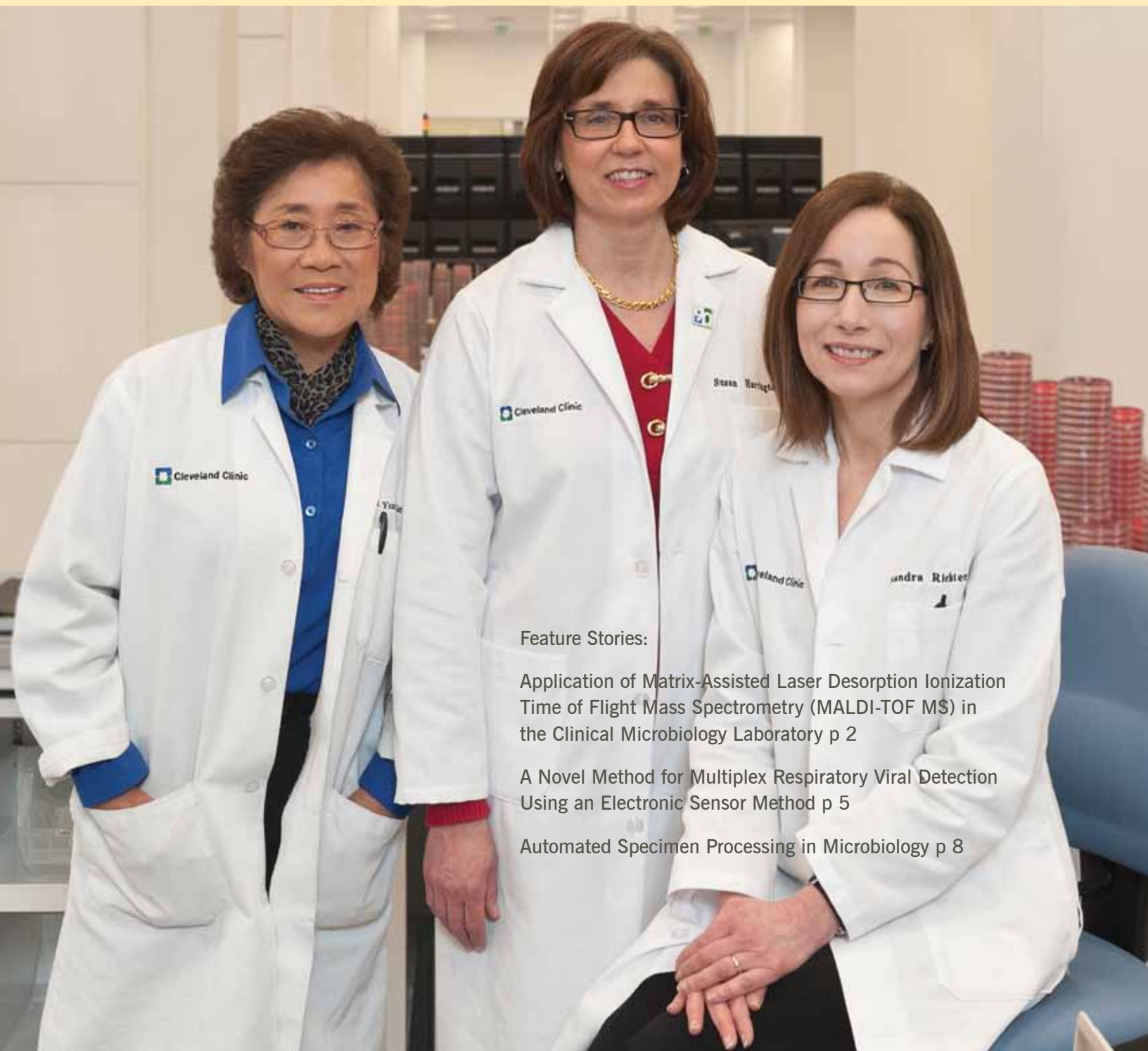


Pathology Innovations

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The Application of Matrix-Assisted Laser Desorption Ionization Time of Flight Mass Spectrometry (MALDI-TOF MS) in the Clinical Microbiology Laboratory

