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## **Automation in Clinical Microbiology**

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اشراف

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**Historically, the trend toward automation in clinical pathology laboratories has largely bypassed the clinical microbiology laboratory. In this article, we review the historical impediments to automation in the microbiology laboratory and offer insight into the reasons why we believe that we are on the cusp of a dramatic change that will sweep a wave of automation into clinical microbiology laboratories. We review the currently available specimen-processing instruments as well as the total laboratory automation solutions. Lastly, we outline the types of studies that will need to be performed to fully assess the benefits of automation in microbiology laboratories.**

Editor's Note: In this issue of the *Journal of Clinical Microbiology*, Paul Bourbeau and Nate Ledebor provide an informed review of an exciting new concept in clinical microbiology, the use of instrumentation to automate the front-end processing and workup of specimens submitted to a laboratory for analysis. The potential value of such instrumentation includes the possibility of substantial cost savings, standardization of initial specimen processing, more rapid and consistent provision of both identification and antimicrobial susceptibility test results, and a diminished risk for laboratory-acquired infections. However, as with any new diagnostic modality in clinical microbiology, there now exists a pressing need for investigations aimed at elucidating the performance characteristics of this new technology. Going forward, it will be imperative that laboratorians assess this new technology in objective, comparative, and preferably prospective clinical studies. Such studies will be necessary to define the true, rather than perceived or hoped-for, value of front-end and total laboratory automation in clinical microbiology. The *Journal of Clinical Microbiology* enthusiastically awaits submission of manuscripts that report the results of such investigations.

In recent years, while automation has steadily spread throughout the clinical chemistry and

clinical hematology areas of diagnostic laboratories, clinical microbiology laboratories have largely been excluded from this trend. Although continuous-monitoring blood culture systems, automated microbial identification, and automated antimicrobial susceptibility testing systems are widely utilized in microbiology laboratories, microbiology specimen processing and culture workup, in particular, remain largely manual tasks, and indeed, few changes to the methods used to perform these tasks have occurred for many years. While we acknowledge that some larger microbiology laboratories utilize urine-plating instrumentation, most microbiology laboratories have little to no automation in their specimen-processing areas, with the exception of some laboratories in Western Europe, Australia, and the Middle Eastern nations. Still fewer laboratories have implemented some version of total laboratory automation (TLA). Driven by a variety of factors, we believe that the level and degree of automation in clinical microbiology laboratories are poised for a dramatic change. While it would probably be an overstatement to suggest that a tsunami of automation is sweeping toward microbiology laboratories, we do believe it accurate to state that a wave of automation is coming to microbiology laboratories and that this change will occur much more

rapidly than most laboratorians may suspect; moreover, the changes associated with selection and implementation of microbiology automation solutions will place significant management and financial challenges upon laboratory leadership. Of the primary drivers of automation, standardization of identification methods to matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) mass spectrometry (MS) and the adoption of liquid microbiology specimen transport have allowed microbiology laboratories to simplify collection and identification systems, creating a work flow that can be optimized with automation. For the purposes of this article, the use of the term “automation” in clinical microbiology laboratories excludes blood culture systems, automated microbial identification systems, and automated antimicrobial susceptibility testing systems; rather, it refers specifically to microbiology specimen-processing instruments and microbiology TLA solutions. In this article, we review historical impediments to implementation of automation in microbiology laboratories and discuss the reasons why we believe that attitudes toward automation are changing. In addition, we review each of the currently available microbiology processing instruments and total microbiology automation solutions.

## **HISTORICAL IMPEDIMENTS TO AUTOMATION IN MICROBIOLOGY**

Several real or perceived factors have contributed to the current dearth of automation in clinical microbiology labs. These include the ideas that microbiology is too complex to automate, no machine can replace a human in the microbiology laboratory, automation is too expensive for

microbiology laboratories, and microbiology laboratories are too small to automate. **Microbiology is too complex to automate.** In comparison to chemistry and hematology specimens of laboratories, most of which are blood or urine based and utilize a limited selection of tube sizes, microbiology specimens are much more complex. Microbiology specimen types include blood, sterile body fluids, tissues, urine, catheter tips, other prosthetic devices, and lower respiratory tract specimens, among others. Moreover, microbiology

