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Unmet diagnostic needs in infectious disease

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ABSTRACT

Accurate diagnosis is critical to providing appropriate care in infectious diseases (ID). New technologies for infectious disease diagnostics are emerging, but gaps remain in test development and availability. The Emerging Infections Network surveyed ID physicians to assess unmet diagnostic needs. Responses reflected the urgent need to identify drug-resistant infections and highlighted the potential for early diagnosis to improve antibiotic stewardship. Information gained from this survey can help inform recommendations for new diagnostic test development in the future.

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1. Introduction

The importance of diagnostic testing in the management of infectious diseases (ID) was recently highlighted in the report of the Infectious Diseases Society of America's (IDSA) Diagnostics Task Force report: "Better Tests: Better Care: Improved Diagnostics for Infectious Diseases" (Caliendo et al., 2013). Similar sentiments are expressed in the report on Antibiotic Resistance Threats in the United States Centers for Disease Control (2013) from the Centers for Disease Control and Prevention (CDC). A number of new diagnostic technologies for ID are rapidly emerging: e.g., broad-range PCR, next-generation sequencing, and matrix-assisted laser desorption/ionization time of flight mass spectrometry. The reports from the IDSA and the CDC highlight deficiencies in current diagnostic methods and call for approval and access to methods that are rapid and available at the point of care, use direct-from-specimen analysis, and demonstrate high levels of sensitivity and specificity across a wide range of disease syndromes. The importance of syndrome-based panels (e.g., for central nervous system, bloodstream and respiratory tract infections) is highlighted in the IDSA report (Caliendo et al., 2013). Both the IDSA and CDC emphasize the critical need for culture-independent testing for specific pathogens and their pattern of susceptibility to antimicrobial agents.

The routine patient contact of participants in the CDC-funded Emerging Infections Network (EIN) provides an opportunity for a direct

assessment of current diagnostic needs from the perspective of care at the bedside. We therefore surveyed EIN members regarding their unmet diagnostic needs. The survey results, reported here, have the potential to focus advocacy, regulatory, and public health activities designed to hasten clinical application of emerging diagnostic technologies.

2. Methods

The EIN is a network of ID physicians in North America that was established in 1995 by the CDC to create a provider-based emerging infections sentinel network (Pillai et al., 2014). EIN members who receive surveys are physician members of IDSA who are actively involved in the practice of ID. This survey was sent electronically or via facsimile to all 1572 physician members in spring 2013.

The survey consisted of brief introductory text and 9 questions (can be viewed at: http://www.int-med.uiowa.edu/Research/EIN/Unmet_Diagnostic_Needs_Query.pdf). All EIN surveys, including this one, include an "opt-out" option, which allows members who are not involved in the aspect of ID practice being queried to answer "not applicable". For this survey, members were able to respond by email that they were not involved in non-culture-based diagnostics without answering any specific survey questions.

In the survey, "unmet" needs were defined as testing not available in the respondent's clinical practice or circumstances where test results are not available in a clinically meaningful timeframe. Survey respondents were asked to rank in order from 1 (least important) to 6 (greatest need) selected unmet needs. Six syndromes (central nervous system infection, community-acquired pneumonia, febrile neutropenia, infectious diarrhea, culture-negative endocarditis) and 6 pathogens (drug

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resistant gram-negative bacilli, methicillin-resistant *Staphylococcus aureus*, drug-resistant *Mycobacterium tuberculosis*, molds, influenza, and HIV resistance) were specifically listed. Free-text answers were encouraged.

Respondents were additionally asked to: consider the potential impact of rapid identification of specific genetic determinants of antimicrobial resistance on their clinical practice (ranked 1–5, no impact to high impact); choose a single test not currently available to them that would be most helpful; score the importance of various test characteristics (i.e., sensitivity and specificity, turnaround time, cost, and availability of outcome data supporting test benefits) when choosing a new test (ranked 1–5, not important to highly important); and to delineate required turnaround times for various tests in terms of clinical utility. Lastly, respondents were asked their opinion regarding whether some ID diagnostic testing is becoming too complicated to be interpreted by non-ID physicians and if there should be “stewardship” for particularly complex or expensive tests.

We used descriptive statistics for analysis and chi-square tests to compare proportions. All analyses were conducted using SAS 9.3 (Cary, NC, USA).

3. Results

A total of 700 respondents (44.5% of EIN physician members) completed the survey; 97 chose the “opt-out” option by indicating that they did not use non-culture-based diagnostics and were excluded. Forty-five percent of respondents estimated that at least 1 out of 4 patients in their practice are immune compromised. Twenty-three percent of respondents were in pediatric practice. As is usual for most EIN surveys, non-respondents were significantly more likely than respondents to have less than 15 years of experience in ID ($P < 0.001$), to have an adult practice ($P < 0.01$), and to work in a community hospital ($P < 0.01$).

