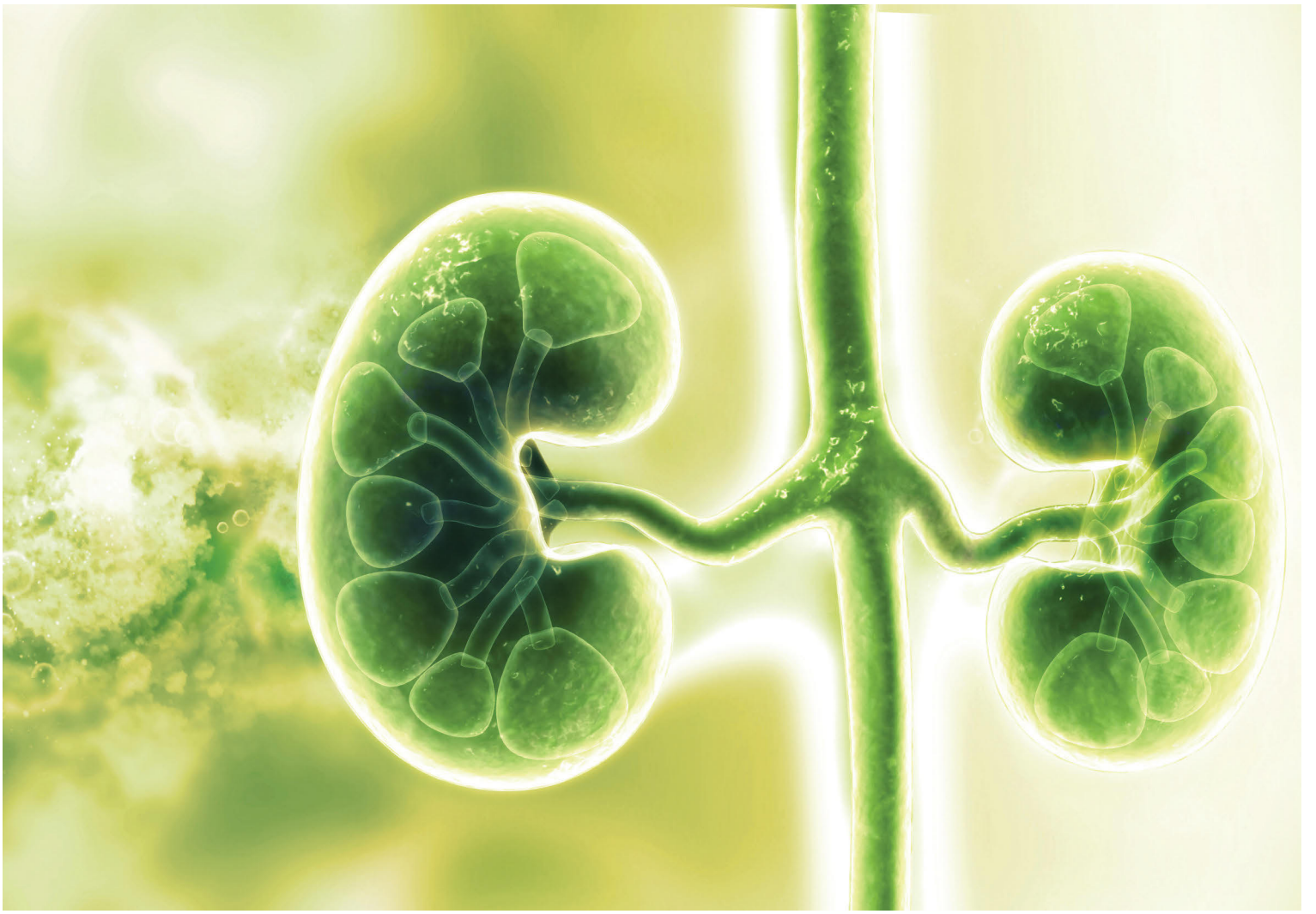
Informed consent is another ethical obligation to consider. Notably, kidney donors think *APO-L1* genetic testing could help them make decisions about donation. A 2018 survey found that 87% of 23 African Americans who had already donated their kidney said they would have wanted to undergo testing had it been offered to them. "Many wanted to learn about their own risk for end-stage renal disease and to prepare for the potential harms," said Gordon, lead author of this report.

Additionally, Gordon found that 96% of donor-respondents thought *APO-L1* testing should be offered routinely, while 61% said being informed about having the two variants would not have impacted their decision to donate.

Of course, potential donors have the right to refuse testing, said Freedman. Individuals might not want to get tested because of the stress that surrounds knowing they have the mutations or because of fears of losing insurance, he said.

Awaiting APOLLO Results

Many doctors are waiting for the results from APOLLO, expected to conclude in 2023, to help guide



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discussions with donors about genetic testing and what the results say about risk. In APOLLO, Freedman and his colleagues at 13 clinical centers are prospectively investigating the effects of *APO-L1* risk variants on outcomes in living donors with African ancestry, as well as outcomes in recipients of kidneys from deceased and living kidney donors with these variants.

"I think that trial will probably help establish what role *APO-L1* genotyping plays in kidney transplant," commented Anthony Gregg, MD, FACMG, president of the American College of Medical Genetics and Genomics. "This is one example of where we're able to leverage our knowledge of genomics to, very likely, change testing policy."

What's Ahead for Labs

Medical centers that decide to offer *APO-L1* genetic testing need to ensure that it occurs in a CLIA-certified lab that offers top quality genetic testing, said Freedman.

Gregg envisions immunology labs with next-generation sequencing technologies at transplant centers as making *APO-L1* testing part of standard procedure.

Currently, transplant labs that perform human leukocyte antigen (HLA) testing may not be the best place for *APO-L1* testing to occur, said Tiffany Roberts, PhD, a transplant immunologist at Trager Transplant Center at Kentucky One Jewish Hospital in Louisville, which is participating in the APOLLO trial but does not yet offer *APO-L1* genotyping in routine clinical care.

HLA laboratories at transplant centers are highly specialized and have a firm grasp of testing in their niche area, "but they may not yet have the experience nor the expertise in molecular testing methodologies to be able to perform *APO-L1* genotyping with the rigor that should be required," said Roberts. Validation and quality control of *APO-L1* testing should be much more stringent than is typically required of assays in an HLA lab, she explained. These issues are likely to be addressed sooner rather than later as "the evidence is in the process of being gathered at this point and suggests that *APO-L1* testing in African American living donors is warranted."

Disclosure: Dr. Freedman and Wake Forest Baptist hold a patent for *APO-L1* gene testing in clinical transplantation.

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BY JEN A. MILLER

STANDING UP TO THE Opioid Epidemic

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AACC is calling for a multidisciplinary, team-based approach that draws on clinical laboratorians' unique expertise

In August, AACC released a position statement on the crucial role clinical laboratories play in combating the opioid crisis, an epidemic that has not showed signs of slowing down. In 2017, 47,000 Americans—more than 130 a day—died after overdosing on opioids, according to the Centers for Disease Control and Prevention (CDC). More people died of drug overdoses in 2016 and 2017 than died in the Vietnam War.

AACC's position statement outlines the expertise that clinical laboratorians have to offer, and how AACC sees members best working with their colleagues in the medical community and in law enforcement. The statement also shows what measures the healthcare system, Congress, and federal agencies can take to work together on this issue.