specimens are collected and transported by utilizing a wide variety of devices, including urine transport tubes, varieties of swab collection devices, sterile containers for tissues, stool specimens, aspirates, and prosthetic material, lower respiratory tract collection devices, and more, not to mention the occasional Mason jar and dessert topping container. An additional aspect of microbiology complexity is the variation in the manners in which specimens are processed. Specimens can be concentrated, macerated, digested, decontaminated, sonicated prior to being plated, or plated directly, and plating can be quantitative, semiquantitative, or nonquantitative. A last aspect of the complexity of microbiology specimen processing is related to media. In addition to tubes for media being of various sizes, the lids of plates that some manufacturers utilize to facilitate plate stacking vary in height and geometry. No machine can replace a human in the microbiology laboratory. A long-standing mantra is that humans are generally considered capable of performing tasks faster than machines and that machines cannot think. The perception that machines cannot exercise the critical decision-making skills required to process microbiology specimens has persisted. Specifically,

human observation of organism growth on agar plates is still considered essential by many. While machines are programmable, humans are more flexible.

Cost of automation. Automation has historically been considered too expensive for microbiology. It simply has not been viewed as cost-effective. Although automation is justified for chemistry and hematology, the relative specimen and test volumes for microbiology are much smaller, making automation seemingly less attractive. Microbiology laboratories are too small for automation. Most microbiology laboratories have been considered to be too small for automation. The sentiment has been that, while automation may have a place in the very largest microbiology labs, it does not have a place in the average-sized laboratory. Because these labs are small, any automation would be underutilized.

## **REQUIREMENTS FOR AUTOMATION**

For automation to be successful, it will need to be flexible in design, embrace the human element, and adapt to the challenges of specimen diversity. Flexibility acknowledges that one size will not fit all and incorporates an open, expandable architecture that can be adapted to a laboratory's available space and potential future growth. Moreover, flexibility will also require that automation systems embrace diversity of equipment manufacturers. Laboratories may select an automation system from one vendor that best fits their needs while selecting analytical instrumentation from a second and/or third vendor. The capability of integrating equipment from these different manufacturers will be critical to microbiology TLA success. Embracing the human element focuses microbiology

technologists on the performance of the most complex tasks, such as selecting colonies for further workup while removing these personnel from tasks, such as plating, that can be performed by an instrument, operated by a less trained individual. It is important to appreciate that automation does not remove decision making for the microbiology technologist; rather, it facilitates decision making and eliminates wasteful activities. Microbiology must move as much as is practical to liquid-based transport devices to facilitate automated plating. One way in which this can occur is replacing traditional wound swabs (Culturette-like) with liquid-based swab transports. For those specimen types that will never be in a liquid-based transport, the automated solutions must be able to accommodate the introduction of manually inoculated media into their systems.

In reviewing the current options available for automation in microbiology laboratories, we have chosen to divide the automation solutions into two groups: instruments that function primarily as specimen processors and systems that offer total microbiology laboratory automation solutions. Tasks performed by processing instruments can include inoculation of tubes and plated media, subculture of broth cultures, plate streaking, plate labeling, bar coding for specimen tracking, and slide preparation. Total microbiology laboratory solutions generally include the functions of specimen processors and add modules to achieve various degrees of total microbiology automation.

## **MICROBIOLOGY SPECIMEN PROCESSORS**

Historically, some laboratories, mainly large reference laboratories, have utilized specimen-processing instruments, such as the inocuLAB (Dynacon, Canada) (no

