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MINIREVIEW

Proceedings of the Clinical Microbiology Open 2018 and 2019 - a Discussion about Emerging Trends, Challenges, and the Future of Clinical Microbiology

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ABSTRACT Clinical Microbiology Open (CMO), a meeting supported by the American Society for Microbiology's Clinical and Public Health Microbiology Committee (CPHMC) and Corporate Council, provides a unique interactive platform for leaders from diagnostic microbiology laboratories, industry, and federal agencies to discuss the current and future state of the clinical microbiology laboratory. The purpose is to leverage the group's diverse views and expertise to address critical challenges, and discuss potential collaborative opportunities for diagnostic microbiology, through the utilization of varied resources. The first and second CMO meetings were held in 2018 and 2019, respectively. Discussions were focused on the diagnostic potential of innovative technologies and laboratory diagnostic stewardship, including expansion of next-generation sequencing into clinical diagnostics, improvement and advancement of molecular diagnostics, emerging diagnostics, including rapid antimicrobial susceptibility and point of care testing (POCT), harnessing big data through artificial intelligence, and staffing in the clinical microbiology laboratory. Shortly after CMO 2019, the coronavirus disease 2019 (COVID-19) pandemic further highlighted the need for the diagnostic microbiology community to work together to utilize and expand on resources to respond to the pandemic. The issues, challenges, and potential collaborative efforts discussed during the past two CMO meetings proved critical in addressing the COVID-19 response by diagnostic laboratories, industry partners, and federal organizations. Planning for a third CMO (CMO 2022) is underway and will transition from a discussion-based meeting to an action-based meeting. The primary focus will be to reflect on the lessons learned from the COVID-19 pandemic and better prepare for future pandemics.

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On May 3rd and 4th, 2018, the first Clinical Microbiology Open (CMO) was held in Palm Beach, Florida. This meeting was supported by the American Society for Microbiology's (ASM) Clinical and Public Health Microbiology Committee (CPHMC), a committee focused on promoting and advancing the practice of clinical and public health microbiology, and the ASM Corporate Council, a group of industry innovators who serve as thought partners for ASM's initiatives (https://asm.org/Corporate-Council/Join-the-ASM-Corporate-Council). The convening assembled 43 individuals for a day and a half discussion about the current and future state of clinical and public health microbiology. The meeting intended to provide an informal and collaborative environment that would foster open and honest discussion about critical challenges and opportunities facing diagnostic microbiology. One of the foundational elements was that it brought together leaders who understand the needs of clinical and public health microbiology laboratories along with industry leaders who can develop innovations to meet those needs, and federal agencies, such as the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) who can create enabling infrastructure. Although these groups depend on each other, this meeting provided a rare opportunity for interaction with an inclusive format that facilitated collaborative discussion, uniquely engaging commercial competitors. These groups have incredible resources, both financial and intellectual, which can be a powerful force for change in our field if properly harnessed. With that in mind, the meeting goal was to leverage the group's expertise and resources to identify issues that would be better addressed with a combined effort between industry and the laboratory, rather than independently.

Laboratory directors were asked to submit an application outlining a topic of interest. If selected, they would give a brief (10 min) presentation to all attendees and then facilitate a small group breakout session to discuss the topic in detail and brainstorm possible solutions and next steps. Following the breakout discussions, a summary was presented back to the group at large with an opportunity for additional discussion. In total, 18 participants presented and covered a wide range of topics, including next-generation sequencing (NGS), emerging diagnostics, laboratory management, and laboratory automation.

Overall, CMO 2018 accomplished its goal: to establish a unique forum for conversations between industry partners and microbiologists to help chart the course for our profession. Based on the success of this meeting, a second CMO (CMO 2019) was held on December 5th and 6th, 2019, in Palm Springs, California. The format was largely unchanged from CMO 2018 with the same guiding principle, i.e., to foster constructive conversation between industry and the laboratory to move diagnostic microbiology forward. The meeting was made possible by the support of ASM and the Corporate Council, which included industry participation from Beckman Coulter, Becton, Dickinson Life Sciences, BioFire Diagnostics, LLC, Cepheid, Copan Diagnostics, Inc., Curetis USA Inc., Diasorin Molecular, LLC, GenMark Diagnostics, Inc., Illumina, Inc, Luminex Corporation, Roche Molecular Systems, and Specific Diagnostics. In total, 48 leaders in the field participated, 23 from clinical and public health laboratories, 23 from industry, 1 from the CDC, and 1 from the FDA.

The CMO 2019 discussions were more focused, illustrating the ongoing nature of the challenges and opportunities. Primary themes included emerging opportunities and challenges in diagnostics, applications of NGS for routine microbiology diagnostics, laboratory diagnostic stewardship, and artificial intelligence (AI). As was the case for CMO 2018, CMO 2019 participants were asked to discuss the opportunities and challenges regarding these topics and if possible, propose solutions and identify the next steps. The following is a summary of these discussions. The purpose of this document is to serve as a foundation for future CMO meetings that will ultimately lead to

advancements in diagnostic microbiology by harnessing the collaborative power of clinical and public health microbiologists and leaders in the industry.