By Sandra S. Richter, MD

Clinical microbiology laboratories perform essential tests to diagnose and guide the treatment of infections. One of the most common microbiologic tests performed is bacterial culture of specimens such as blood, cerebrospinal fluid, urine or sputum. The specimen is inoculated to nutritive media followed by incubation. Each type of colony that grows on the plate must be identified and classified as normal flora or a possible pathogen causing infection. Despite this age of advanced medical technology, days are often required to identify organisms recovered from culture. Recently, clinical microbiology laboratories throughout the world have begun to implement new mass spectrometry technology for organism identification. This proteomic method is faster and more accurate than the biochemical identification performed routinely in most clinical laboratories.

Mass spectrometry (MS) has been used for the past 50 years to ionize and then identify molecules by determining their individual mass-to-charge (m/z) ratio. Early MS ionization methods were destructive and could not be used to analyze large molecules such as proteins. A soft ionization technique (matrix assisted laser desorption/ionization, MALDI) that does not fragment large molecules was invented in the 1980s.¹ A matrix solution (usually α -cyano-4-hydroxycinnamic acid) protects large molecules from fragmentation by absorbing photonic energy from the laser ("desorption"). Single-charged molecules are created and travel in a tube toward a detector. The time of flight (TOF) is directly proportional to mass and used to calculate a mass-to-charge ratio. Charting of the mass-to-charge ratios for individual ions creates a series of peaks called a spectrum that is compared to a reference database (Fig 1). Increasing availability of gene sequences for microorganisms led to the recognition that many of the mass spectral peaks in the 2,000-20,000 dalton range represent ribosomal proteins.² Other peaks represent proteins that play key roles in cell function and structure. The stability and reproducibility of mass spectral patterns make MALDI-TOF MS a robust identification method. The accuracy of MALDI-TOF MS bacterial and yeast identifications is similar



to more labor intensive and expensive gene sequencing methods.³⁻⁶

Using one of the two MALDI-TOF MS systems currently available in the United States is simple. A small amount of bacterial growth from a culture plate is applied to a target plate and covered with 1 μ l of matrix solution. For yeast, an extraction step with application of 0.5 μ l formic acid directly to the isolate is required before the matrix overlay. The target plate is placed in the instrument where a laser irradiates the sample to create ions inside the instrument's vacuum chamber. The time of flight before detection of these electrically charged particles is based on their particular masses and

used to create a spectrum or “signature.” Computer software compares the spectrum to a database and if there is a match the identification is generated within minutes of ionization. The purchase price of a MALDI-TOF MS system is approximately \$200,000, but the labor and reagent cost to generate the identification is \leq \$.50.^{6,7}

