Letter to the Editor

Just because we can doesn't mean we should: appropriate utilization of novel diagnostic methods in the clinical microbiology laboratory

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Approximately 14 billion laboratory tests are performed annually in the United States across numerous subspecialty laboratories including microbiology, hematology, chemistry, and molecular genetics (1). Studies estimate that more than two-thirds of all medical decisions are contingent upon, or influenced by, the results of these tests (1). While the exponential expansion of available laboratory tests allows for more definitive diagnoses and disease classifications, it also comes with myriad potential negative downstream effects (2-4).

The potential benefits and issues that may arise secondary to the vast array of diagnostic tests available today are aptly illustrated by some of the most advanced testing methodologies in the field of microbiology and infectious disease diagnostics. Microbial genomic sequencing methods provide laboratorians and infectious disease practitioners with the ability to overcome the often-suboptimal sensitivity of traditional culture- and biochemical-based diagnostics (5,6). These ultra-sensitive molecular diagnostics, such as next-generation sequencing (NGS), allow for identification of organisms that were previously undetectable and provide the clinician with the data necessary to initiate appropriately tailored antimicrobial therapy. This personalized approach is crucial in mitigating the expansion of antimicrobial resistance, which is due in part to the widespread use of broad antimicrobial regimens.

Although these molecular tests are paving the way for a new era of infectious disease diagnostics, their increasing sensitivity and complexity are directly contributing to obstacles in test result interpretation (7). As microbiological tests become more sensitive, two prominent issues arise: (I) false positives increase and (II) detection of incidental and inconsequential microbial organisms become more frequent. The former is a well-accepted issue (2), of which laboratorians and most clinical providers are aware. Conversely, as molecular infectious disease diagnostics become more sensitive, miniscule amounts of environmental microbial particles such as nucleic acids, proteins, and genomic remnants of successfully treated nonviable organisms are now capable of being detected, despite not representing the true etiologic infectious agent (7). This decreased specificity of these ultra-sensitive testing methodologies (5-8) creates a dilemma for the laboratorian regarding the reporting of these results and for the clinician who must decide how to interpret the results.

This complicated issue is highlighted by a recently encountered scenario in our diagnostic molecular microbiology laboratory. An immunocompetent patient clinically suspected to have a central nervous system (CNS) bacterial infection was cultured and placed on broad-spectrum antibiotics, eventually undergoing multiple debridement procedures. Organisms continuously failed to grow in culture and the antimicrobial regimen was altered numerous times in an attempt to clear the presumed

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infection. Finally, the clinical team became aware of a test utilizing broad-range polymerase chain reaction (PCR) with NGS and decided to order this test. While the test was pending, the patient began subjectively improving. NGS subsequently resulted with detection of *Aspergillus fumigatus*, a common environmental fungal species often detected incidentally, but known to potentially cause infection in immunocompromised individuals. The clinicians were met with the challenge of how to interpret these results in a patient who had no risk factors for fungal infection, had undergone numerous surgical procedures, and had no other definitive evidence of a causative organism. The decision hinged on whether this represented a true infection or an environmental contaminant; considering this to be a true infection carried the risk of the patient potentially suffering from end-organ damage from prolonged (>1 year) antifungal therapy, whereas considering this an environmental contaminant risked failing to treat a true, potentially lethal, CNS fungal infection.

In prior consultation, the microbiology laboratory had recommended against ordering this test, as it was unclear whether any result would represent true infection, and the evidence for testing in this patient population is limited (9). Despite admission by the clinical team that they were unsure of how to interpret the information if the NGS resulted with an unlikely pathogen, the test was still ordered. This case illustrates a subconscious idea that "more testing is better". While this is an understandable sentiment, and may reflect a provider's dedication to "doing everything they can for their patient", it is our duty as laboratorians to inform our clinical colleagues that more testing can potentially lead to serious patient harm if it is unclear how the results will be interpreted. Through these conversations, both laboratorians and clinicians can practice exemplary laboratory testing stewardship.

It is important to note that this concept of laboratory stewardship is continuously evolving. When first introducing a new testing method, it is normative practice to begin with very narrow criteria for when testing is indicated and then broaden the criteria as information and experience are gained. Thus, while the utility of NGS in infectious disease diagnostics is progressing rapidly, the laboratorian must remain cognizant of scenarios in which this methodology may not be optimal.

While the issue we encountered occurred in the molecular microbiology laboratory, this issue is not confined to this particular specialty, laboratory, or institution. Indeed, appropriate test utilization has been a longstanding issue for which working groups have been attempting to address. One organization that has introduced initiatives to improve test utilization is the American Society of Clinical Pathology via their *Choosing Wisely* campaign (10). This program is designed to increase awareness among laboratorians, healthcare providers, and the general public regarding the importance of appropriate test utilization. Through the implementation of educational resources, this program aims to increase the quality of patient care, reduce the costs associated with excessive or inappropriate laboratory testing, and utilize both assay resources and personnel more effectively (10).

Many test utilization initiatives are primarily regionally- or institutionally-dependent. However, numerous opportunities exist for individual institutions to incorporate laboratory stewardship teams who may either retrospectively or prospectively audit certain tests. These tests may be audited based on their high cost or novelty, as these types of tests, if performed, incur potentially negative economic and management-related consequences, respectively. One approach that our institution has implemented involves active review of all reference send-out tests above a certain cost threshold. This includes an evaluation to ensure that the test ordered was the intended test, that a cheaper alternative does not exist, and that the clinical scenario is appropriate for the test. This process often involves a discussion between the laboratory medicine resident or fellow and the ordering provider to ensure that this test will provide actionable information for the provider and patient. This review process has resulted in decreased costs, which has benefitted the laboratory, hospital and patient. It also serves as a quality assurance method, which is endorsed by all clinical departments, as it ensures that the most effective test will be ordered and allows for important discussions regarding what the results may imply and how best to interpret them.

Implementation of measures to enhance test utilization is becoming more critical as laboratory testing becomes more specialized. As Sikaris stated, the "clinical value of testing… revolves around the selection of test that will beneficially influence clinical outcome and the interpretation of results so that the reports facilitate beneficial clinical actions" (3). As the availability and complexity of diagnostic tests increase, knowing what one will do with the results of these tests is just as important as knowing what to test for.

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Footnote

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