EXECUTIVE SUMMARY OF THE PROCEEDINGS OF CLINICAL MICROBIOLOGY OPEN 2019

The primary theme of CMO 2019 was harnessing the diagnostic potential of innovative technologies. It is widely recognized that the field of clinical microbiology is amid unprecedented technological innovation, which promises to improve diagnostic testing in ways not previously thought possible. Among the participants, there was great enthusiasm and robust conversation around the possibilities of these technologies, as well as optimism that viable options exist for overcoming the barriers that hinder the full realization of these technologies. Conversations centered on two key areas: (i) innovative technologies and applications, including expanding next-generation sequencing (NGS) use in clinical microbiology, rapid antimicrobial susceptibility testing (AST), improving fungal diagnostics, point of care testing (POCT), and artificial intelligence (AI), and (ii) operational challenges and opportunities, including workforce shortages, promoting investment in the laboratory, and laboratory diagnostic stewardship (Table 1).

In addition to the possibilities of new technology, the field of clinical microbiology is poised to harness opportunities in other areas. Specifically, there is growing interest in laboratory diagnostic stewardship and the laboratory's role in test utilization to control costs and ensure optimal patient care. With several different medical disciplines utilizing laboratory services, the opportunities for laboratory diagnostic stewardship programs to impact patient care are numerous. However, there is significant variation in practice across health care institutions. As a result, the structure of laboratory diagnostic stewardship programs and the needs of each organization will vary. Despite the variation in stewardship approaches, there are common opportunities and challenges to address for laboratory diagnostic stewardship to match the effectiveness of other parallel programs, such as antimicrobial stewardship.

Staffing in the clinical microbiology laboratories was another area that elicited passionate discussion. Though most laboratories face significant challenges in finding and hiring qualified clinical microbiologists, the field of microbiology is changing rapidly, which may present opportunities for improvement in the current staffing situation by drawing younger individuals into the field.

These important issues were discussed in detail with the goal of identifying the potential applications and benefits of each while also seeking to understand the obstacles that must be overcome. The summaries below discuss these topics in greater depth and highlight key action items required to move our field into the future.

CAPITALIZING ON TODAY'S OPPORTUNITIES IN DIAGNOSTIC MICROBIOLOGY

The future of next-generation sequencing in clinical microbiology. NGS and potential applications to diagnostic microbiology have generated tremendous excitement and promise. The possibilities of NGS, including rapid strain typing, direct detection of microorganisms from clinical specimens, identification of resistance genes, and actionable pathogenicity markers, have been discussed (1). As our understanding of the role complex microbial communities play in shaping human health improves, NGS may soon be able to provide routine microbiome analyses to help define and manage conditions ranging from antibiotic-associated enterocolitis to cancer. However, several technical, practical, and scientific challenges must be overcome for the diagnostic potential of NGS to be realized.

(i) The clinical need for NGS in clinical microbiology must be defined. The microbiology and infectious diseases communities need large-scale investigations of the performance characteristics, clinical utility, and challenges (operational and clinical) of NGS to better understand its contributions to patient management. This will require a multifaceted approach, including (i) partnerships between microbiology and molecular pathology laboratories within institutions to establish frameworks for implementation,

TABLE 1 Executive summary: major topics of discussion

Topic	Key opportunities	Key challenges	Next steps
Widespread use of NGS in clinical microbiology	Rapid strain typing Direct detection from clinical specimens Detection of resistance genes and virulence factors	Defining the specific clinical need Lack of standardized databases, interpretation, and quality control protocols Cost relative to conventional methods	Create guidelines to standardize best laboratory practices
Big data in clinical microbiology	Antimicrobial resistance profiling based on patient risk factors Analysis of protein profiles generated by MALDI-TOF MS AST variance detection Improved image and NGS dataset analyses	Computing power required Microbiologists trained in bioinformatics Artificial intelligence programs needed to perform analyses Variability in microbiology specimens	Performing collaborative outcome studies which include laboratories, information technology, and data scientists
Laboratory diagnostic stewardship	Optimized use of multiplex PCR testing Reduction in unnecessary test utilization Cost control	Integration of LIS with EMR to facilitate data analyses Provider buy-in Ensuring interventions Lack of data demonstrating clinical outcomes of new technology	Generate outcomes data Publish guidelines to establish a laboratory stewardship program Create order templates to assist in test ordering Develop best practices for uniformity in community laboratory stewardship practices Improve laboratory test catalogs
Staffing shortage	Capitalize on technology skills of younger generation microbiologists	Decreasing no. of training programs Pandemic-induced fatigue Extended training required for new hires Limited opportunities for advancement within the laboratory	Promote alternative training mechanisms Advocate for improved pay
Promoting investment in the clinical laboratory	Capitalize on innovations that can be used to improve patient care	Laboratories are often considered a cost-center Siloed thinking in finance departments Indirect benefit of laboratory testing on patient care and cost savings	Perform outcome studies to demonstrate the benefit of investment in laboratory technology Include business analysts in laboratory stewardship programs Engage Chief Financial Officers in ASM-sponsored sessions Participate in pathology management groups and meetings
Rapid susceptibility testing	Improved patient outcomes through faster therapeutic decision making Improved rapid phenotypic testing methods Enhanced predictive value for genotypic susceptibility methods	Cost compared to conventional methods Biological and technical challenges must be overcome Polymicrobial specimens	Microbiology laboratories and industry collaborate to demonstrate improved patient care with rapid AST methods
Point of care testing for infectious diseases	Improved access to testing Near-patient diagnosis facilitating treatment decisions	Easy access promotes overutilization Inaccurate results when performed outside the laboratory Difficult to capture data from POCT Inferior performance to laboratory-based testing	Study the impact of COVID-19 at-home testing
Molecular diagnostics for fungal infections	Improved diagnosis of fungal infections in vulnerable patients	Difficult to validate due to low frequency Cost prohibitive clinical trials False-positive results due to environmental contamination	Develop collaborative groups to create a more efficient test development and evaluation process

(ii) multicenter partnerships among laboratories to generate large sample sets to investigate rare conditions, and (iii) identifying sources of funding for studies, including extramural and/or federal grants.