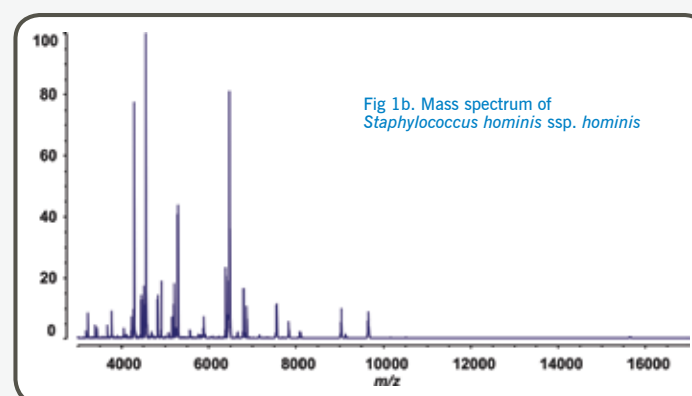
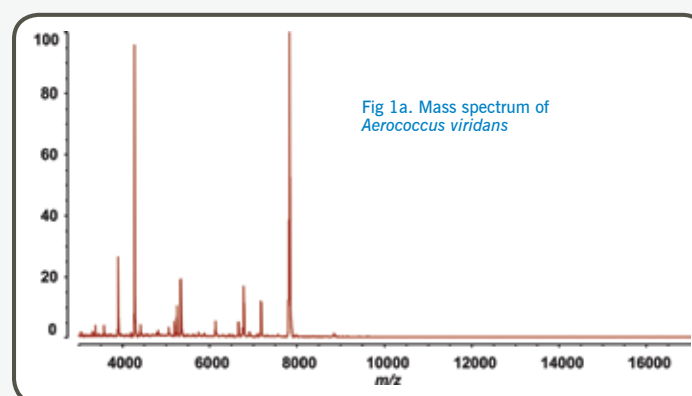
Manufacturers of MALDI-TOF MS systems are initially seeking FDA clearance for identification of bacteria and yeast isolates from culture. Studies show MALDI-TOF MS will also reliably identify mycobacterial and mould isolates.^{8,9} In addition to testing pure culture isolates growing on solid media, there are other applications of MALDI-TOF MS in clinical microbiology. Organisms from positive blood culture broths can be identified by MALDI-TOF MS after additional processing steps if the broth does not contain charcoal.¹⁰⁻¹¹ Bacteria causing urinary tract infections can be detected by performing MS directly on urine samples if the bacteria are present in high numbers.¹² However, lower levels of bacteria that may also represent an infection are not reliably detected in urine. Although the hydrolysis of carbapenems by bacterial isolates has been demonstrated after a short incubation (≤ 2.5 h),¹³ other mechanisms of carbapenem resistance such as porin mutations or efflux cannot be detected by MALDI-TOF MS.

Until the FDA has reviewed multicenter clinical trial data for MALDI-TOF MS systems, these devices are considered research-use-only technology. Laboratories must validate a system internally according to CLIA guidelines before using MS technology to provide identifications of organisms that guide clinical care.

Rapid organism identification allows clinicians to prescribe the most appropriate treatment for infections sooner and de-escalate therapy from broad-spectrum agents that drive antimicrobial resistance. The development of MALDI-TOF MS allowing more accurate identifications of bacteria and yeast in minutes rather than days is an important innovation that should improve clinical outcomes.

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About the Author



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Dr. Richter is Chair of the College of American Pathologists (CAP) Clinical Pathology Education Committee and a member of the CAP Council on Education. She is a Diplomat of the American Board of Medical Microbiology, a Fellow of the Infectious Diseases Society of America, and a member of the American Society for Microbiology Committee on Postgraduate Educational Programs. Dr. Richter is an Advisor to the Clinical Laboratory Standards Institute (CLSI) Subcommittee on Antimicrobial Susceptibility Testing. She serves as the Secretary for the CLSI Staphylococcal and Streptococcal Working Group and is a member of the CLSI Intrinsic Resistance Working Group. Dr. Richter is a volume editor for the Manual of Clinical Microbiology and serves on the editorial boards of the Journal of Clinical Microbiology and Diagnostic Microbiology and Infectious Diseases.

Dr. Richter received her undergraduate and medical degrees from the University of Missouri. She completed a residency in clinical pathology and a fellowship in medical microbiology at the University of Iowa Hospitals and Clinics.

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A Novel Method for Multiplex Respiratory Viral Detection Using an Electronic Sensor Method

By Belinda Yen-Lieberman, PhD

Background

Respiratory viruses are responsible for an estimated 80% of respiratory tract infections yearly. These infections can range from a mild, self-limiting illness to severe disease that can cause death. More severe disease is seen in the young, the immunocompromised and the elderly. It is estimated that an average 24,000 deaths annually are attributed to influenza in the United States.¹ In children, respiratory syncytial virus (RSV) is the most common cause of severe lower respiratory tract infection worldwide. Timely detection of these viruses can lead to initiation of proper antiviral treatment, decreased use of unnecessary antibiotics, reduced transmission of disease from person to person and better clinical outcomes.²