Too often, the role of laboratory professionals is not apparent to other healthcare professionals working on the front lines, noted Alec Saitman, PhD, DABCC (CC, TC), director of clinical toxicology and special chemistry at Providence Regional Laboratories in Portland, Oregon, and member of the AACC Policy and External Affairs Core Committee that created the position statement. "It's critical that we as clinical laboratorians position ourselves in a way that shows that lab testing for drugs of abuse, particularly opiates, is an important part of fighting this crisis," Saitman said.

Synthetic Drugs Demand Specialized Expertise

Much of the statement focuses on synthetic opioids like tramadol, fentanyl, and U-47700. Overdoses from these substances made up a significant portion of all opioid overdoses. In fact, they killed 28,869 people in 2017, a 46% increase from the year before, according to CDC.

While some synthetic opioids are made by pharmaceutical companies, many are created in illegal labs and sold on the street. Slight modifications to their structures can produce a variety of analogs resulting in differences in potency and toxicity. They also may be cut with other drugs like heroin, methamphetamine, or cocaine.

This means that exactly what's in synthetic drugs varies locally, which is important to know in the case of a mass poisoning. "Many times we're the first people to access the patient's blood or urine samples. Clinical laboratorians will see what is really prevalent in the community," said James H. Nichols, PhD, professor of pathology, microbiology, and immunology at Vanderbilt University Medical Center in Nashville, who also is a member of the AACC Policy and External Affairs Core Committee. "From a public health perspective, and as you look at the Drug Enforcement Agency and the judicial system, they're seeing particular drugs that are prevalent in terms of sales and the street marketing of prescription medications, but we are seeing the actual patient samples in real time."

This is a key point AACC makes in the position statement. "Laboratories are often the first to identify synthetic drugs circulating on the street and can provide insight into their variety and frequency of their use in local communities," the statement says. "Leveraging the expertise of clinical laboratory professionals to identify the use of synthetic opioids can help clinicians and first responders make informed treatment decisions and help public health and safety officials identify the cause of overdose outbreaks and coordinate a response."

Close coordination is also necessary because analogs are developed so quickly that tests to detect them don't always keep up, and new testing panels are often obsolete by the time they receive Food and Drug Administration (FDA) clearance. "The potential for false negatives when testing for synthetic drugs necessitates close collaboration between laboratories and the physicians ordering the tests, especially when the results have implications for critical treatment decisions," the statement says.

"There's a lack of awareness, even within the medical community, of exactly what drug testing can and cannot provide," Saitman emphasized. In addition to immunoassays not always being developed fast enough to detect every synthetic opioid analogue, a urine test can't detect how much and exactly when a drug was taken, which may not be obvious to a physician ordering the tests, he added.

The statement also raises awareness of how clinical laboratories are developing specialized mass spectrometry assays to close the gap between what immunoassays can detect and how fast analogs are developed. "The timeliness and accuracy of testing for synthetic opioids could improve further if forensic, public health, and clinical laboratories collaborate to build shared libraries of chemical structural and mass spectral data," the statement says. "Laboratories that lack access to mass spectrometry methods could benefit from an expedited regulatory approval pathway for commercial availability of synthetic opioid test panels."

This is important in identifying the exact cause of local mass poisonings. If a particularly dangerous drug such as carfentanil is detected, a laboratory could alert clinicians and public health officials to take precautions by ordering and distributing extra naloxone to first responders.

Time for a Team-Based Approach

AACC is also calling for greater collaboration between laboratories, public health, and law enforcement agencies to bring about a more effective response. The statement makes the case for why laboratory experts must be included on

"Many times we're the first people to access the patient's blood or urine samples. Clinical laboratorians will see what is really prevalent in the community."

– JAMES H. NICHOLS, PHD

clinical care teams to help with test ordering and interpretation, and for laboratory directors to be available to provide detailed interpretive comments and services for sophisticated tests as warranted. It also calls for clinicians and first responders to consult with laboratories to ensure treatment decisions for overdose patients are as effective as possible, and for overdose patients themselves to be educated about precautions to take with synthetic opioids and provided with access to medication-assisted treatment.

"The lab often is not valued as much as we should be or recognized as having a critical role, not only in providing accurate results that clinicians can act on but also in working with providers to optimize testing," said Stacy E.F. Melanson, MD, PhD, associate professor of pathology at Brigham and Women's Hospital in Boston. Melanson served on the committee that developed the AACC Academy Laboratory Medicine Practice Guideline, "Using Clinical Laboratory Tests to Monitor Drug Therapy in Pain Management Patients" (J Appl Lab Med 2018;2:471-2). "We have a large amount of data, we have a large amount of knowledge, and we need to advocate for ourselves, which this statement does," Melanson said.

Through greater collaboration, laboratory medicine professionals can partner with clinicians to provide test results that fit their work flows, a relationship that could speed innovation, she said. "If there's a problem or something we can improve, we can work together with clinicians to create the right solution," she said.

The statement also identifies where more funding is needed. AACC calls on Congress to provide money to scale-up the number of clinical and public health laboratories that can identify novel synthetic drugs at state and local levels, and to develop stakeholder partnership networks that facilitate rapid information sharing to target synthetic opioid response and prevention resources.

In addition, the statement calls for expanding opioid surveillance programs for synthetic drugs by leveraging timely de-identified data from clinical and public health laboratories; for the Drug Enforcement Administration to provide clinical and public health laboratories access to analysis of seized materials to help with timely identification of novel synthetic opioids; and for FDA to expedite the regulatory approval of testing panels developed to rapidly detect synthetic opioids.