longer being sold) for plating of urine specimens. Although limited in speed and functionality, the InocuLAB was shown to plate specimens more reproducibly than technicians performing manual plating (3). The current generation of specimen processors has far more functionality than was found in instruments such as the inocu-LAB. The four currently available specimen processors are (listed in alphabetical order by manufacturer) the Innova processor (BD Diagnostics, Sparks, MD), the Inoqula full automation/manual interaction (FA/MI) specimen-processing device (BD Kiestra B.V., Drachten, Netherlands), the Previ Isola automated plate streaker (bioMérieux, Inc., Hazelwood, MO), and the walk-away specimen processor (WASP; Copan Diagnostics, Murrieta, CA). Each of the 4 instruments is capable of automating the processing of a variety of liquid-based specimens. Innova. The Innova instrument has 5 specimen drawers, with each holding up to 40 containers, for a maximum capacity of 200 containers (Fig. 1). Specimens can be added as they arrive in a lab (bar coded, with lid/cap intact). Innova uses a universal decapper that decaps/recaps different-sized containers without any manual adjustment. A drawer can hold only a single-sized tube at any one time. There are 6 input stacks with a capacity of 45 plates each (270 plates total). Different agars (including bi-plates) can be loaded into each stack, or all stacks can hold the same type of agar. The Innova specimen processor includes a full library of traditional streaking patterns; streaked plates are ejected into an output carousel (5 stacks) and can be organized in output stacks by groups so that no sorting is required after streaking. The Innova utilizes reusable 1-, 10-, and 30-ml Nichrome loops. No disposable supplies are required for specimen plating with the Innova. Inoqula FA/MI.



FIG 1 Innova specimen processor.

The Inoqula FA/MI (full automation /manual interaction) specimen processor can be utilized for automated inoculation of liquid specimens and manual plating of other types of specimens (such as wound swabs) as well as for slide preparation (Fig. 2). The streaking process is performed using a magnetic rolling bead, and up to 5 inoculated plates can be struck out at one time, yielding a throughput of up to 400 plates/h. The instrument holds up to 30 types of plated (including bi-plates) and 7 types of tubed media. Inoculated plated media can be sorted in up to 4 different cassettes for different atmospheres of incubation. The manual interaction section of the Inoqula FA/MI instrument permits manual inoculation of nonliquid specimens, such as catheter tips and wound swabs. Once inoculated, these manually inoculated specimens are struck out with magnetic beads, as occurs with liquid-based specimens. A disposable pipette is required for each liquid-based specimen. Studies assessing the inoculation performance of the

InoqulA processor have been performed. Kleefstra et al. reported that the InoqulA system produced more isolated colonies than manual plating while also showing good reproducibility (4). Rydback et al. also reported more isolated colonies with the InoqulA processor than were obtained with manual plating while also noting significant variation in results between technicians for manual plating (5).



FIG 2 InoqulA specimen processor.

Sturm et al. reported similar numbers of isolated colonies using the InoqulA system and manual plating (6). Previ Isola. The Previ Isola automated plate streaker has 5 different-sized racks, one size for each of 5 different-diameter specimen tubes (Fig. 3). All specimens must be uncapped before being placed in the instrument. There are 5 input cassettes with a capacity of 30 plates in each stack (150 plates total). Different-agar plates (including bi-plates) can be loaded into each stack, or all stacks can hold the same type of agar. Streaked plates are ejected into output cassettes (3 stacks, 30 plates each) and can be organized by groups so that no sorting is required after streaking. Two different specimen volumes can be

inoculated based on plating protocols. A disposable pipette is required for each specimen, and a disposable applicator is required for each plate. The applicator produces a unique radial-comb streak pattern, and there are no other streaking-pattern options. The maximum capacity is 180 plates/h. Studies assessing the Previ Isola instrument's inoculation performance have been carried out. Chapin et al. reported a 54% decrease in hands-on time for the Previ Isola instrument compared to that for manual planting ( $P = 0.0001$ ) and that samples with 2 to 3 different organisms were statistically more likely to be properly isolated with the Previ Isola instrument (7). Andrea et al. reported that plating only urine and preprocessed stool specimens results in an approximate savings of \$20,000 per year in their laboratory (8). Utilizing feces diluted in saline, Zimmerman and Trampe reported that the Previ Isola instrument reduced processing time compared to that for manual culture, while the suitability of the Previ Isola process and manual plating were judged to be superior or equivalent for 52% and 6% of specimens, respectively (9). Mischnik et al. evaluated the performance of the Previ Isola instrument on wound specimens with polyurethane swabs in liquid Amies medium in comparison to manually plated wound viscose swabs in Amies medium. They reported that the quality of colony growth on culture media for further investigations was superior with Previ Isola-inoculated plates compared to manual plates (10). WASP. The WASP (walk-away specimen processor) utilizes specimen load and unload conveyors with different-sized pallets for different diameter tubes (Fig. 4). It uses a universal decapper that decaps/recaps different-sized containers without any manual adjustment. There are 9 medium silos, with a total capacity of 342 to 370 plates (including bi-plates). Each silo or multiple silos can hold a single type of