Due to low sensitivity of respiratory viral rapid antigen tests and the long turn-around time of viral culture, many laboratories are using PCR-based methods for detection of respiratory viruses.³ Many laboratories have used multiplexed Respiratory Viral Panel (RVP) tests during the past two to three years. These multiplex RVP tests have demonstrated the ability to detect many respiratory viruses in most patients with influenza-like illness (ILI). However, some of these multiplex RVP tests are labor intensive with long turnaround and hands-on times before results are available (usually between 7-9 hours per run).

eSensor technology from GenMark Diagnostics (GenMarkDx, Carlsbad, CA) is a novel assay that uses a solid-phase electrochemical method on the XT-8 platform for detection of nucleic acid targets. Targets are detected by a voltage change when DNA binds to capture probes on a gold electrode. We evaluated the eSensor RVP that includes 7 different viruses with a total of 14 targets used for subtyping with our current PCR multiplex method that includes a small multiplex RVP. (Flu A, Flu B and RSV plus DFA for the remaining 5 respiratory viruses.) (Table 1)

Table 1. Viral targets included in eSensor RVP

Viral Target	Abbreviation
Influenza A	Flu A
Influenza A H1	Flu A H1
Influenza A H3	Flu A H3
Influenza A 2009 H1N1	Flu A H1N1
Influenza B	Flu B
Respiratory syncytial virus A	RSV A
Respiratory syncytial virus B	RSV B
Parainfluenza virus 1	PIV 1
Parainfluenza virus 2	PIV 2
Parainfluenza virus 3	PIV 3
Human metapneumovirus	hMPV
Human rhinovirus	HRV
Adenovirus B/E	ADV B/E
Adenovirus C	ADV C

Methods

The leftover de-identified samples from our routine respiratory viral tests were used for this study following approval by the internal review board. Samples were tested with the eSensor XT-8 system and IUO respiratory viral panel kit (GenMark Diagnostics, Inc.) according to the package insert. Nucleic acids were extracted from 200 μ l of each specimen using the easyMAG (bioMerieux, Inc.) after the addition of 10 μ l of bacteriophage MS2 internal control (included in the kit). Conventional endpoint PCR was performed (using TC9700) in 35 μ l volumes using 5 μ l of extracted sample and the multiplex master mix provided in the kit. The thermal cycling protocol consisted of 1 cycle at 50°C for 30 minutes for reverse transcription; 1 cycle at 95°C for initial PCR activation; followed by 40 3-step cycles of 30 seconds at 94°C, 60 seconds at 60°C and 60 seconds at 72°C for

denaturation, annealing and extension, respectively. After PCR, 5 μ l of exonuclease was added to each reaction and the mixture was returned to the thermal cycler for 20 minutes at 37°C to create single-stranded DNA, followed by 2 minutes at 95°C for enzyme inactivation. 100 μ l of hybridization buffer that contained ferrocene-labeled signal probes specific for the viral targets was added to each reaction. 125 μ l of the mixture was added to the test cartridge, which was loaded onto the eSensor XT-8 instrument for analysis.



Culture/DFA comparator testing was performed on all samples (R-mix for culture and IFA using monoclonal antibodies specific for various respiratory viruses).

Table 2. Patient demographics

Demographic	N (%)
Sex	
Male	117 (45.2)
Female	142 (54.8)
Age (years)	
0-1	27 (10.4)
>1-5	22 (8.5)
>5-21	26 (10.0)
>21-65	130 (50.2)
>65	54 (20.8)
Status	
Outpatient	89 (34.4)
Hospitalized	115 (44.4)
Emergency department	55 (21.2)

Results

Patient demographics are summarized in Table 2. Adults and children were sampled and there was an approximate equal distribution of inpatients, outpatients and emergency room patients. Of the 259 samples evaluated, 130 (50.1%) were positive for at least one virus. Twenty-three samples (8.8%) detected at least 2 viruses. A total of 157 respiratory viruses were detected with the most prevalent being HRV (9.3%), Flu A 2009 H1N1 (8.1%) and Flu B (7.7%). For 86 of the results, the eSensor and culture/DFA results were concordant. There were 71 samples in which the DFA was negative while the RVP was positive. After sequencing analysis, 64 of 71 (90.1%) results were concordant with the RVP results giving an overall concordance of 95.5%.