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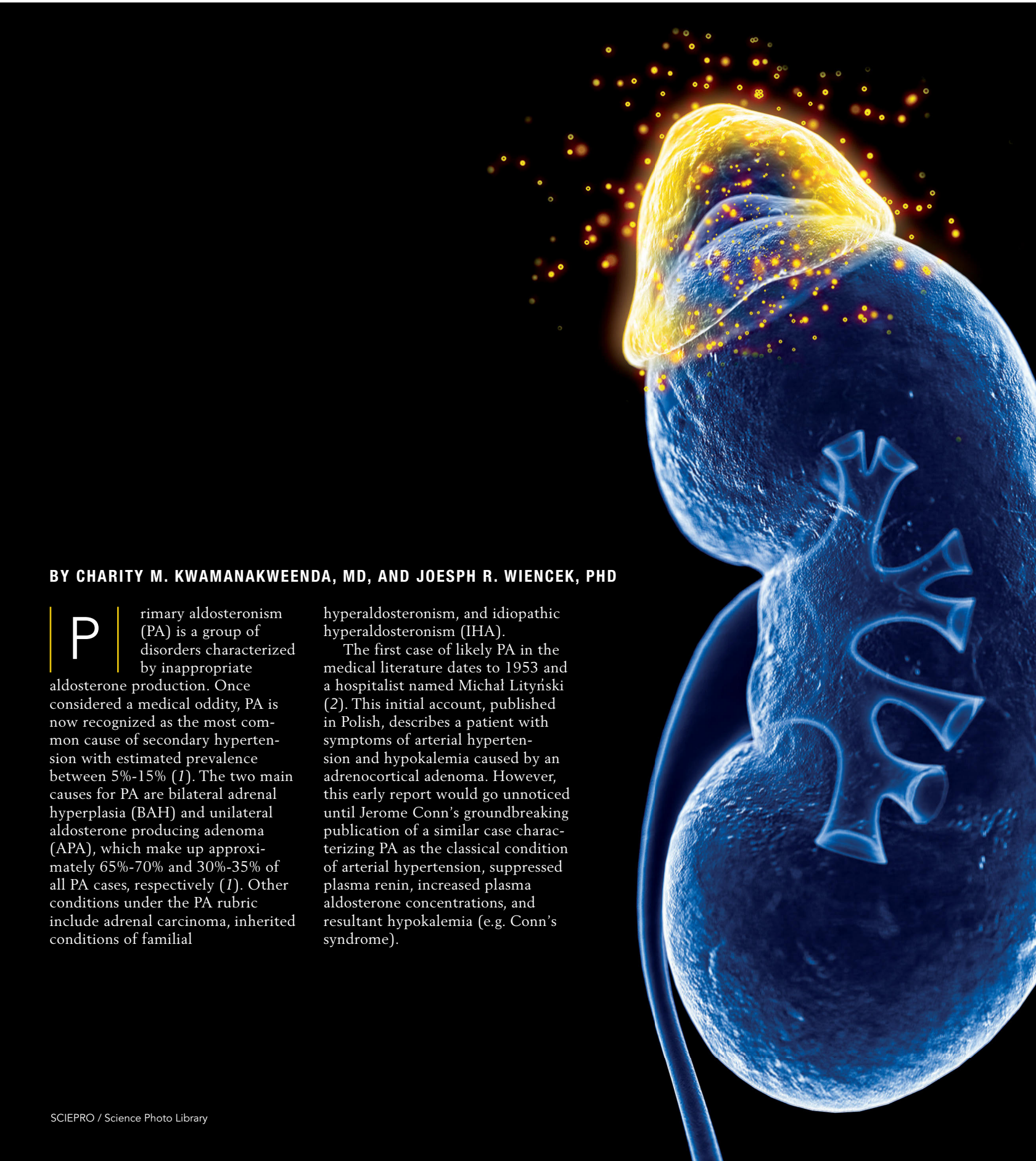

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BY CHARITY M. KWAMANAKWEENDA, MD, AND JOESPH R. WIENCEK, PHD

Primary aldosteronism (PA) is a group of disorders characterized by inappropriate aldosterone production. Once considered a medical oddity, PA is now recognized as the most common cause of secondary hypertension with estimated prevalence between 5%-15% (*1*). The two main causes for PA are bilateral adrenal hyperplasia (BAH) and unilateral aldosterone producing adenoma (APA), which make up approximately 65%-70% and 30%-35% of all PA cases, respectively (*1*). Other conditions under the PA rubric include adrenal carcinoma, inherited conditions of familial hyperaldosteronism, and idiopathic hyperaldosteronism (IHA).

The first case of likely PA in the medical literature dates to 1953 and a hospitalist named Michał Lityński (*2*). This initial account, published in Polish, describes a patient with symptoms of arterial hypertension and hypokalemia caused by an adrenocortical adenoma. However, this early report would go unnoticed until Jerome Conn's groundbreaking publication of a similar case characterizing PA as the classical condition of arterial hypertension, suppressed plasma renin, increased plasma aldosterone concentrations, and resultant hypokalemia (e.g. Conn's syndrome).

PRACTICAL APPROACHES TO THE DIAGNOSIS OF PRIMARY HYPER-ALDOSTERONISM

With results that can be difficult for physicians to interpret, patients being worked up for this disease benefit from multidisciplinary teams

PA is a Major Public Health Concern

The 2016 Endocrine Society guidelines for PA labeled the disorder a major public health concern (*1*). Patients with PA have higher cardiovascular morbidity and mortality than patients with essential hypertension with similarly elevated blood pressure (BP), making it important to diagnosis these patients early.

However, for physicians who do not encounter this diagnosis frequently, the diagnostic work-up can be difficult, as many patients and analytical variables need to be considered. Fortunately, the Endocrine Society guidelines offer guidance for screening high-risk patients for PA as well as a diagnostic algorithm (Figure 1).

Patients meeting one of these criteria should be screened for PA:

1. Sustained BP >150/100 mm Hg on each of three measurements obtained on different days.
2. Hypertension (BP>140/90 mm Hg) resistant to three conventional antihypertensive drugs (including a diuretic).
3. Controlled BP (<140/90 mm Hg) on four or more antihypertensive drugs.
4. Hypertension and spontaneous or diuretic-induced hypokalemia.
5. Hypertension and adrenal incidentaloma.
6. Hypertension and sleep apnea.
7. Hypertension and a family history of early onset hypertension or cerebrovascular accident at a young age (<40 years).
8. All hypertensive first-degree relatives of patients with PA.

Screening Test of Choice for Suspected PA

Any patient with one or more of these criteria should be screened initially with the aldosterone-to-renin ratio (ARR), regarded as the gold standard and most reliable screening test for PA (*1*). However, due to several reasons, the ARR should be interpreted in the context of the plasma aldosterone concentration and plasma renin activity (PRA) or plasma direct renin concentration (DRC). Inappropriately low renin may lead to an artificially elevated ARR. The ARR also may be affected by any changes caused by physiological factors that can affect the renin-angiotensin-aldosterone system.

The Endocrine Society recommends several ARR cutoffs as a starting point for clinicians working up patients with suspected PA (Table 1). However, the methodology used to measure aldosterone and renin can have a huge impact on the interpretation of the ARR (*3,4*).

Measurement Methods for Aldosterone and Renin

Several different analytical methods are available to measure aldosterone (*3*). Gas chromatography mass spectrometry (MS) is considered the original reference method. Over time, commercially available and in-house-developed radioimmunoassays (RIA) became widespread but today are less favorable due to human and environmental radioactivity exposure concerns. Easy to use and automate, chemiluminescent immunoassays are also universally available, but they provide non-equivalent sensitivity and specificity compared with liquid chromatography tandem MS (LC-MS/MS) methods. LC-MS/MS is gaining support as the new reference method.

Laboratories can measure renin indirectly by PRA or directly as renin mass with DRC. PRA assays measure the generation of angiotensin I from angiotensinogen by renin's enzymatic activity (*3*). Renin activity assays by LC-MS/MS are replacing older RIA methods (*5*).

DRC assays measure the enzyme's direct concentration or enzyme's presence. Although both approaches are used clinically in the diagnostic work-up of PA, each method offers inherent differences.

Renin assessed by PRA is a tried and true analytical methodology. The conversion of angiotensinogen to angiotensin I by renin needs to be performed in buffered conditions and often at two reaction temperatures (37°C and 4°C utilized as a "blank"). Reaction incubation times also can vary from 1 to 3 and even 18 hours depending on the concentration of renin in a patient's sample (*3*).

Recent published methods of PRA by LC-MS/MS demonstrate improvements from the once popular RIA methods such as wide dynamic ranges (0.11-10.0 ng/mL/h), elimination of radiotracers and duplicate incubations, as well as the possibility of standardization of methods through the use of a high-quality calibrators available for angiotensin I (*5*). Even though PRA assays can be laborious, may contain radioisotopes as do RIA methods, or rely on expensive LC-MS/MS instrumentation and expertise, an abundance of literature demonstrates that they offer suitable low-end precision and clinically established cutoffs.