(ii) Reference databases for the validation and interpretation of assays must be developed. The microbiology community needs to dedicate resources to developing a more robust database of whole microbial genomes, which has been done for human genomics. FDA has drafted guidance for developing a curated database, such as the FDA ARGOS database (2). However, there is a need for a roadmap that standardizes the approach to accomplish this guidance, through a collaborative effort among FDA, professional organizations, and industry.

(iii) Guidelines on the interpretation of NGS results must be developed. The successful implementation of NGS for routine use will require standardization in several key areas. It was suggested that the development of a collaborative network could be an important next step in creating guidelines that would facilitate the following: (i) creation of robust and curated databases, (ii) development of consensus interpretative guidelines, and (iii) identify potential sources of nucleic acid contamination and develop standardized strategies to mitigate risks. Nucleic acid contamination can present problems in both test reagents and clinical specimens. This is well documented and can lead to inaccurate result interpretation.

This topic stimulated robust discussion, a complete description of which is beyond the scope of the manuscript, but an in-depth review of many pertinent issues can be found in these references (3, 4).

(iv) The cost of NGS will need to decrease to become an effective diagnostic tool. Although the cost, turnaround time, and accuracy of NGS have improved, NGS is still expensive and labor-intensive compared with culture and PCR-based diagnostic tests, which are faster and more economical. It is critical to take into consideration both cost and clinical utility to realize the full potential for routine diagnostic use.

Harnessing the potential of big data through artificial intelligence. "Big data" is a term that refers to large, hard-to-manage data sets. As we progress into an increasingly data-heavy era in health care, the clinical microbiology laboratory has opportunities to harness big data to improve patient care. Examples of how data sets could be better utilized include (i) integrating a patient's medical history with their microbiology results to predict antimicrobial resistance and change empirical treatment to definitive treatment, (ii) analyzing protein profiles generated through daily matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) to increase the accuracy of results, (iii) notifying technologists of key variances in data sets, such as errors detected during analysis of antimicrobial susceptibility testing (AST) profiles, and (iv) improving culture growth image analysis, automated Gram stain analysis, and analysis of NGS data sets.

The size of NGS data sets generally exceeds the capacity of humans to efficiently analyze and interpret. This challenge may be overcome by the application of AI, which can facilitate the expansion of NGS into routine clinical use (5–7). Outside the laboratory, AI also has the potential to improve infectious diseases diagnostics by assisting the provider with ordering through algorithms that inform choices between different testing options. These preanalytical applications of AI, also known as decision support, are expanding in laboratory diagnostic stewardship programs (8).

The corresponding use of digital image analysis, such as the reading of X-rays to diagnose tuberculosis, and digital microscopy is rapidly expanding, most commonly through use in total laboratory automation (TLA) (9). Significant advancements have been made in automated culture interpretation, such as "no growth" assessments and interpretation of chromogenic media results (10). Reading stool ova and parasite trichrome smears is labor-intensive and rarely yields a positive result. The low positivity rate in the United States also presents challenges in maintaining staff competency, an issue that might be resolved with automated digital image analysis. Automated image analysis has been shown to enhance the evaluation of trichrome stains for parasite

detection (11). However, the variability in microbiology specimens and consequent smear quality associated with other stains, such as Gram stain interpretation, may pose significant challenges to automated image analysis.

Laboratory diagnostic stewardship in clinical microbiology. Some define laboratory stewardship as "correctly ordering, retrieving, and interpreting laboratory tests". Diagnostic Stewardship has variously been defined but might best be described as "the appropriate use of laboratory testing to guide patient management". The former is "doing things right" and the latter is "doing the right thing". In this discussion, the term "laboratory diagnostic stewardship" will be used and is defined by the CDC as, "ordering the right tests, for the right patient, at the right time, to provide the right treatment."

New technologies, such as multiplex syndromic panels, as well as expanding reference laboratory test menus, have led to enormous growth and diversification of testing options in clinical microbiology (12). These advances offer a tremendous opportunity for improved patient care if used in the appropriate clinical context (13). As a result, there is growing enthusiasm for institutions to develop laboratory diagnostic stewardship programs to facilitate the appropriate use of laboratory resources to maximize their impact on patient care while controlling costs (14).

There are several important components to implementing an effective laboratory diagnostic stewardship program in microbiology. First and foremost, there must be a scientific and clinical understanding of the value of the tests that will be subject to stewardship intervention. Second, a stewardship structure must be established to ensure and promote appropriate test utilization. As an antimicrobial stewardship committee, a laboratory diagnostic stewardship committee can be a mechanism for optimizing test utilization throughout an institution. These programs should have multidisciplinary participation and be guided by board-certified clinical microbiologists as well as other relevant stakeholders, such as infectious diseases physicians, clinical pharmacists, hospitalists, infection preventionists, and emergency department practitioners. The stewardship program must take a holistic approach and consider benefits both to the patient and the institution. It may also encourage the use of adjunct testing if it fulfills an important role in patient care.

Once the organization and membership of the stewardship committee have been established, another key element of the committee is having the ability to generate internal, institution-specific data. This should be the backbone of any laboratory diagnostic stewardship committee. Only with data can stewardship committees make informed decisions about how to optimize test selection. In addition, these data are critical for monitoring the impact of interventions and determining whether that intervention achieved its desired goal. Of primary concern is ensuring that an intervention does not have an adverse impact on patient care. It may be appropriate to pilot new technology and consider whether it is worth continuing after institutional data are collected.