Results

	CCF RVPAN 22 (30.1%)	GENMARK(RVP) 54 (73.9%)
FLU A	3 (4.1%)	6 (8.2%)
FLU B	4 (5.5%)	5 (6.8%)
RSV	10 (13.7%)	9 (12.3%)
ADV*	1 (1.4%)	7 (9.6%)
PIV 3*	4 (5.4%)	8 (10.8%)
PIV*	0	0
PIV 2*	0	0
HMPV*	0	2 (2.7%)
HRV	NA	13 (17.6%)
COR	NA	4 (5.4%)
Co-infections	0	8 (10.9%)
NEG	51 (69.9%)	29 (39.2%)

(*Detected by DFA)

Discussion

Results from the eSensor RVP were comparable to the gold standard viral culture and DFA. Discordant results were minimal. The multiplex eSensor RVP has a 5.5-hour turnaround time and is relatively easy to perform. In addition, the RVP detected co-infections, which is important for cohorting of patients.

This evaluation was performed on adult and pediatric patients from the Cleveland Clinic health system. Approximately one third of the samples were from the outpatient setting, which is where the majority of patients would present with flu-like symptoms. Therefore, we feel our results are generalizable to other patient populations.

This assay is an innovative multiplex test for the detection of an expanded panel of respiratory viruses. It is especially suitable for immunocompromised and hospitalized patients with respiratory symptoms that can be undiagnosed with conventional testing. Its ease of use allows the eSensor RVP to be easily implemented in a busy hospital laboratory. The eSensor RVP test has been FDA cleared for *in vitro* diagnosis use (2012).

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About the Author



Belinda Yen-Lieberman, PhD, MS, is medical director of Clinical and Molecular Virology, Serology and Cellular Immunology in the Department of Clinical Pathology and Department of Molecular

Pathology at Cleveland Clinic. She is also professor of pathology at the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University.

Dr. Yen-Lieberman has authored more than 100 articles for numerous medical journals on a wide range of topics involving viruses and infectious disease, including studies involving HIV, hepatitis B, hepatitis C and influenza A vaccine, tests for herpes simplex types 1 and 2, and tuberculosis. Dr. Yen-Lieberman also serves on the editorial boards of the *Journal of Clinical Virology*, *Journal of Clinical and Vaccine Immunology* and the *Journal of Clinical Microbiology*. She has served on the CLIA Subcommittee M53-A (Criteria for Laboratory Testing and Diagnosis of Human Immunodeficiency Virus Infection-Approved Guideline) and CLIA MM06-A2 (Quantitative Molecular Methods for Infectious Diseases: Approved Guideline). She currently serves on the Advisory Board of the AIDS Clinical Trial Group (ACTG/NIH) Virology Quality Assurance Program and a member of the AIDS Clinical Trial Group (Virology), the CDC HIV Rapid Testing Quality Assurance Workgroup, and the Special Emphasis Panel Study Section of the National Institute of Allergy and Infectious Diseases/ National Institutes of Health.

Dr. Yen-Lieberman received her bachelor of science degree in microbiology from Southern Illinois University and her master of science and doctorate degrees in immunology and biochemistry at the University of Arkansas. She later completed fellowships in clinical and cellular immunology at Case Western Reserve University and the Cleveland Clinic Foundation.