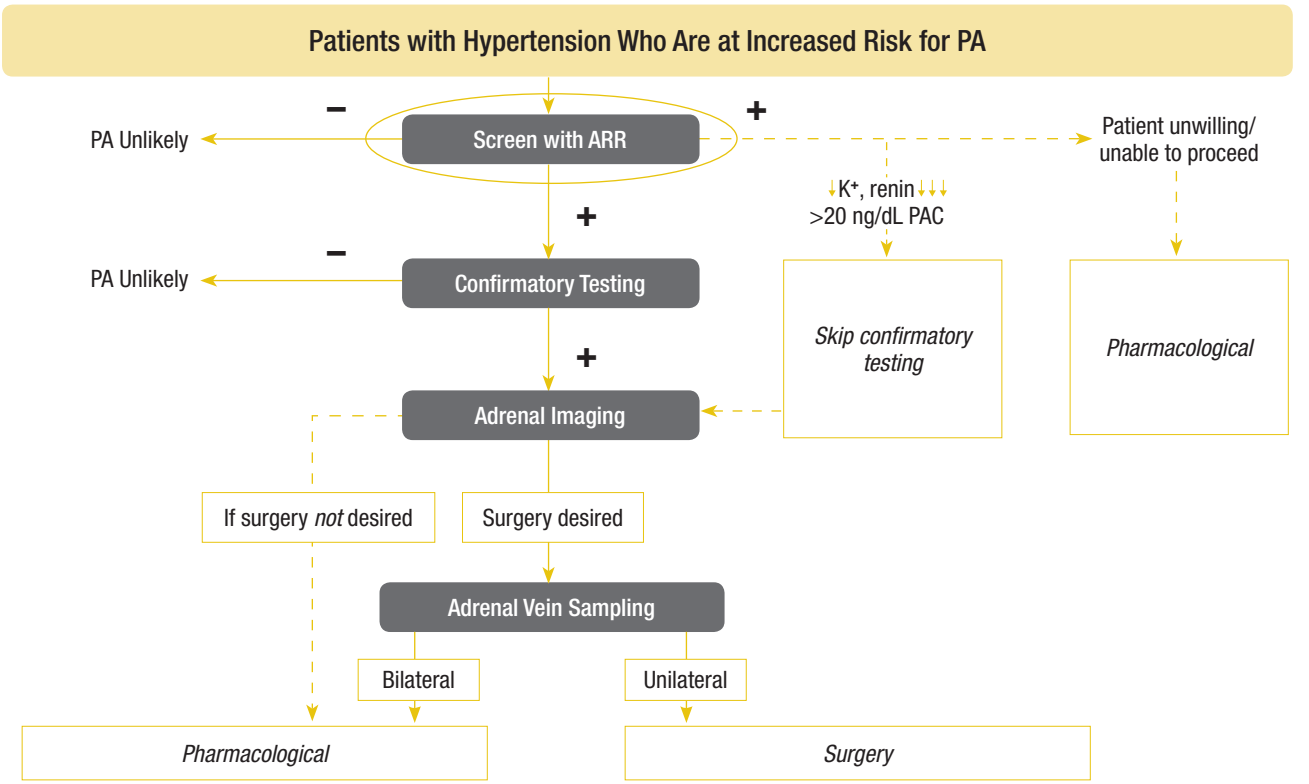
Assays that measure DRC utilize the basic capture and detection antibody schemes found in enzyme-linked immunosorbent assays or "sandwich assays" (*3*). These assays originally were immunoradiometric but since have been converted to automated chemiluminescent immunoassays. Unlike PRA, DRC assays are known to provide opportunities for walk-away automation, faster turnaround times, instrument connectivity to laboratory information systems, as well as a shared platform on which aldosterone can also be measured. However, limited supporting literature, poor correlations with PRA, and no clinically defined cutoffs limit widespread acceptance of this technique as a diagnostic test for PA. DRC assays are also susceptible to false increases due to conversion of renin to prorenin at temperatures around 4°C (*3*).

ARRs Present Interpretation Challenges

The ARR is considered a highly variable screening test that, if misinterpreted, can lead to delays in diagnosing and treating patients with PA (*3*). Diagnostic sensitivity of the ARR ranges from 64%-100% and specificity from 87%-100% (*4*). This high level of variability is attributed to within-subject variation, differences of laboratory assays used to measure renin or aldosterone, and many other preanalytical factors such as patient preparation protocols and prescribed medications. Additionally, ARR cutoffs provided in the 2016 Endocrine Society guidelines remain unchanged from the 2008 version even though advances have been made in aldosterone and renin methods such as LC-MS/MS and immunoassay (1,6).

The ARR may be falsely low or high due to several well-documented reasons (1). A good history and

F1 Endocrine Society recommended diagnostic algorithm for primary aldosteronism (modified from *1*).



Abbreviations: Plasma Aldosterone Concentration, PAC; Aldosterone-to-Renin Ratio, ARR

medication reconciliation are important to avoid testing patients with interfering factors that could lead to false-negative or false-positive results. False positives can be seen in hyperkalemic patients because this directly stimulates aldosterone production. Medications that directly inhibit renin can lower PRA while oral contraceptives or estrogens can directly lower DRC. On the other hand, hypokalemia impairs aldosterone production and can lead to false negatives. Mineralocorticoid receptor antagonist (MRA), angiotensin-converting enzyme inhibitors (ACE I), angiotensin II receptors (ARBs), diuretics, sodium restriction, and pregnancy all can cause false-negative ARR.

Specimen collection for aldosterone and renin testing should be performed mid-morning after a patient has been awake for at least 2 hours. Labs should avoid performing testing when samples have been obtained outside of appropriate collection times or in patients with interfering co-morbidities and/or medications. However, in some conditions it may not be feasible or safe to remove the confounding agent. Because of the importance of diagnosing patients with PA early, the Endocrine Society recommends that laboratories perform and interpret the ARR keeping these confounding factors in mind (*1*).

Diagnostic Teams Can Help Interpret ARRs

The challenges of a PA work-up demonstrate why laboratorians are critical to clinicians in diagnosing this disease. Recently the Institute of Medicine Committee on Diagnostic Error in Health Care endorsed using teams comprised of clinical experts to promote the diagnosis of many disorders (*7*). This report also identifies pathologists and other clinical laboratory experts as key contributors to these teams.

Such a group of experts is sometimes referred to as a diagnostic management team (DMT). A DMT is a collaborative group of laboratory and clinical experts who provide evidence-based, clinically useful, patient-specific interpretive reports that do not merely regurgitate laboratory data. To be considered DMTs, these groups must meet regularly (e.g. daily, weekly) to discuss cases and to formulate interpretations that utilize patient-specific clinical information that is valuable for patient care and readily viewable in electronic health records.

Patients being worked up for PA can benefit from the clinical expertise of a DMT that guides clinicians about ARR cutoffs for an institution's assays and helps to identify confounders such as medications, abnormal potassium status during testing, and possible effects of renal insufficiency. All of this information should be considered in the context of a patient's entire clinical picture to identify situations in which there is high likelihood of false-positive or false-negative results or identify results that are borderline and require additional work-up.