One challenge for many microbiology laboratories is that laboratory information systems (LIS) cannot often facilitate complex data analyses. Ideally, these systems would be integrated into the electronic medical record with a bi-directional exchange of information. This integration could lead to clinical and laboratory data analysis and a better understanding of test utilization and the impact of laboratory results on patient care. An extension of these analyses would allow laboratory stewardship programs to monitor the impact of their interventions on patient care as well as laboratory utilization. There are several important next steps needed to advance the practice of laboratory diagnostic stewardship, which include (i) generating outcomes data to inform evidence-based guidelines and recommendations, (ii) publication of guidelines or recommendations on how to develop and implement a laboratory diagnostic stewardship program, which could facilitate the standardization of diagnostic stewardship efforts, (iii) creation of order templates that describe strengths and weaknesses of different tests/testing approaches to assist providers in test selection, (iv) develop best practices for teaching/communicating laboratory diagnostic stewardship so that

uniform approaches can be used across our discipline, and (v) improving the information provided in laboratory test catalogs.

Staffing the clinical microbiology laboratory. The shortage of medical laboratory scientists (MLS) is an acute problem for all disciplines within laboratory medicine but is a unique challenge for clinical microbiology laboratories due to the specialized training required. While this is not a new issue, it has been brought to the forefront by the increased demands of the ongoing COVID-19 pandemic, which necessitated an unprecedented expansion of microbiology testing. The pandemic exacerbated many of the long-standing issues laboratories have faced in hiring and retaining qualified staff.

The factors contributing to this staffing shortage are multifaceted but start with an inadequate number of qualified employees entering the workforce. This is a product of a decreasing number of MLS training programs (15). While overall contributors to decreasing numbers of training programs are unclear, one likely reason is the cost associated with running these programs as they require access to laboratory space and equipment and must provide hands-on experiences. These kinds of programs are inherently more costly than traditional classroom-based learning models. The Bureau of Labor and Statistics estimated in 2017 that by 2020 over 11,000 job openings would be available for MLS, with only approximately 5,000 expected to enter the workforce (https://www.labtestingmatters.org/home-page/responding-to-the-continuing-personnel-shortages-in-laboratory-medicine/). These figures turned out to be gross underestimates in the face of what the pandemic required of laboratory staffing.

The challenge of finding qualified personnel is exacerbated by challenges in retention, which has only intensified during the COVID-19 pandemic. A Dark Daily report cited data collected by a College of American Pathologists survey, which found that 31% of laboratory workers listed "increased burnout" as one of their top stressors (https://www.darkdaily.com/2021/01/04/critical-shortages-of-supplies-and-qualified-personnel-during-the-covid-19-pandemic-is-taking-a-toll-on-the-nations-clinical-laboratories-says-cap/) for laboratory staff during the COVID-19 pandemic. However, the pandemic has also brought important recognition to the laboratory staffing issue that may prompt employers to implement measures to improve employee retention, such as increased pay and additional vacation allowances.

Several staffing challenges are unique to the clinical microbiology laboratory. First, is the long period it takes to fully train a bench-level MLS. The specific duration of training will depend on the experience of the MLS as well as the complexity of the laboratory duties being learned but may take up to a year. The consequence of this is that even when new employees are hired, it takes extended periods to train them and provide relief to existing staff. Second, although automation has been adopted in many larger laboratories, most clinical microbiology procedures are still practiced traditionally, with manual plate reading and interpretation. This style of microbiology is more labor-intensive and is still common, especially in smaller community-based settings where it can be especially challenging to recruit new employees. Third, the work of an MLS is complex and is not always revenue-generating. MLS often spend a significant amount of time performing nonrevenue generating activities, such as training, teaching, and performing QC, which may limit the incentive for institutions to invest in competitive MLS salaries. Lastly, the opportunities for career advancement are typically limited within the microbiology laboratory and as a result, many MLS must seek opportunities outside the laboratory to advance their career.

The COVID-19 pandemic highlighted the importance of clinical microbiology and in so doing, brought attention to the laboratory workforce shortage. From the onset of the pandemic, laboratories struggled to keep up with extraordinary COVID-19 testing needs, which gained national attention. As the pandemic continues, an opportunity exists to further highlight the importance of the clinical microbiology laboratory workforce and promote investment in MLS staffing and develop alternative training models.

The ASM-Weber State University Microbiology Certificate program is an example of an alternative training model (https://weber.edu/mls/ASMdegreepage.html). This online

certificate program provides students with the coursework virtually, and in-person clinical practicums at surrounding area laboratories, to make them eligible for national certification. The design of the program is flexible to attract working professionals and those who have a baccalaureate degree and want to work in the clinical laboratory.

Promoting investment in the clinical laboratory. Many finance divisions operate under the premise of "cost savings initiatives" (CSI), which means that most new diagnostics are considered "in addition to" testing and do not fully replace current assays, thus increasing laboratory operational and capital budgets. Even though many new diagnostics have been shown to significantly impact patient care and promote the principle of "lifesaving initiatives" (LSI). While there is a frequent discussion on the preparation of cost justifications, finance divisions remain siloed, focusing only on laboratory CSI and are reluctant to incorporate LSI or hospital-wide CSI, such as nonlaboratory metrics of decreased length of stay, within justifications for increased costs.