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Automated Specimen Processing in Microbiology

By Susan Harrington, PhD

In this era of rising healthcare expenditures, laboratories are challenged to provide state-of-the-art services at the lowest possible cost. Compounding these financial challenges are issues related to maintaining sufficient numbers of technical staff to perform laboratory testing. A recent national survey of laboratory managers estimates that approximately 13% of the current laboratory workforce may retire in the next several years. Many labs currently face vacancy rates of 5 to 10% for bench-level technologists and technicians.²

Laboratories often turn to automating procedures traditionally performed by manual methods to address labor shortages, reduce costs and decrease turnaround times. Automation has been routine in chemistry and hematology laboratories for decades. With the exception of instruments that perform DNA extraction and amplification by polymerase chain reaction, automation is relatively rare in microbiology laboratories. In fact, the main test offered in microbiology, routine culture, has remained relatively unchanged for about a century. By and large, specimens suspected to harbor bacterial and fungal pathogens are still cultured on agar media, where significant pathogens can be identified and tested for susceptibility to a panel of relevant antibiotics. However, one key critical step of the culture method – the initial planting or processing of the specimen onto the agar plate media – can now be automated.

Specimens commonly processed in microbiology include urine, stool, sputum, swabs from wounds, tissues and body fluids. Careful specimen processing takes time and must be performed consistently, without contamination of the cultures with extraneous environmental organisms. For some specimen types, planting a calibrated sample volume onto the agar may be required for proper interpretation of results. With an eye toward standardizing this process and decreasing the time required for manual processing, several commercial companies have developed automated instruments capable of doing the work of human hands.⁵

Cleveland Clinic's Robert J. Tomsich Pathology and Laboratory Medicine Institute recently invested in an instrument manufactured by Copan™ called the Walk Away Specimen Processor, or WASP™. This instrument is capable of transferring liquid specimens to agar plates using standard bacteriologic loops

and streaking methods. Utilizing barcodes on the side of sample tubes or cups, the microprocessor within the WASP reads the label and is able to plant a predetermined volume of the specimen according to stored protocols. The planting protocol is based on the specimen source and is taken directly from provider orders placed in the laboratory information system. The instrument is capable of vortexing the specimen, decapping the tube, planting, streaking and then recapping each sample tube before moving on to the next. Tubes and containers of various sizes can be accepted. The WASP streaks the plates using streaking patterns chosen by the operator. Agar plates are sorted according to incubation temperature and atmosphere, further reducing plate manipulation.

One important caveat to automated specimen processing is the need for specimens that are liquid. Non-liquid specimens cannot be managed. Fortunately, for the typical microbiology laboratory, the majority of samples cultured on agar media are urine. Stool specimens in Cary Blair transport, swabs in liquid solution and body fluids may also be accommodated. To increase capacity, Copan has developed a proprietary chemical agent that can be used to liquefy sputum specimens so that sputum may also be included in the repertoire of samples. Tissues, hardware and specimens for mycobacterial culture are among specimens unsuitable for automated processing at this time. We estimate that about 70% of the clinical specimens currently manually streaked for culture may be placed on the WASP.

In addition to plating and streaking the sample onto the agar, the WASP labels the plates, using information downloaded through an interface connected to the laboratory information system. These three steps (planting, streaking and labeling) accomplish the major time savings. Estimates from timing studies performed in the laboratory with urine specimens suggest that the WASP will save 18 and 40 seconds per sample in labeling and planting/streaking, respectively. When those numbers are multiplied by hundreds of specimens each day, significant savings may be achieved.

Although the major function of the WASP is to plant specimens and streak the agar plates, the WASP has been designed as a modular system. Additional features include a gram stain preparation station, a broth planting and subculture module,



and a station that can set up plates for susceptibility testing by the Kirby-Bauer method. In the future, we expect it to be able to spot targets for MALDI TOF analysis.

The major benefit of the WASP is in savings of technical time for laboratory personnel. Technical staff may be repurposed to duties more suited to their level of education, increasing job satisfaction. Reducing the number of repetitive motions performed by human hands can also contribute to an improved work experience for employees by decreasing stress on tendons and joints. Other benefits are also expected. In clinical laboratories, human errors such as not inoculating or streaking plates or selection of the wrong plates for culture do occur. As the instrument works from information stored in the barcode, these types of errors should be very rare as long as the correct information is put into the laboratory information system.