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Implementing an endocrine DMT for suspected PA can positively impact patient care. Recently, Wiencek *et al.* performed a small pilot study to assess the effect of a DMT using patient-specific interpretive reports in facilitating appropriate diagnoses of patients being screened for PA (*8*). This retrospective cohort study included four primary care physicians (PCPs) and 32 patients with ARRs ordered before, and 27 patients after, a DMT was implemented. Before the DMT existed, four patients had unnecessary testing/procedures (e.g., diagnostic imaging and laboratory testing) and eight may have experienced diagnostic delays. After the DMT started, the four PCPs adhered closely to guidelines and DMT recommendations for all PA evaluations (e.g., appropriate repeat ARR, imaging, specialty consults, and/or confirmatory testing).

T1 **Aldosterone to renin ratio (ARR) published cutoffs for suspected primary aldosteronism (modified from *1*).**

	PRA, ng/mL/hr	PRA, pmol/L/min	DRC, mU/L	DRC, ng/L
PAC (as ng/dL)	20	1.6	2.4	3.8
	30	2.5	3.7	5.7
	40	3.1	4.9	7.7
PAC (as pmol/L)	750	60	91	144
	1000	80	122	192

Abbreviations: Plasma Aldosterone Concentration, PAC; Plasma Renin Activity, PRA; Direct Renin Concentration, DRC

Provocative Confirmatory Testing

As mentioned, the ARR can be difficult to interpret because of the chance of false-positive and negative ratio results. For this reason, the Endocrine Society recommends provocative confirmatory testing (*1*). Currently, diagnostic work-ups of PA employ one or more of the following approaches:

1. **Oral sodium loading test.** Patient is advised to increase sodium intake to about 6 grams (>200 mmol) for 3 days after which a 24-hour urine sodium and urine aldosterone is measured. A urinary aldosterone <10 µg/24 h (28 nmol/d) makes PA unlikely. An elevated urinary aldosterone >12 µg/24 h (>33 nmol/d) makes PA highly likely. This test is not recommended in patients with severe uncontrolled hypertension, renal insufficiency, cardiac arrhythmia, or severe hypokalemia.
2. **Saline infusion test.** Patient stays in a recumbent position an hour before and during the infusion of 2 liters of 0.9% saline over 4 hours in the morning. Renin, aldosterone, cortisol, and potassium are drawn at time 0 and after 4 hours. BP and heart rate are monitored throughout the test. A post infusion aldosterone <5 ng/dL (140 pmol/L) makes PA less likely and levels >10 ng/dL (280 nmol/L) makes PA more likely. Values between 5-10 ng/dL are intermediate. This test is also contraindicated in patients with severe uncontrolled hypertension, renal insufficiency, cardiac arrhythmia, or severe hypokalemia.
3. **Fludrocortisone suppression test.** Patient is given 0.1 mg of oral fludrocortisone every 6 hours for 4 days, potassium chloride supplements to keep plasma potassium close to 4.0 mmol/L, and high sodium diet to maintain urinary sodium excretion rate of at least 3 mmol/Kg body weight. On the fourth day, plasma aldosterone and PRA are measured at 10 a.m. and plasma cortisol at 7 a.m. and 10 a.m. Plasma aldosterone >6 ng/dL (170 nmol/L) on day 4 at 10 a.m. confirms PA provided PRA is <1 ng/mL/h and 10 a.m. plasma cortisol is lower than the 7 a.m. measurement.
4. **Captopril challenge test.** Patient is given 25–50 mg of captopril orally after sitting or standing for at least 1 hour. PRA, plasma aldosterone, and cortisol are measured at time 0, and at 1 or 2 hours after the challenge, with the patient remaining seated during this period. Plasma aldosterone is normally suppressed by captopril but remains elevated while PRA remains suppressed in patients with PA. False negatives have been reported in patients with APA and in those with IAH.

There are certain instances in practice where confirmatory testing is not always performed. An example of this would be in a patient with spontaneous hypokalemia who has undetectable plasma renin with PAC >20 ng/dL (550 pmol/L). This is most likely PA and confirmatory testing is not necessary. Other patients might be unwilling or unable to proceed, in which case an MRA typically would be prescribed.

Subtype Classification for PA Treatment

All patients with confirmed PA should undergo subtype classification (*1*). Subtype classification is important because it helps to guide patient management. The recommended initial study is adrenal computed tomography (CT). A CT is vital to exclude large masses that may represent adrenocortical carcinoma and also to assist in making decisions for surgical interventions when appropriate.

Adrenal venous sampling (AVS) should be performed by an experienced radiologist before a patient proceeds to surgery. AVS is the gold standard test used in distinguishing between unilateral and bilateral adrenal disease (9). This test is operator-dependent and may be done unstimulated or Cosyntropin-stimulated under either bolus or continuous infusion conditions.

Not all cases need to undergo AVS. Younger patients (age <35 years) with spontaneous hypokalemia, marked aldosterone excess, and unilateral adrenal lesions who have radiological features consistent with a cortical adenoma on adrenal CT scan may not need AVS before proceeding to unilateral adrenalectomy (*9*). The clinical and radiological findings are evident enough to be able to proceed with surgery.

The treatment of PA depends on subtype classification, surgical candidacy, and patient choice. Laparoscopic adrenalectomy is the treatment of choice for patients with unilateral PA. Patients do very well after surgery with normalization of plasma aldosterone and potassium concentrations. These patients end up with reduced or normalized blood pressure, requiring fewer to no antihypertensive medications. They also have reduced cardiac hypertrophy and fibrosis (*9*).

For patients unable or unwilling to undergo surgery, medical management with an MRA, such as spironolactone and eplerenone, are the treatment of choice. Notably, patients who have positive ARR but who are unwilling or unable to undergo further investigations may be treated medically with an MRA.

Medical management is recommended for managing bilateral PA, such as in bilateral adrenal hyperplasia. Spironolactone is recommended as the primary agent, and eplerenone may be used as an alternative choice. Spironolactone is dosed once daily while eplerenone is dosed twice daily. Patients on medical management should have their potassium monitored as hyperkalemia is the most common side-effect of these medications.

Summary

PA remains a challenging diagnosis. Many factors influence the work-up of patients with suspected PA. As the overall rate of screening is expected to increase, collaboration between clinical laboratorians and other clinical experts will be key (*1*). Ultimately, a team-based approach could lead to helpful discussions about assay variability and diagnostic stewardship, which in turn could facilitate earlier disease detection.

Many factors influence the work-up of patients with suspected PA. As the overall rate of screening is expected to increase, collaboration between clinical laboratorians and other clinical experts will be key.

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Regulatory Roundup

FDA Issues Draft Recommendations on Minimizing Biotin Interference With Lab Tests

The Food and Drug Administration (FDA) has issued draft guidance providing recommendations on testing in vitro diagnostic devices for biotin interference. This draft guidance follows a 2017 safety communication in which FDA reported that taking high levels of biotin could interfere with lab tests that use this compound to bind target proteins, such as tests for hormones and cardiac markers. The 2017 safety communication provided recommendations for patients, healthcare professionals, and laboratory personnel on how to mitigate potential biotin interference. Now, this new draft guidance provides additional recommendations for in vitro diagnostic device manufacturers on how to test for biotin interference on in vitro diagnostic devices that use biotin technology. The guidance also outlines best practices for communicating the results of biotin interference testing to the end-users of diagnostic devices such as laboratory personnel.

Moving forward, FDA plans to work with researchers and healthcare professionals to improve understanding of how biotin interferes with laboratory tests. The agency also intends to advise diagnostic manufacturers as they develop tests that use biotin technologies to ensure that these tests bear minimal risk of biotin interference.