medium. The WASP utilizes two Toshiba selective compliant assembly robot arm (SCARA) robots to move specimens and plates. It includes a full library of streaking patterns, and streaked plates can be organized by groups so that no sorting is required after streaking. Each of two separate cultures can be inoculated to half of a plate and then separately labeled, a practice that is very cost-effective for epidemiological screening cultures. Inoculated plates can be labeled on the side or bottom of the plate. The WASP utilizes reusable 1-, 10-, and 30-ml Nichrome loops with an automatic loop changer



FIG 3 Previ Isola specimen processor.

. No disposable supplies are required for specimen plating with the WASP. An optional Gram SlidePrep module is available for slide preparation. Bourbeau and Swartz evaluated the performance characteristics of the WASP (11). They determined that no cross-contamination occurs during plating of urine transport tubes and ES swabs. They also demonstrated that subculture of Lim broth tubes by the WASP produced results identical to those produced by manual

subculture. Lastly, they demonstrated that plating of urine transport tubes by the WASP is highly reproducible (11). Jones et al. demonstrated increased detection of *Staphylococcus aureus* nasal colonization using ES swabs plated with the WASP in comparison to that with manually inoculated wound fiber swabs (12). The factors to consider in the selection of a microbiology specimen processing instrument were reviewed by Greub and Prod'homme (13). They recommended that the following factors be included in the selection of a particular specimen-processing platform: accuracy, capacity, manufacturer's technical support, flexibility (specimen types, loops, inoculation protocols, medium options, laboratory information system [LIS] issues), capacity, flexibility, modularity, and costs (initial costs, costs for any required disposable supplies, and operational labor costs).



FIG 4 WASP.

## MICROBIOLOGY TLA SOLUTIONS

There are currently 3 microbiology TLA solutions in use or in development (listed in alphabetical order by manufacturer): Kiestra TLA (BD Kiestra B.V., Drachten, Netherlands), full microbiology laboratory automation (FMLA; bioMérieux, Inc., La Balme, France), and the WASPLab (Copan

Diagnostics, Murrieta, CA). Certain common elements exist or are envisioned for all 3 systems. These include conveyor/track systems to move plates to and from incubators, digital cameras to capture plate images at specified intervals, automated incubators with digital reading stations, and proprietary software to facilitate these processes. They utilize various versions of computer-driven robotic plate management to automate specimen processing and workup. By adding TLA to automated specimen processing, significant additional benefits can accrue for microbiology laboratories. Because medium is not sitting on a workbench waiting to be read, there is continuous incubation of plated media, rather than intermittent periods of incubation, as traditionally occurs in microbiology laboratories. Plate reading can be performed when incubation is adequate on a plate and is not tied to a traditional lab work schedule. When plates are required for workup, they can be efficiently retrieved, obviating the need to handle multiple stacks of plates. Plate image records are retained, which facilitates review of growth over time, irrespective of the number of technologists who may work on the culture. With stored image analysis, microbiologists have the ability to examine a patient's culture history, both over time and between different specimens. Lastly, this workflow will facilitate improvement in the quality of supervisory culture review and enhance the training of new technologists. Kiestra TLA. The Kiestra TLA (total lab automation) system was first installed in a clinical microbiology laboratory in 2006, and there have been a total of 38 installations to date (Fig. 5). The Kiestra TLA system is comprised of distinct modules linked together by a conveyor/track system, the modules of which can be combined in various ways to create the full TLA system. These modules include the SorterA,