The primary mechanism by which laboratories advance diagnostics is through the acquisition of new technology, typically at a significant cost. This financial investment often requires a justification by demonstrating a return on investment (ROI). Given the nature of reimbursement for laboratory testing, it is increasingly difficult to demonstrate that a given test yields a financial benefit. The complexities of reimbursement and the siloed financial thinking of most institutions make it nearly impossible to convince hospital finance groups that additional costs incurred in the laboratory resulted in savings. Often, these savings are realized in budgets outside the laboratory and are spread among a variety of groups (i.e., decreased lengths of stay, decreased pharmacy costs, etc.). The diagnosis-related group (DRG) model further challenges the laboratory ROI calculation because it can be difficult to know the amount of reimbursement received for a given test.

There are two key areas in which clinical laboratories can work to promote investment in the microbiology laboratory. First, there is a need for outcome studies on ROI for new and customizable laboratory testing. Second, business analysts should be included in laboratory diagnostic stewardship programs to help analyze ROI on nonlaboratory metrics, such as length of stay, readmission rates, and test reimbursement. Third, as a discipline, direct engagement is needed among health care leadership groups and laboratory administration groups. Participation in Executive War College (Conference on Laboratory and Pathology Management) meetings (or similar) and attendance in laboratory finance and administration sessions could be an important step in networking with laboratory administrators and experts, leading to an enhanced understanding of the business and financial success of the organization. Fourth, an ASM-sponsored session should be organized that engages the chief financial officer(s) in a discussion on the financial aspects of laboratory testing.

EMERGING DIAGNOSTICS AND DIAGNOSTIC TESTING GAPS

Rapid susceptibility testing. AST is one of the most important functions of the clinical microbiology laboratory and there is increasing progress in the development of methods that can rapidly determine antimicrobial susceptibility and resistance patterns in bacterial isolates. Currently, most rapid susceptibility tests are genotypic and detect antimicrobial resistance gene (ARG) targets, typically from the Enterobacterales, non-Enterobacterales Gram-negative rods, enterococci, and staphylococci. Genotypic results are useful for detecting resistance but cannot determine susceptibility in some circumstances, such that phenotypic testing is required to confirm susceptibility and facilitate de-escalation of therapy.

Rapid phenotypic AST methods provide results 12 to 24 h faster than traditional methods. Although not available yet, in an ideal scenario, rapid phenotypic AST would be cost-effective and fast enough that therapy could be withheld until results are available, thus helping to combat the ongoing rise in antimicrobial resistance due in part to overprescribing. Several rapid phenotypic methods are in development.

Cost is a potential barrier toward widespread, routine use of rapid phenotypic AST. Because AST is a high-volume test in the laboratory, even slight increases in testing

costs could have a significant impact on laboratory budgets. This issue might be mitigated by implementing rapid AST in select, high-impact clinical scenarios, such as meningitis and bacteremia. Another approach to keep costs from increasing significantly would be to incorporate rapid, inexpensive disk diffusion testing as part of laboratory automation.

Several biological and technical challenges must be addressed for reliable rapid AST. A key element is the standardization of inoculum, which can have a profound effect on results (16), particularly in accelerated testing (17, 18). Another challenge is the growth phase of the inoculum, which can significantly impact the observed potency of antimicrobial agents. In traditional AST, the inoculum is carefully adjusted using visual standards and/or optical density measurements with or without the use of automation. The use of the logarithmic growth phase is ensured using inoculum from fresh colonies or colonies suspended and allowed to grow for a defined period in broth (19). Both inoculum and growth phase are difficult variables to control and/or adjust for in rapid phenotypic AST, especially when performed directly from clinical specimens because organisms may not be at densities or in the growth phase this is optimal for accurate and consistent AST results.

There are numerous examples of rapid genotypic testing methods for predicting resistance that have an important impact on patient care, most commonly through testing positive blood culture bottles from septic patients. However, the application of genotypic methods directly on clinical specimens that may contain multiple species of bacteria, such as sputum or endotracheal aspirates, poses a challenge as it can be difficult to determine which resistance gene belongs to which pathogen. To address this problem, the College of American Pathologists (CAP) has added a compliance checklist item requiring laboratories to link the resistance gene marker with the appropriate organism in the laboratory report. In addition, some resistance mechanisms, such as efflux, porin changes, and heteroresistance, can be difficult to detect using genotypic methods. Lastly, some genetic mechanisms are so diverse (e.g., extended-spectrum beta-lactamases [ESBLs]) that it is difficult to detect all the critical molecular targets such that resistance can be ruled out (20, 21).

Yet, there is great potential for the continued adoption of both rapid molecular and phenotypic AST methods in the laboratory. Molecular methods have proved to be effective at improving patient outcomes and reducing the cost of bloodstream infections. It will be incumbent upon microbiology and industry partners to work together to ensure that the necessary outcomes studies are performed, and business cases assembled, to support the use of these tests.

Point of care testing (POCT) for infectious diseases. At the time of the CMO 2019, use of POCT for infectious diseases was not widespread, other than tests used for the diagnosis of tuberculosis and some STIs (primarily outside the United States) (22). Consequently, the impact of POCT results on patient care, specifically therapy decisions, was not known. The COVID-19 pandemic has certainly impacted the use of POCT for infectious diseases. Prepandemic there was already momentum toward moving some testing out of the laboratory to near-patient locations to facilitate timely diagnoses and treatment decisions. The COVID-19 pandemic further pushed for rapid and frequent surveillance testing not only in healthcare-associated POC locations but also in the patient's home. This led to the approval of an unprecedented number of FDA emergency use authorization (EUA) POC COVID-19 tests, some of which could be performed by the public at home. The success or failure of these tests is yet to be determined, but the microbiology and infectious diseases community should be prepared to study the effects of this unique circumstance.