NEMAURA'S NONINVASIVE CONTINUOUS GLUCOSE MONITOR RECEIVES CE MARK

The CE mark has been granted to Nemaura Medical for SugarBeat, a needle-free continuous glucose monitor that consists of a disposable adhesive skin-patch connected to a rechargeable transmitter. This device provides real-time, continuous glucose readings at 5-minute intervals, which accumulate to provide users with a so-called ambulatory glucose profile. Users can then overlay these glucose profiles across multiple days to observe trends, patterns, and the extent of their glucose fluctuations. Nemaura believes that individuals with type 2 diabetes could use this in place of traditional periodic HbA1c readings to manage their glucose levels. Other features of SugarBeat include a visual alert that indicates when glucose levels are falling or rising above minimum and maximum thresholds, and an audible alert or physical vibration that SugarBeat sends through a user's phone when glucose levels fall below dangerously low levels. Additionally, users have the option to wear the SugarBeat patch on non-consecutive days.

FDA CLEARS ICUBATE IC-GN ASSAY FOR THE DETECTION OF BLOODSTREAM INFECTIONS

iCubate has obtained Food and Drug Administration (FDA) clearance for the iC-GN assay, a qualitative test that is designed to help decrease the burden of bloodstream infections and subsequent sepsis among critically ill patients. By detecting specific DNA targets, the iC-GN assay identifies gram-negative organisms associated with gram negative bacteremia, including *Acinetobacter baumannii complex*, *Escherichia coli*, and *Klebsiella pneumoniae*. The test also detects gene markers that indicate antibiotic resistance, including *KPC* and *NDM*, which are associated with resistance to carbapenems. The iC-GN will complement iCubate's previously cleared iC-GPC assay, which identifies five of the most common gram-positive organisms associated with gram-positive bacteremia, including *Staphylococcus aureus*. The iC-GPC also identifies clinically relevant antibiotic resistance markers specific to methicillin-resistant *Staphylococcus* and vancomycin-resistant *Enterococcus*. Both tests run on iCubate's multiplex polymerase chain reaction molecular diagnostics platform.

SPEEDX GETS OK FROM HEALTH CANADA FOR ANTIBIOTIC-RESISTANT STI TEST

Health Canada has cleared SpeeDx's ResistancePlus MG test for distribution across all Canadian provinces. This is the first molecular diagnostic test in Canada that detects sexually transmitted infection caused by *Mycoplasma genitalium*, along with genetic markers

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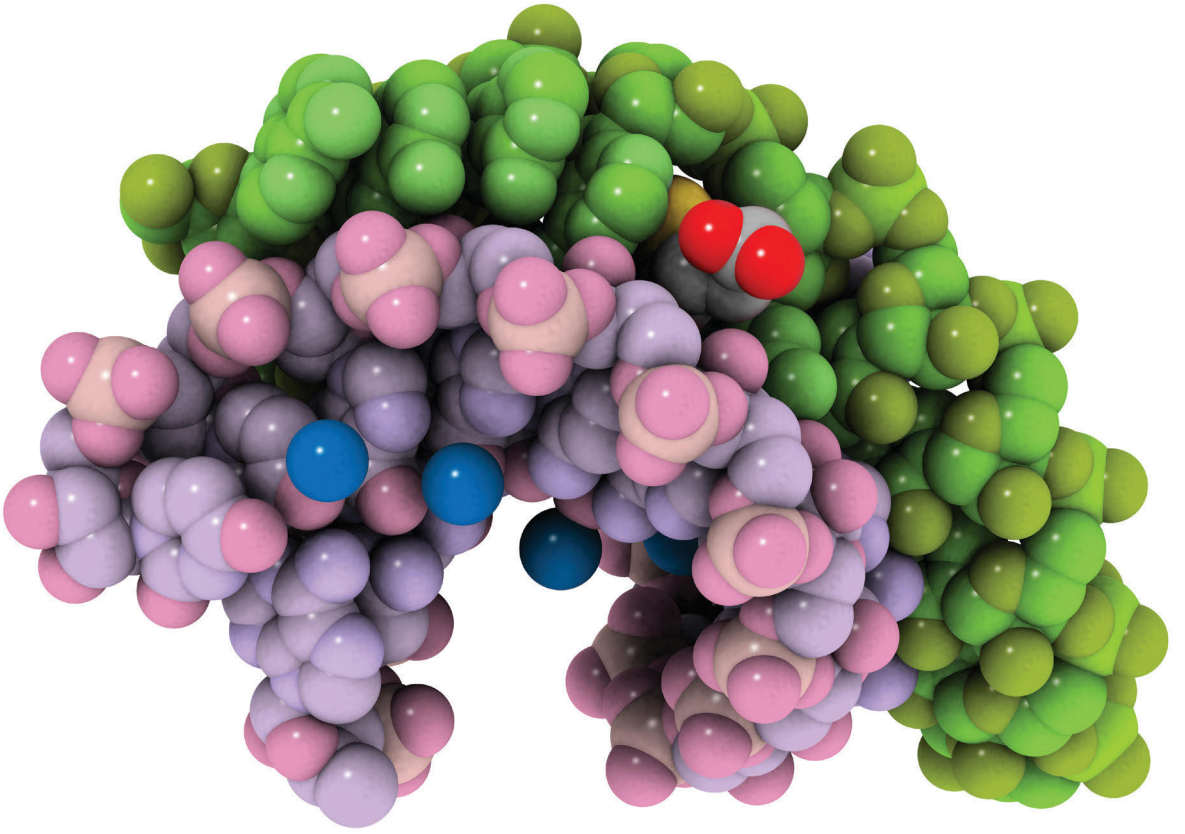

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linked to antibiotic resistance. Resistance to azithromycin, a common macrolide antibiotic treatment for *M. genitalium*, has been increasing in areas where healthcare providers use *M. genitalium* detection alone to guide treatment. ResistancePlus MG could help to reverse this trend, and new evidence indicates that when providers use this test as part of a resistance-guided therapy protocol, cure rates for *M. genitalium* infection improve, rising from 60% to higher than 92%. The test is already in use across Europe, the United Kingdom, Australia, and New Zealand. While the Food and Drug Administration (FDA) has not yet cleared a test for the combined detection of *M. genitalium* and macrolide resistance markers, SpeeDx is also finalizing clinical trials in the U.S. in preparation for FDA submission later this year.

AKONNI BIOSYSTEMS GETS FDA NOD FOR MULTIPLEX MOLECULAR TESTING PLATFORM

The Food and Drug Administration (FDA) has granted 510(k) clearance to Akonni Biosystems for the TruDiagnosis system, a multiplex molecular diagnostic device designed for point-of-care use. The system includes the TruDx 2000 Imager and the TruArray consumable test kit, the latter of which features gel-drop microarray technology and a novel microfluidic design that integrates on-chip polymerase chain reaction with one to hundreds of microsensors in a single chamber. The system delivers results in 15 minutes for immunoassays, and in 1-3 hours for nucleic acid-based tests. The first assay cleared for use on this platform is a saliva test that identifies genetic signatures associated with patient metabolization of the blood-thinning drug Coumadin, and that is intended to help doctors adjust a patient's therapeutic Coumadin dose to safer and more effective levels. Following this FDA clearance, Akonni plans to partner with other diagnostic companies to develop additional diagnostic assays for use on the TruDiagnosis system.