BarcodA, and InoqulA TLA systems (the specimen processing and streaking modules) (refer to Microbiology Specimen Processors above for more detail on the InoqulA device), the ReadA incubators with digital imaging equipment, and the ErgonomicA workbenches. In 2013, BD Kiestra plans to introduce a new incubator model which will be called ReadA Compact to replace the current ReadA incubators. The open architecture of the Kiestra TLA system permits laboratories to use various numbers of ReadA incubators (CO<sub>2</sub> or non-CO<sub>2</sub>) and SorterA, BarcodA, and InoqulA instruments, depending upon total specimen volumes. Future planned enhancements to the Kiestra TLA system include instrumentation to automate microbial identification and antimicrobial susceptibility testing utilizing automatic colony picking by the MaltitofA lab automation system, combined with Bruker's MALDI Biotyper. In assessing the impact of Kiestra TLA in their laboratory, Bentley et al. reported a reduced culture turnaround time and an increase in the laboratory production index (LPI) (number of samples/staff member/day) from 37.35 prior to Kiestra implementation



FIG 5 Kiestra TLA system.

to 75.90 after Kiestra implementation (2.03-fold increase) (14). In another laboratory, Humphrey et al. reported a 2.6-fold increase in their LPI following the introduction of the Kiestra TLA system (15). FMLA. The bioMérieux FMLA (full microbiology lab



automation) system is currently under development (Fig. 6). Components of the FMLA system include the Previ Isola automated plate streaker (refer to Microbiology Specimen Processors above for more detail on the Previ Isola processor) and the smart incubator system (SIS), linked together by a conveyor/track system. The SIS will be available in CO<sub>2</sub> and non-CO<sub>2</sub> atmospheres and include image analyzers. A key component of the FMLA system is Myla software, a microbiology middleware solution which links together FMLA components while integrating various information systems and microbiology instruments. An eventual goal of bioMérieux is to integrate Vitek MS (MALDI-TOF instrument) into the FMLA system while automating the preparation of colonies/suspensions required for antimicrobial susceptibility testing and the Vitek MS. WASPLab. The WASPLab was first installed in a clinical laboratory in 2012 (Fig. 7). The components of the WASPLab system include the WASP (refer to Microbiology Specimen Processors above for more detail on the WASP) and CO<sub>2</sub> and non-CO<sub>2</sub> incubators, linked together by a conveyor/track system and middleware.

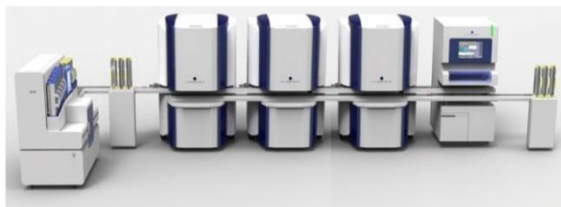


FIG 6 FMLA system.

Like the FMLA incubators and the ReadA Compact incubator, the WASP Lab features incubators that assign each plate a unique address or “shelf.” Because each plate has an individual location, technologists operating the system can request the instrument to send the plates for manual review with little delay. Each incubator also includes an image acquisition station that

captures plate images using a variety of light sources and at a variety of angles at programmable time intervals. Plates with detectable growth can be reloaded on the WASPLab, where automated broth inoculation and Kirby-Bauer disk dispensing can be performed. The WASP instrument can be modified to permit MALDI-TOF target plate seeding with either the Bruker MALDITOF plate or the bioMérieux Vitek MS plate. The WASPLab can also be connected to an Inpeco (Switzerland) sorting station and track which will sort chemistry, hematology, and microbiology tube specimens based on the appropriate test. The Inpeco track will connect all sections of the laboratory to a single distribution system, which routes specimen containers to the appropriate laboratory section.



FIG 7 WASPLab.

## **MICROBIOLOGY AUTOMATION RESEARCH NEEDS**

The scientific literature assessing the benefits of microbiology automation is sparse. As noted by the references for this article, there are few peer-reviewed publications, with most of the presentations in abstract form. While the benefits of microbiology automation can often be inferred, well-performed studies are needed to accurately assess the financial, operational, and clinical impacts of incremental or total laboratory automation in