POCT pose some challenges that need to be addressed to ensure they are used for maximal benefit to patient care. In the CMO 2019 discussions, concern was expressed that the ease and accessibility of POCT may contribute to test overutilization and inaccurate results when performed outside the laboratory.

One example of a successful POCT for ID is molecular group A *Streptococcus* (GAS) testing. As a common disease with a typical presentation, GAS can now be diagnosed in nontraditional environments, such as grocery store-based pharmacies. Testing in these environments offers tremendous advantages in the convenience from the consumer point of view (i.e., parents). However, more data are needed to demonstrate that test results are used appropriately, including the link to therapy when positive.

The COVID-19 pandemic has led to an unexpected change in the deployment of POCTs. It will be important to learn from this experience and better understand the utilization of POCT at home. The future of POCT seems clearer in healthcare-based environments because most institutions have established POCT programs that help to ensure testing is performed with fidelity. The technological development of POCT molecular tests has opened an opportunity for smaller health care settings, such as freestanding emergency departments, urgent care clinics, primary care physician offices, and others, to perform testing with performance characteristics that exceed those of previously available antigen-based tests. This is a potentially revolutionary innovation, which may facilitate the broad distribution of highly accurate POCT into environments not previously capable of performing molecular testing and can help review systematic problems as they arise.

Improving molecular diagnostics for fungal infections. Fungal infections are associated with high morbidity and mortality, although they are not as common as bacterial or viral infections (23). Conventional fungal diagnostics still rely on culture and microscopic identification, which are slow, time-consuming, and require specialized expertise. Given the limitations of culture-based diagnostics, fungal antigen tests, such as *Aspergillus* galactomannan, 1,3-beta-D-glucan, and *Histoplasma* antigen, serve as an important supplement to culture. However, both culture and antigen-based methods may show negative results even in autopsy-proven cases of fungal infections. This suboptimal performance leaves a diagnostic testing gap, which may be filled by molecular diagnostics. Currently, there are few FDA-approved molecular tests for fungi, and those that are available primarily diagnose yeast infections, not those caused by filamentous fungi. As a result, molecular diagnostics (except for *Aspergillus* spp. PCR) are not included in fungal disease diagnostic criteria, largely due to a lack of standardization (24, 25). Because fungal diagnostics are relatively low-volume tests, there is a little commercial incentive to invest in bringing these diagnostics to market. However, it was clear in the CMO 2019 discussions that manufacturers understood the clinical need for improved fungal diagnostics. Three key areas where molecular diagnosis could improve care were identified, including (i) *Pneumocystis* pneumonia (low incidence but high test volume), (ii) mucormycosis (poor clinical outcome infection, early detection for early intervention), and (iii) endemic mycoses (histoplasmosis, coccidioidomycosis, and blastomycosis).

The primary barriers to developing novel diagnostics for invasive fungal infections are costs, especially clinical trial costs for these rare diseases, and return on investment. Manufacturers must target immunocompromised patient populations and have access to their specimens for research and development. Ideally, large repositories of such samples would exist, but developing such a resource requires a coordinated effort across multiple centers due to the low frequency of these infections. In alignment with the manufacturers, clinical laboratories would have to ask if the cost and time required to develop such a repository would be justified. Second, performing the necessary outcomes studies to show the clinical impact of these diagnostic tests will be challenging, due to the high cost of evaluating performance in these low-frequency infections. Third, despite the collective agreement that a need exists to develop fungal diagnostics, the cost of performing a clinical study for IVD-clearance is prohibitive for these comparatively low volume tests.

There are also technical challenges obstructing the development of molecular diagnostic assays for fungal pathogens. Highly sensitive molecular diagnostic tests are plagued by false-positive results due to environmental mold contamination. This

requires ultraclean manufacturing facilities, which significantly adds to the expense of both development and manufacturing. Furthermore, immunocompromised patients are at higher risk of developing infection with a wide array of filamentous fungal pathogens, and it is difficult to design a comprehensive test capable of ruling out fungal infection definitively because genetic databases have relatively few complete genome sequences of fungal pathogens.

What approaches might manufacturers take to reduce the costs of test development and improve the development pipeline for invasive fungal diagnostic tests? The high cost of these studies is not only due to the rigorous criteria required by the FDA but also due to working with academic medical centers to perform the necessary studies. Hospitals should collaborate with the industry to lower the costs of clinical trials leading to better diagnostics for the clinical laboratories. To promote test development and overcome the barriers, the Fungal Diagnostic Laboratory Consortium (FDLC), including 27 clinical laboratories, was created. The goal of the FDLC is to facilitate the clinical validation process in which industry partners and consortium members would collaborate to submit tests to FDA jointly as opposed to individual submissions. The FDLC would also serve as a collaborative entity that can perform diagnostic-driven clinical trials to verify new commercial tests and generate outcome data on the clinical impact of novel fungal diagnostics (26).

Summary and conclusions. Shortly after CMO 2019 concluded, COVID-19 emerged and forced clinical and public health laboratories to direct their resources toward addressing the needs of the pandemic. The Herculean efforts that followed represented many of the opportunities, as well as some of the challenges, that had been discussed in both CMO 2018 and 2019. Topics such as emerging technologies, test development, regulatory environments, NGS, and staffing shortages were all central points of discussion and critical elements of responding to the COVID-19 pandemic.