FDA APPROVES ABBOTT'S ALINITY S BLOOD AND PLASMA SCREENING SYSTEM

Abbott has received Food and Drug Administration (FDA) approval for the Alinity s System, which is designed to screen blood and plasma more efficiently and within a smaller space than currently available systems. The Alinity s System runs up to 600 tests per hour and is largely automated, with a minimum walk-away time of 3 hours. It gives blood donation centers the ability to track all activities and actions associated with blood and plasma donation and screening in accordance with regulatory requirements. The system also features solution bottles that work like a lock and key, meaning that they can only be inserted into the correction location on the instrument. Additionally, the Alinity s enables lab technicians to continuously load and unload samples and supplies without pausing or stopping the system, and features a software interface, menu, and sample loading layout that are all designed to be intuitive.

Industry Playbook

Resolution Bioscience, Janssen Partner on cfDNA Co-Diagnostic for Prostate Cancer

In collaboration with Janssen Research & Development, Resolution Bioscience is developing the Resolution HRD liquid biopsy assay as a companion diagnostic for the Janssen therapeutic niraparib, a poly ADP ribose polymerase inhibitor that is designed to treat metastatic castration-resistant prostate cancer. This assay recently received Breakthrough Device Designation from the Food and Drug Administration, and Janssen is currently using it to identify prostate cancer patients with homologous recombination deficiency (HRD) mutations and gene deletions in phase II and III clinical studies of niraparib.

The Resolution HRD liquid biopsy assay detects HRD mutations and gene deletions in cell-free DNA (cfDNA) and distinguishes between single copy and biallelic gene deletions. It also detects homozygous deletions and identifies when deleterious mutations and heterozygous deletions are present in the same gene, a combination that causes biallelic loss of function. If approved as a companion diagnostic for niraparib, the Resolution HRD assay could become the first commercial test to detect all these alterations from a blood draw.

"Built on our proprietary cfDNA next-generation sequencing technology platform, we expect the Resolution HRD assay will enable Janssen to identify patients with prostate cancer who may benefit from niraparib therapy," said Mark Li, CEO of Resolution Bioscience. Due to the assay's noninvasive approach, Resolution Bioscience believes that it could also help expand patient access to other targeted prostate cancer therapies.

FIND, UNITAID TO STUDY USE OF NGS FOR DIAGNOSIS OF DRUG-RESISTANT TB

The Foundation for Innovative New Diagnostics (FIND) and Unitaid have launched the Seq&Treat program to evaluate the use of next-generation sequencing (NGS) for diagnosis of drug-resistant tuberculosis (TB) in low- and middle-income countries (LMICs). In October 2019, the partners will begin to implement this program across Brazil, China, Georgia, India, and South Africa. The project's goals include generating clinical evidence to support World Health Organization global guidance for the use of targeted NGS for drug-resistant TB diagnosis; evaluating proof-of-principle delivery models for integrating targeted NGS into existing diagnostic workflows; and facilitating the inclusion of recommended NGS solutions into global procurement mechanisms for LMICs.

"The implementation of sequencing for patient care in LMICs has been limited due to perceptions of high cost, technical and workflow complexity, and lack of infrastructure on both supply and demand sides," said Catharina Boehme, CEO of FIND. "This significant investment from Unitaid

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will enable us to challenge these ideas by demonstrating sustainable and scalable sequencing models in high-burden TB countries."

CARIS LIFE SCIENCES, DEBIOPHARM TO DEVELOP ASSAY FOR DETECTION OF RARE FGFR FUSIONS

Caris Life Sciences has teamed up with Debiopharm International to develop a companion diagnostic test that will identify patients eligible for Debiopharm's phase II clinical trial of Debio 1347. Debio 1347 is a selective fibroblast growth factor receptor (FGFR) inhibitor that is designed to treat patients with non-central nervous system solid tumors. The companion diagnostic for this drug will use Caris' Molecular Intelligence Transcriptome, a new whole transcriptome sequencing assay that detects rare FGFR fusion events that signal the presence of such tumors. This test is RNA-based, which means that unlike DNA-based methods, it detects any fusion event independent of breakpoint locations and fusion partners.

"This collaboration represents a key milestone in the advancement of a new tumor-agnostic approach," said Angela Zubel, chief development officer at Debiopharm International. "We believe that a whole transcriptome assay is particularly relevant to detect oncogene fusions and to identify tumor expression profiles that could benefit from Debio 1347 therapy."

BECKMAN COULTER LIFE SCIENCES ACQUIRES CYTOBANK

Beckman Coulter Life Sciences recently bought Cytobank, a company that provides scientists with a cloud-based single-cell data analysis platform optimized for high-parameter workflows. The platform enables users to visualize and analyze several single-cell datasets simultaneously, thereby accelerating high-dimensional mass and flow cytometry data analysis. This platform complements Beckman Coulter's CytoFLEX LX flow cytometer, which is the newest version of the CytoFLEX Platform and features six lasers and 21 color parameters.

Beckman Coulter hopes that their acquisition of Cytobank will meet the growing need for high-complexity workflow and data analysis. "We are excited to add Cytobank's innovative software solutions and customer workflow-focused team to our flow cytometry business," said Mario Koksch, MD, PhD, the Flow Cytometry Business Unit vice president and general manager at Beckman Coulter. "We can now provide more standardized, yet flexible high-end data analytics

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solutions to pharma/biopharma and leading academic clinical research customers."

TABULA RASA, CQUENTIA AIM TO IMPROVE DELIVERY OF PGX RESULTS

Tabula Rasa HealthCare (TRHC) and CQuentia are collaborating to offer pharmacogenomics (PGx) services to patients and providers. TRHC is a healthcare technology company that provides solutions to mitigate medication risk, while CQuentia's services include a clinical genomics testing lab and a personalized medicine analytics platform. Under the terms of their agreement, CQuentia will use TRHC's MedWise platform to deliver pharmacogenomics results to ordering physicians. To facilitate this, TRHC will establish application programming interfaces with CQuentia to receive PGx data directly from CQuentia's lab.

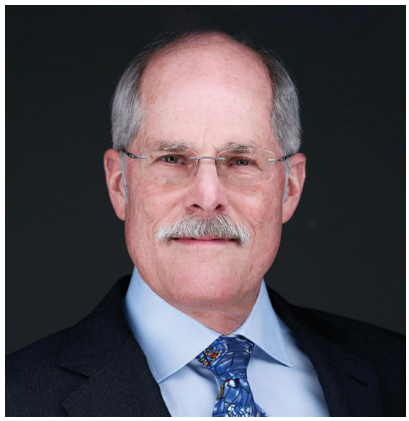
"Unlike traditional drug-gene pair analysis, which marginalizes the potential impact of PGx, MedWise uses PGx data to inform precision across a patient's entire medication regimen," said Alan Meeker, CQuentia's CEO. "CQuentia has determined that TRHC's unique and valuable approach to incorporating PGx lab data into medication safety analysis makes TRHC the ideal partner to present PGx lab results to its clients."