microbiology laboratories. While there is evidence that automated processing instruments produce more isolated colonies than manual plating, there remain questions to be answered related to the downstream benefit of having more isolated colonies on the primary culture plates. What is the measureable impact on labor and supplies for culture workup? What is the effect on the time to organism identification and antimicrobial susceptibility testing result? Is there an effect on the time to final reporting of the culture? There have been limited studies examining productivity increases following implementation of total microbiology laboratory automation. Additional studies are warranted to assess potential benefits in different types and sizes of laboratories. More complex questions can be raised regarding the benefits of total microbiology laboratory automation. What is the measureable impact of TLA on labor and supplies for culture workup? What is the effect on the time to organism identification and antimicrobial susceptibility testing result? What is the effect on the time to final reporting of the culture? What is the impact of earlier examination of plates because the images indicate that there is sufficient growth for identification/antimicrobial sensitivity tests? Lastly and perhaps most importantly, studies are needed to assess the clinical impact of what, we assume, will be more-rapid organism identifications and more-rapid antimicrobial susceptibility test results. How will patient care be impacted by faster test results? It is reasonable to assume that the clinical benefits will vary depending upon the patient population assessed, e.g., inpatient versus outpatient and intensive care unit patient versus non-intensive care unit inpatient. Consequently, we envision that a series of studies will be required to properly assess outcome measures in various situations. In summary, we believe that we are entering an age of

monumental change for clinical microbiology laboratories. While a precise assessment of the full impact of these changes is in its infancy, there is no doubt in our minds that the benefits of automation on laboratory efficiency and indirectly on clinical care will be profound.

## REFERENCES

1. Garcia E, Ali A, Choudhry S. 2013. The American Society for Clinical Pathology 2012 vacancy survey of clinical laboratories in the United States. *Lab Med.* 44:3–7.
2. National Accrediting Agency of Clinical Laboratory Sciences. 2009. Program revitalization: strategy for survival. National Accrediting Agency of Clinical Laboratory Sciences, Rosemont, IL.
3. Lue YA, Krause CJ, John AB. 2002. Abstr. 102nd Gen. Meet. Am. Soc. Microbiol., abstr 81.
4. Kleefstra M, Visser C, van der Kaap M. 2011. Abstr. 21st Eur. Congr. Clin. Microbiol. Infect. Dis./27th Int. Congr. Chemother., abstr P1801.
5. Rydback J, Walder MH, Tjerberg I. 2011. Abstr. 21st Eur. Congr. Clin. Microbiol. Infect. Dis./27th Int. Congr. Chemother., abstr R2477.
6. Sturm PD, Cuppen PJ, Siebes CJ, Kuipers S. 2010. Abstr. 20th Eur. Congr. Clin. Microbiol. Infect. Dis., abstr P1766.
7. Chapin KC, Andrea SB, Andrade M, Tellier LA. 2012. Abstr. 112nd Gen. Meet. Am. Soc. Microbiol., abstr 734.
8. Andrea SB, Andrade M, Tellier LA, Chapin KC. 2012. Abstr. 112nd Gen. Meet. Am. Soc. Microbiol., abstr 733.

9. Zimmerman S, Trampe M. 2010. Abstr. 20th ECCMID, abstr P1764.

10. Mischnik A, Mieth M, Busch CJ, Hofer S, Zimmermann S. 2012. First evaluation of an automated specimen inoculation for wound swab specimens by use of the Previ Isola system compared to manual inoculation in a routine laboratory: finding a cost-effective and accurate approach. *J. Clin. Microbiol.* 50:2732–2736.

11. Bourbeau P, Swartz BL. 2009. First evaluation of the WASP, a new automated microbiology plating instrument. *J. Clin. Microbiol.* 47:1101–1106.

12. Jones GA, Matthews R, Cunningham R, Jenks P. 2011. Comparison of automated

processing of flocked swabs with manual processing of fiber swabs for detection of nasal carriage of *Staphylococcus aureus*. *J. Clin. Microbiol.* 49:2717–2718.

13. Greub G, Prod'homme G. 2011. Automation in clinical bacteriology: what system to choose? *Clin. Microbiol. Infect.* 17:655–660.

14. Bentley N, Farrington M, Doughton R, Pearce D. 2011. Abstr. 21st Eur. Congr. Clin. Microbiol. Infect. Dis., abstr P-1792.

15. Humphrey G, Malone C, Gough H, Awadel-Kariem FM. 2011. Abstr. 21st Eur. Congr. Clin. Microbiol. Infect. Dis., abstr P-1793.