Cross-contamination of specimens and maintaining accuracy and reproducibility can be challenging when multiple personnel perform specimen processing. Although studies with clinical specimens cultured in real time are lacking, publications in which spiked urine specimens were alternated

with sterile saline demonstrated no cross-contamination between samples when automated specimen processing instruments, including the WASP, were assessed.^{3,4} Our evaluation of the WASP (unpublished) and one published study show it to be accurate compared to current manual methods.³ Differences in technique between technical personnel can contribute to lack of reproducibility.¹ Planting and streaking accomplished with the WASP robotic arm attached to a calibrated loop should enhance reproducibility of results.

The WASP is but one example of how automation microbiology is catching up to other sections of clinical pathology. To complement automated specimen processing, industry experts are currently developing fully automated culture systems.⁶ In the future we will likely see processing instrumentation attached to conveyors leading into incubators. Camera systems that can detect microbial growth on agar plates have been developed. It will be possible for an automated system to read cultures via a camera and discard negative plates without human intervention. Positive cultures might even be evaluated



by staff in remote locations. The technologist could then send a plate with significant growth to an automated instrument that can select colonies and setup identification and susceptibility testing, as directed by the user. Several companies are developing such systems and some large labs in Europe already have begun to implement this technology. Classical microbiology is evolving. It will be interesting to see how these innovations will fit into clinical practice in the future.

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About the Author



Susan Harrington, PhD, is a staff microbiologist at the Cleveland Clinic Pathology and Laboratory Medicine Institute. She directs the Mycobacteriology and Specimen Processing sections of the main

campus laboratory and was recently named director of the Microbiology Laboratory at Fairview Hospital. Dr. Harrington also serves to integrate microbiology testing across the Cleveland Clinic Health System. She is actively involved in teaching Medical Laboratory Science students, residents, medical students and fellows. Current research interests include the diagnosis and susceptibility testing of rapidly growing mycobacteria and optimization of specimen processing procedures.

Dr. Harrington received her undergraduate degree from the University of Pittsburgh and completed a masters degree in public health at the Johns Hopkins Bloomberg School of Public Health. She earned a PhD in bacterial pathogenesis at the University of Maryland and completed a clinical microbiology fellowship at the NIH Clinical Center. Her first position as a laboratory director was at Albany Medical Center in Albany, NY.

Dr. Harrington serves on the Board of Governors for the ASCP Board of Certification, and actively participates on committees for the Board of Certification. She has been a member of the American Society for Microbiology (ASM) since 1984 and currently volunteers on the Professional Practice Committee and the editorial board of the *Journal of Clinical Microbiology*. Dr. Harrington speaks at regional meetings and has authored many peer-reviewed journal articles. She is certified as a diplomate of the American Board of Medical Microbiology.

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Dr. Goldblum receives the Mostofi Distinguished Service Award from USCAP President Linda Ferrell, MD.

Dr. Goldblum is Recipient of Mostofi Distinguished Service Award

John R. Goldblum, MD, chair of the Department of Anatomic Pathology in the Pathology and Laboratory Medicine Institute, received the F.K. Mostofi Distinguished Service Award at the 102nd Annual Meeting of the United States & Canada Academy of Pathology (USCAP) meeting in Baltimore.

The F.K. Mostofi Distinguished Service Award was established as a tribute to the long and dedicated service of Dr. Kash Mostofi, a prolific author and teacher, to the International Academy of Pathology. This award is presented to a member of the USCAP who has rendered outstanding service to the International Academy of Pathology and its US-Canadian Division.