Respondents indicated that their most important pathogen-specific unmet diagnostic need was the prompt identification of drug-resistant aerobic gram-negative bacilli (mean score 4.33 out of 5) (Fig. 1A). Identification of drug-resistant *Mycobacterium tuberculosis* had the second-highest score (3.93 out of 5). Additional pathogens mentioned in the open-text field included: *Borrelia burgdorferi*, *Clostridium difficile*, *Aspergillus species*, *Coccidioides immitis*, and human parechovirus. Respondents felt that rapid detection of extended-spectrum β -lactamase (ESBL) resistance markers, the *Klebsiella pneumoniae* carbapenemase (KPC), or the presence of *mecA* would strongly impact patient care (all with mean scores ≥ 4 out of 5).

The clinical syndrome ranked most highly as in need of improved diagnostics was culture-negative endocarditis (mean score 3.90 out of 5). Infectious diarrhea was the second-ranked syndrome (mean score 3.87 out of 5) (Fig. 1B). Other syndromes suggested in the free text included: osteomyelitis/septic arthritis, prosthetic joint infections/orthopedic hardware infections, and hospital- or ventilator-associated pneumonia.

When asked to choose a single test not currently available to them (not available in their practice, or not invented yet) that would be most helpful, 18% of 451 members providing a response identified pathogen-based testing for respiratory infection (lower and upper respiratory tract); 15% requested testing that could distinguish viral from bacterial infection and another 15% requested testing for antibiotic resistant organisms, including aerobic gram negative bacilli and staphylococci.

Test accuracy and adequate turnaround time were identified as the most important test characteristics (mean scores 4.72 out of 5 and 4.61 out of 5, respectively) when choosing to use a new diagnostic test. “Adequate” turnaround time was categorized as < 1 hour for rapid influenza testing (92%), < 12 hours for direct detection of bacterial bloodstream infection (89%), and up to 24 hours for identification of drug-resistant tuberculosis (86%). The availability of outcome data supporting the benefits of testing was ranked only slightly higher than cost of the testing (4.1 out of 5 versus 4.07 out of 5).

The majority (67.5%) of respondents felt that some testing is becoming too complex for non-ID physicians, and 79% believed that there should be stewardship for particularly complicated or expensive tests. Forty-six percent of respondents selected multiplex molecular respiratory panels, broad-range PCR testing, and antigen-based tests for fungal infection as tests that should be restricted or require prior approval.

4. Discussion

New technologies have improved our ability to accurately and rapidly diagnose many infections, but the need for additional advancements is increasingly recognized (Caliendo et al., 2013; Centers for Disease Control, 2013). This survey of practicing ID physicians suggests areas for future test development that mirror expert opinion. In particular, physicians report the need for testing that can enhance our ability to identify drug-resistant organisms and demonstrate an appreciation for judicious use of high-complexity testing through stewardship.

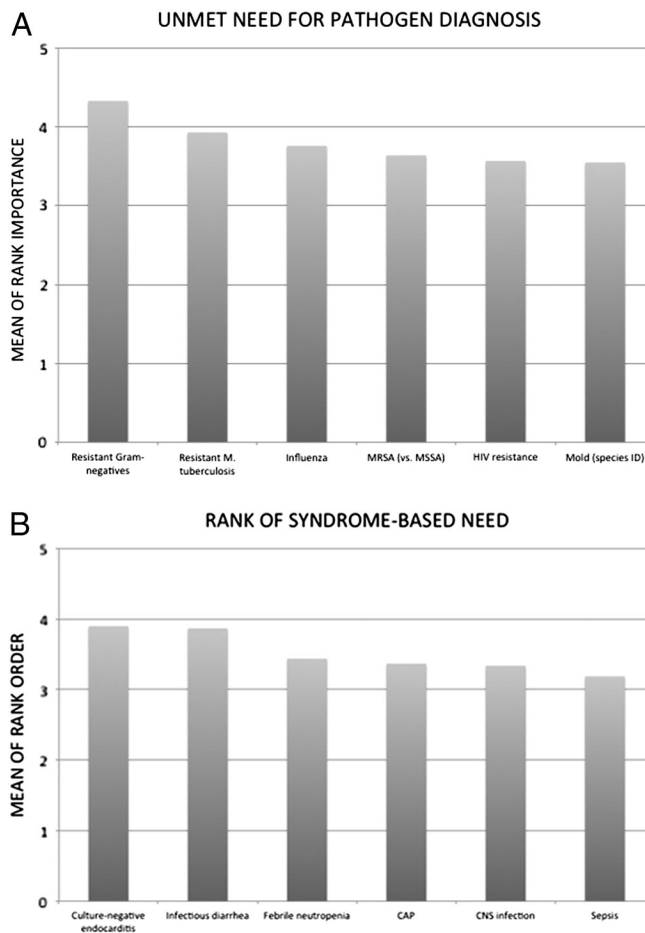


Fig. 1. Rank of unmet pathogen and syndrome-based needs.