Over the past 18 months, clinical and public health microbiology laboratories have directly confronted many of these issues, and though few would reflect on this experience as positive, some silver lining can be found in what the field of clinical microbiology has learned and accomplished. The power of novel diagnostics and the need for laboratories to use these technologies to respond to emerging threats was evident early in the pandemic. As the pandemic begins to recede, the medical community should look back and marvel at the speed at which clinical and public health microbiology laboratories, as well as industry partners, responded to develop and implement unprecedented testing capacity. What started with challenges in obtaining testing and swab supplies quickly turned into a shortage of all other supplies required to practice clinical microbiology. Alongside industry partners, the medical community worked to manage supply chain shortages for nearly every aspect of diagnostic testing.

One key item discussed during CMO 2018 was that of FDA oversight of emergency use authorization (EUA) as it pertained to the development of Zika virus testing. Those conversations proved prophetic as COVID-19 forced the very same issue to the forefront. Given the demand for testing, FDA EUA regulation was quickly changed, which allowed the microbiology community to respond rapidly through the development of diagnostic tests during the early phases of the pandemic.

Another positive aspect of the pandemic is that it enhanced the visibility of significant skill and expertise that is required to perform clinical diagnostic testing, as well as emphasized the importance of the MLS workforce. It also illustrated the significance of the laboratory staffing shortage, and it is hoped that this may be an impetus for positive change in supporting that profession. Addressing the laboratory staff shortage will be a topic of future CMO discussions, especially in the context of responding to and preparing for a pandemic.

The CMO's goal has been to facilitate productive and thoughtful conversations between clinical and public health microbiologists and our industry partners, as well as other key players such as the FDA, CDC, CAP, and health care payers. Ultimately, the hope is that these discussions will lead to action, which advances diagnostic

microbiology and improves patient care. To that end, the third CMO is in the planning phase and will shift from a discussion-based meeting to an action-based meeting in which defined goals are established and plans developed to meet those goals. The primary agenda item will be to create a blueprint for expanding the use of NGS in clinical microbiology laboratories. This has been the most consistent topic of conversation at the prior CMOs, and the pandemic has illustrated the untapped potential of NGS in clinical microbiology laboratories. The group will discuss a potential program to establish the clinical utility of NGS-based assays through outcomes-based research, including study designs, frameworks to generate data, and funding opportunities (27). Additionally, the group will hold a focused session on "lessons learned from the COVID-19 pandemic" to improve future pandemic preparedness. Lastly, a focus session will be held to capture the lessons learned from the COVID-19 pandemic to ensure preparedness for the next one. Information about CMO 2022 will be posted to www.asm.org in early 2022.

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REFERENCES

1. Church DL, Cerutti L, Gurtler A, Griener T, Zelazny A, Emler S. 2020. Performance and application of 16S rRNA gene cycle sequencing for routine identification of bacteria in the clinical microbiology laboratory. Clin Microbiol Rev 33:e00053-19. https://doi.org/10.1128/CMR.00053-19.
2. Administration FaD. 2019. Database for reference grade microbial sequences (FDA-ARGOS). https://www.fda.gov/medical-devices/science-and-research-medical-devices/database-reference-grade-microbial-sequences-fda-argos. Accessed 9/20/2021.
3. Gargis AS, Kalman L, Lubin IM. 2016. Assuring the quality of next-generation sequencing in clinical microbiology and public health laboratories. J Clin Microbiol 54:2857–2865. https://doi.org/10.1128/JCM.00949-16.
4. Hutchins RJ, Phan KL, Saboor A, Miller JD, Muehlenbachs A, Workgroup CNQ. 2019. Practical guidance to implementing quality management systems in public health laboratories performing next-generation sequencing: personnel, equipment, and process management (phase 1). J Clin Microbiol 57:e00261-19. https://doi.org/10.1128/JCM.00261-19.
5. Lepuschitz S, Weinmaier T, Mrazek K, Beisken S, Weinberger J, Posch AE. 2020. Analytical performance validation of next-generation sequencing based clinical microbiology assays using a k-mer analysis workflow. Front Microbiol 11:1883. https://doi.org/10.3389/fmicb.2020.01883.
6. Ferreira I, Beisken S, Lueftinger L, Weinmaier T, Klein M, Bacher J, Patel R, von Haeseler A, Posch AE. 2020. Species identification and antibiotic resistance prediction by analysis of whole-genome sequence data by use of ARESdb: an analysis of isolates from the Unyvero lower respiratory tract infection trial. J Clin Microbiol 58:e00273-20. https://doi.org/10.1128/JCM.00273-20.
7. Eyre DW, De Silva D, Cole K, Peters J, Cole MJ, Grad YH, Demczuk W, Martin I, Mulvey MR, Crook DW, Walker AS, Peto TEA, Paul J. 2017. WGS to predict antibiotic MICs for Neisseria gonorrhoeae. J Antimicrob Chemother 72:1937–1947. https://doi.org/10.1093/jac/dkx067.
8. Kassirer JP, Kopelman RI. 1988. Intuitive and inspirational, or inductive and incremental? Hosp Pract. (Hosp Pract (off Ed) 23:21–24. 26–7. https://doi.org/10.1080/21548331.1988.11703531.
9. Bailey AL, Ledeboer N, Burnham CD. 2019. Clinical microbiology is growing up: the total laboratory automation revolution. Clin Chem 65:634–643. https://doi.org/10.1373/clinchem.2017.274522.
10. Smith KP, Kirby JE. 2020. Image analysis and artificial intelligence in infectious disease diagnostics. Clin Microbiol Infect 26:1318–1323. https://doi.org/10.1016/j.cmi.2020.03.012.
11. Mathison BA, Kohan JL, Walker JF, Smith RB, Ardon O, Couturier MR. 2020. Detection of intestinal protozoa in trichrome-stained stool specimens by use of a deep convolutional neural network. J Clin Microbiol 58:e02053-19. https://doi.org/10.1128/JCM.02053-19.
12. Kirby JE. 2019. Our pathogens are not standing still and neither can we. Clin Lab Med 39:xiii–xxiv. https://doi.org/10.1016/j.cll.2019.06.001.
13. Doern GV. 2014. The value of outcomes data in the practice of clinical microbiology. J Clin Microbiol 52:1314–1316. https://doi.org/10.1128/JCM.00712-14.
14. Zhi M, Ding EL, Theisen-Toupal J, Whelan J, Arnaout R. 2013. The landscape of inappropriate laboratory testing: a 15-year meta-analysis. PLoS One 8:e78962. https://doi.org/10.1371/journal.pone.0078962.
15. Garcia E, Kundu I, Kelly M, Soles R. 2019. The American Society for Clinical Pathology's 2018 vacancy survey of medical laboratories in the United States. Am J Clin Pathol 152:155–168. https://doi.org/10.1093/ajcp/aqz046.
16. Smith KP, Kirby JE. 2018. The inoculum effect in the era of multidrug resistance: minor differences in inoculum have dramatic effect on MIC