Dr. Goldblum specializes in the interpretation of biopsy and resection specimens in the fields of soft tissue pathology and gastrointestinal pathology for Cleveland Clinic patients as well as non-Cleveland Clinic patients throughout the United States and foreign countries. He is the co-author of the world's largest selling textbooks on soft tissue tumors and gastrointestinal pathology. He has lectured extensively nationally and internationally in the field of anatomic pathology, and has published more than 270 publications, mostly in the areas of GI and soft tissue pathology.

Dr. Goldblum received his bachelor of science and medical degrees from the University of Michigan, where he also pursued his anatomic pathology residency and surgical pathology fellowship. He joined the Department of Anatomic Pathology at Cleveland Clinic in 1993, where he has been ever since. Under his guidance, the department transformed to a completely subspecialized department in 2004. Aside from continuing to develop his own expertise in GI and soft tissue pathology, Dr. Goldblum has focused his professional efforts on developing the subspecialty model and mentoring junior faculty to successful academic careers.

Dr. Goldblum has served as faculty for many years at the American Society of Clinical Pathology (ASCP), and was the recipient of the 2012 CAP Excellence in Teaching Award. At USCAP, Dr. Goldblum has been a member of the Education Committee for 14 consecutive years, serving as a member, short course coordinator and chair, for which he finished his sixth year. Dr. Goldblum has provided four separate USCAP short courses, has been moderator and presenter at both the GI and soft tissue Evening Specialty Conferences, served as faculty for two separate long courses (GI and soft tissue), directed the highly successful USCAP Practical Pathology Seminars course since its inception, and served as Diagnostic Pathology faculty for eight consecutive years, teaching both GI and soft tissue pathology. He has been an active member for the Academy's long-term strategic planning initiative and has served as a member of the Innovative Education Products Committee since its inception.



Dr. McKenney Receives Arthur Purdy Stout Prize at USCAP

Jesse K. McKenney, MD, staff pathologist in the Department of Anatomic Pathology, received the 2013 Arthur Purdy Stout Prize at the 102nd Annual Meeting of the United States & Canada Academy of Pathology (USCAP) meeting in Baltimore.

Awarded annually to a surgical pathologist under the age of 45, the prize is intended to recognize significant career achievements by young surgical pathologists whose research publications, whether clinical or basic, have had a major impact on diagnostic pathology.

Dr. McKenney received his undergraduate degree from Texas A&M University in Dallas, and received his medical degree at the University

of Texas Southwestern Medical School, also in Dallas. He did his pathology residency at Emory University in Decatur, Georgia, and his fellowships in surgical pathology at Stanford University Hospital in Stanford, California, and in soft tissue pathology at Emory. He joined the Cleveland Clinic staff in 2012.

Pathology Innovations Magazine

offers information from the medical staff in the Cleveland Clinic Pathology & Laboratory Medicine Institute about its research, services and laboratory technology.

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Dr. Minca Receives Young Investigator Award from AMP

Congratulations are in order for Eugen Minca, MD, resident in Pathology, who recently received the Young Investigator Award from the Association for Molecular Pathology (AMP). Dr. Minca's poster, "ALK gene rearrangement testing in non-small cell lung carcinoma: correlation between ultrasensitive IHC and FISH," was presented at AMP's annual meeting in Long Beach, California.

The AMP Young Investigator Award recognizes the best abstracts submitted by trainees who are AMP members and who present outstanding basic or applied research in poster format at AMP's annual meeting.

In his presentation, Dr. Minca concluded "Ultrasensitive IHC can reliably detect ALK-encoded protein over-expression resulting from ALK gene rearrangements in NSCLC. The very high concordance between IHC and FISH warrants the routine use of IHC as the initial component of an algorithmic approach to clinical ALK molecular testing in NSCLC, followed by reflex FISH confirmation of IHC-positive cases."

Dr. Elsheikh Elected to ASC Executive Board

Tarik Elsheikh, MD, was elected to the American Society of Cytopathology (ASC) Executive Board. The ASC announced its new officers and executive board members during the ASC 60th Annual Scientific Meeting in Las Vegas.



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