Antibiotic-resistant organisms are a serious health threat (Centers for Disease Control, 2013). Overuse of antimicrobials contributes to both the rise and persistence of drug resistant organisms, and there is an urgent need for strategies to shorten the duration of multidrug empiric therapy (Perez et al., 2013) and to stop unnecessary prescribing. Diagnostic tests that can quickly identify specific pathogens are critical to antibiotic stewardship efforts that seek to promote narrow-spectrum, targeted treatment for infectious illness as opposed to empiric broad-spectrum therapy (Bauer et al., 2010; Huang et al., 2013; Perez et al., 2013). Survey respondents consistently ranked highly the identification of resistant organisms with emphasis on better testing for multidrug-resistant aerobic gram-negative bacilli.

An important caveat pertinent to testing for the genes responsible for resistance in gram-negative organisms is the complexity of the resistance mechanisms. The absence of ESBLs, cephalosporinases, and carbapenemases does not preclude beta-lactam resistance as a result of cell wall porin closure and/or activity of efflux pumps (Bush, 2001; Paterson and Bonomo, 2005). Molecular test development will need to cover a wide range of possible resistance mechanisms, which presents a significant challenge. Rapid phenotypic resistance testing may be an alternative approach. Our respondents did feel that methods that identified ESBL or KPC resistance mechanisms alone would provide useful information even if other mechanisms of resistance were unknown.

In several cases, tests ranked highly as “unmet” needs (for example, rapid resistance testing for staphylococci, testing panel for infectious diarrhea) were actually commercially available or close to receiving Food and Drug Administration approval at the time the survey was given. This suggests that clinicians are not aware of tests that are available or that developed tests desired by clinicians are not available to them in their practice. Lack of availability may be due to the complexity of the

testing strategies, the economics of the laboratory, or the absence of outcome data that could be used to support adoption of new tests. It is critical that physicians advocate for testing to be implemented locally or that send out mechanisms are available if they feel that such testing will positively impact patient care. In addition, it is important that laboratories educate physicians about new diagnostic assays that are available.

Testing strategies that utilize new technologies are often more expensive and complex than traditional methods (Baron, 2006; Fournier et al., 2013). Physicians are becoming familiar with the concept of “stewardship” (interventions designed to improve appropriate use) as associated with antibiotic use (Tamma and Cosgrove, 2011), and over half of our survey respondents felt that diagnostic testing could benefit from stewardship as well. Diagnostics stewardship could address overuse of testing, guidance regarding test selection and interpretation, and implementation of workflow that ensures that critical results are received and acted on in a timely manner.

An important component of effective stewardship is an evidence base that can be used to guide decisions (Tamma and Cosgrove, 2011). Outcome and cost-effectiveness data are urgently needed that can impact testing at both the patient and the system levels (Caliendo et al., 2013). Survey respondents ranked availability of outcomes data highly as an important characteristic to consider when choosing a new diagnostic test.

Our study has limitations. The opinions of non-respondents, those that opted-out, and other physicians not included in the EIN may be different. Although respondents for any EIN survey usually have more years of experience and a higher percentage of pediatric members usually respond than the comparable percentage of members with adult practices, these differences potentially may bias the results for this survey. Furthermore, the perspectives of physicians in other clinically relevant specialties were not assessed.

As new technologies evolve, it is important to stay focused on developing tests that address unmet needs and that conserve, rather than consume, our resources. The call for tests to identify resistant aerobic gram-negative bacteria reflects the increasing problems of drug-resistant infection and limited antibiotic development. Recognition of the importance of judicious testing through stewardship also parallels increased awareness of rising healthcare costs. Information gained from this survey can help inform recommendations for new diagnostic test development in the future.

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Conflict of interest

AJB and KEH have collaborated with BioFire Diagnostics (Salt Lake City, UT, USA) on federally funded projects. AJB has intellectual property in and receives royalties from BioFire Diagnostics. KEH has performed contract work for SanofiPasteur.

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