determination. Antimicrob Agents Chemother 62:e00433-18. https://doi.org/10.1128/AAC.00433-18.
17. Smith KP, Richmond DL, Brennan-Krohn T, Elliott HL, Kirby JE. 2017. Development of MAST: a microscopy-based antimicrobial susceptibility testing platform. SLAS Technol 22:662–674. https://doi.org/10.1177/2472630317727721.
18. Brennan-Krohn T, Smith KP, Kirby JE. 2017. The poisoned well: enhancing the predictive value of antimicrobial susceptibility testing in the era of multidrug resistance. J Clin Microbiol 55:2304–2308. https://doi.org/10.1128/JCM.00511-17.
19. Institute CaLS. 2015. MO7-A10. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard – Tenth edition. Clinical and Laboratory Standards Institute, Clinical and Laboratory Standards Institute.
20. Pogue JM, Heil EL. 2020. The clinical impact of a negative molecular beta-lactamase gene test for Enterobacteriaceae: let's not let perfect be the enemy of really good. J Clin Microbiol 58:e02098-19. https://doi.org/10.1128/JCM.02098-19.
21. Humphries RM, Spafford K, MacVane S. 2020. Reply to Pogue and Heil, "the clinical impact of a negative molecular beta-lactamase gene test for Enterobacteriaceae: let's not let perfect be the enemy of really good. J Clin Microbiol 58:e02114-19. https://doi.org/10.1128/jcm.02114-19.
22. Whitlock GG, Gibbons DC, Longford N, Harvey MJ, McOwan A, Adams EJ. 2018. Rapid testing and treatment for sexually transmitted infections improve patient care and yield public health benefits. Int J STD AIDS 29:474–482. https://doi.org/10.1177/0956462417736431.
23. Benedict K, Jackson BR, Chiller T, Beer KD. 2019. Estimation of direct healthcare costs of fungal diseases in the United States. Clin Infect Dis 68:1791–1797. https://doi.org/10.1093/cid/ciy776.
24. Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, Verweij PE, Clancy CJ, Wingard JR, Lockhart SR, Groll AH, Sorrell TC, Bassetti M, Akan H, Alexander BD, Andes D, Azoulay E, Bialek R, Bradsher RW, Bretagne S, Calandra T, Caliendo AM, Castagnola E, Cruciani M, Cuenca-Estrella M, Decker CF, Desai SR, Fisher B, Harrison T, Heussel CP, Jensen HE, Kibbler CC, Kontoyiannis DP, Kullberg BJ, Lagrou K, Lamoth F, Lehrnbecher T, Loeffler J, Lortholary O, Maertens J, Marchetti O, Marr KA, Masur H, Meis JF, Morrisey CO, Nucci M, Ostrosky-Zeichner L, Pagano L, Patterson TF, Perfect JR, Racil Z, et al. 2020. Revision and update of the consensus definitions of invasive fungal disease from the european organization for research and treatment of cancer and the mycoses study group education and research consortium. Clin Infect Dis 71:1367–1376. https://doi.org/10.1093/cid/ciz1008.
25. Arvanitis M, Anagnostou T, Fuchs BB, Caliendo AM, Mylonakis E. 2014. Molecular and nonmolecular diagnostic methods for invasive fungal infections. Clin Microbiol Rev 27:490–526. https://doi.org/10.1128/CMR.00091-13.
26. Zhang SX, Babady NE, Hanson KE, Harrington AT, Larkin PMK, Leal SM, Jr., Luethy PM, Martin IW, Pancholi P, Procop GW, Riedel S, Seyedmousavi S, Sullivan KV, Walsh TJ, Lockhart SR, Fungal Diagnostics Laboratories C. 2021. Recognition of diagnostic gaps for laboratory diagnosis of fungal diseases: expert opinion from the fungal diagnostics laboratories consortium (FDLC). J Clin Microbiol 59:e0178420. https://doi.org/10.1128/JCM.01784-20.
27. Miller MB, Atrzadeh F, Burnham CA, Cavalieri S, Dunn J, Jones S, Mathews C, McNult P, Meduri J, Newhouse C, Newton D, Oberholzer M, Osiecki J, Pedersen D, Sweeney N, Whitfield N, Campos J, Clinical ASM, Public Health Microbiology C, the ASMCC. 2019. Clinical utility of advanced microbiology testing tools. J Clin Microbiol 57:e00495-19. https://doi.org/10.1128/JCM.00495-19.