INVITAE BUYS JUNGLA TO ADVANCE ITS GENETIC VARIANT INTERPRETATION SERVICES

Medical genetics firm Invitae has signed an agreement to acquire Jungla, the developer of a cloud-based platform designed to help clinicians and patients understand the results of genetic and genomic tests. Called the Functional Modeling Platform (FMP), Jungla's technology combines clinical knowledge with advances in functional genomics, biophysics, cellular engineering, machine learning, and distributed systems. In a November 2018 pilot study, Invitae and Jungla evaluated FMP's performance when predicting the clinical relevance of DNA variants found in individuals undergoing testing for hereditary disease. The study found that support from Jungla's FMP helped Invitae to clarify the interpretation of variants and move them from the uncertain category to pathogenic or benign status. Invitae therefore expects this acquisition to enhance its ability to interpret genetic variants and to deliver more affordable genetic testing for use in mainstream medical care.

Ask The Expert

Scientific Impact and the H-Index



EXPERT
William E. Schreiber, MD

What is the h-index?

A: The h-index is a means of measuring scientists' impact on their field, determined from two quantities: the number of publications by a scientist and the number of times those publications have been cited. Think of it as the intersection of productivity (papers published) and recognition (citations). The higher the h-index, the greater a scientist's academic footprint.

In what ways does the h-index matter?

Jorge Hirsch, a physicist, created this index in 2005. Since then, scientists in other fields have begun using it too, as of course many scientists and other academics compete for promotions, research grants, and professional awards. The committees and review panels that hand out these distinctions expect to see an applicant's record of accomplishment, and much of that evidence is in peer-reviewed journals and other publications.

Assigning importance to individual publications is a subjective, time-consuming process. In contrast, the h-index is determined directly from data available through the internet. No subjective judgment is required, and it is easy to compare an h-index number among individuals and against established benchmarks.

How would a researcher calculate this number?

Identify all your publications, then look up the number of citations for each paper on Google Scholar, Web of Science, or Scopus (the latter two databases require a subscription). Order the publications from highest to lowest number of citations. Then, go down the list until the number of citations for a paper is less than the number of papers you have counted. The h-index is equal to the number of papers (h) that have been cited at least that many times each.

What is a good h-index?

That is a matter of opinion. A colleague and I surveyed typical values for academic physicians in 14 medical specialties (Am J Clin Pathol 2019;151:286-91). We found that, on average, assistant professors have an h-index of 2-5, associate professors 6-10, and full professors 12-24. These are mean or median values only—the distribution of values at each rank is very wide. If you hope to win a Nobel Prize, your h-index should be at least 35 and preferably closer to 70.

If you belong to a university department, you are likely to hear about quantitative measures of academic performance. By understanding the h-index, you are in a better position to evaluate its pros and cons as a yardstick for scientific achievement.

Is it really that simple to characterize a scientist's achievements?

Although simple to calculate, the h-index does not capture the full story of a scientist's contributions. For example, single author papers count the same as multi-author papers. And there is no extra credit for being the first or last author, which usually indicates a greater role in the project.

In addition, self-citation can inflate one's score. And the h-index never decreases, so it is not a good indicator of recent activity. Most reviewers consider the h-index as one piece of a larger picture, rather than a definitive ranking tool.

The h-index doesn't involve lab medicine. Why should I care about it?

If you belong to a university department, you are likely to hear about quantitative measures of academic performance. By understanding the h-index, you are in a better position to evaluate its pros and cons as a yardstick for scientific achievement. This will be helpful when evaluating the work of professional colleagues or when arguing your own case for promotion.

William E. Schreiber, MD, is a professor of pathology and laboratory medicine at The University of British Columbia and clinical director of chemistry at LifeLabs in Burnaby, British Columbia.
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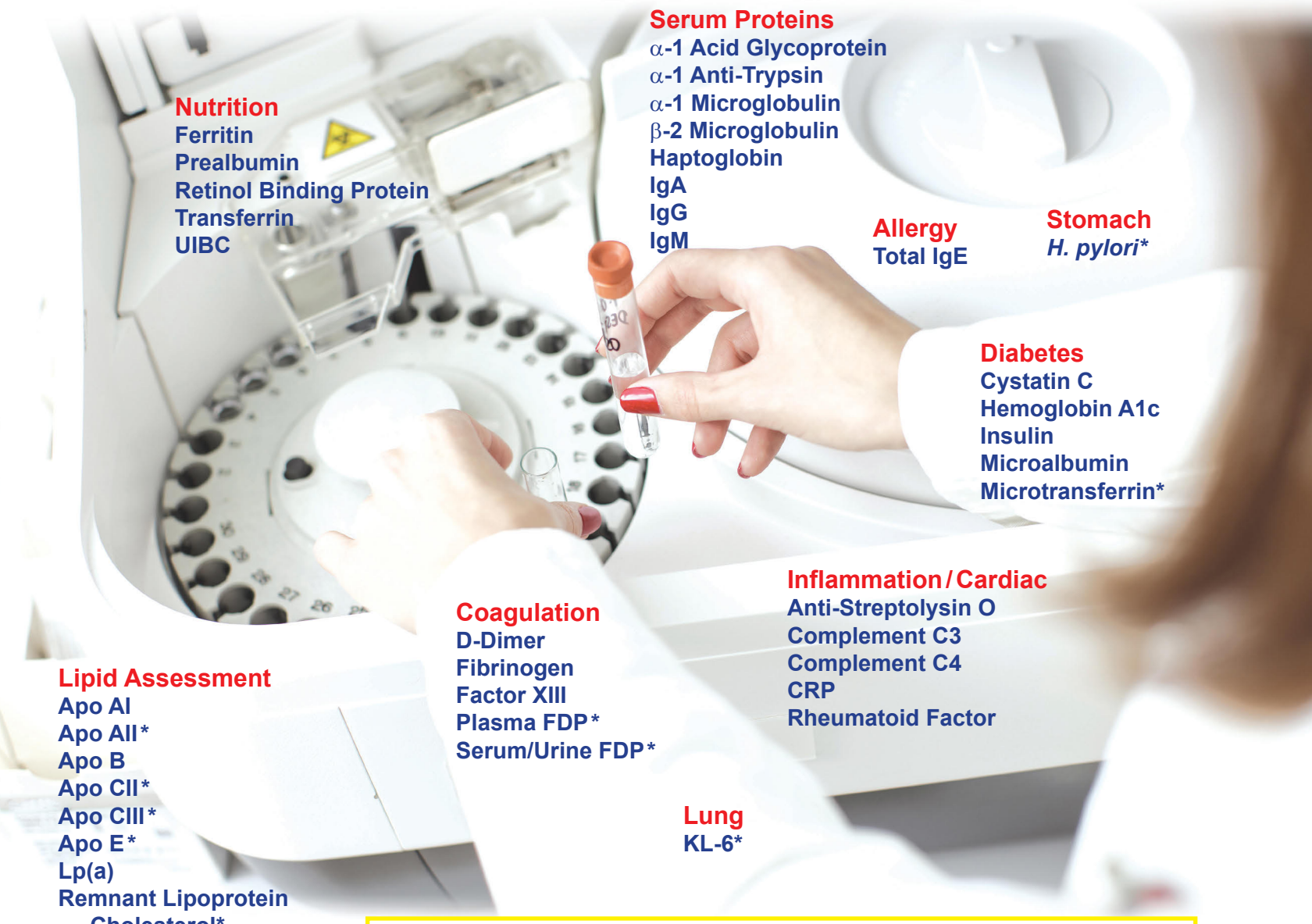

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