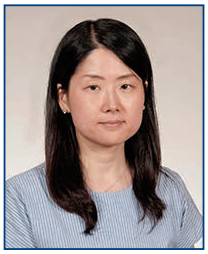
Updates on Rapid Diagnostic Tests in Infectious Diseases

by Masako Mizusawa, MD

UMKC School of Medicine

Rapid diagnostic tests are powerful tools for the timely optimization of antimicrobial use.



Masako Mizusawa, MD, PhD, MS, is in the Section of Infectious Diseases, Department of Internal Medicine, University of Missouri - Kansas City, Kansas City, Missouri.

Abstract

In the last two decades there have been dramatic advances in development of rapid diagnostic tests. Turnaround time of the assays have significantly been shortened which led to reductions in time to appropriate antimicrobial therapy and improvement of patient clinical outcomes. Molecular-based assays generally have better sensitivity than conventional methods, but the cost is higher. The results need to be interpreted cautiously as detection of colonized organisms, pathogen detection in asymptomatic patients, and false negative/positive can occur. Indications and cost-effectiveness need to be considered for appropriate utilization of rapid diagnostic tests.

Introduction

Detection of pathogens plays a major role in the clinical care of the patients with infectious diseases. Traditional diagnostic testing for infectious diseases such as microscopic examination, antigen detection, serology, cultures, and biochemical reactions are still being used, and sometimes essential for determination of infectious disease etiologies. However, those traditional methods tend to suffer from long turn-around time. For example, bacteria generally require 1-2 days to have growth on culture media, and conventional biochemical identification and susceptibility tests require additional one to two days to result. In the meantime, the patients tend to remain on empiric broad spectrum antibiotics which could lead to selection of antimicrobial resistance.

New technologies such as nucleic-acid amplification, mass spectrometry, and genomic sequencing have revolutionized diagnostic testing for infectious diseases by providing rapid and robust results. Introduction of rapid diagnostic testing in collaboration with antimicrobial stewardship has led to appropriate antimicrobial use and improvement of clinical outcomes.[1]

This article is a concise summary of rapid diagnostic tests for infectious diseases currently available in the United States.

Rapid Molecular Assays Molecular Multiplex Syndromic Panel Testing

There are currently 4 molecular multiplex syndromic panels available in the U.S.: Blood stream infections, respiratory tract infections, gastrointestinal infections and meningitis/encephalitis. The common advantages of those panels are simultaneous detection of multiple targets and rapid turnaround time that could shorten time to appropriate antimicrobial treatment and improve associated

clinical outcomes. The common disadvantages of those panels are the limited numbers of detectable pathogens and higher cost than conventional methods.

Blood Stream Infections

Blood stream infections are often associated with significant morbidity and mortality.[2] Multiple studies demonstrated associations between delay in initiation of appropriate antimicrobial therapy and increased mortality for patients with blood stream infections.[3–6] Identification of the pathogens in blood cultures is essential for directing appropriate antimicrobial therapy and improving patient outcomes. There are currently four FDA-cleared molecular multiplex assays for blood culture pathogen identification: FilmArray BCID panel (bioMérieux, Marcy l'Etoile, France), Verigene Gram Positive Blood Culture ID assay (BCID-GP) and Gram Negative Blood Culture ID assay (BCID-GN) (Luminex Molecular Diagnostics, Toronto, Canada), Accelerate PhenoTest BC kit (Accelerate Diagnostics, Tucson, AZ), and ePlex Blood Culture Identification Gram-Positive Panel (BCID-GP) and Gram-Negative Panel (BCID-GN) (GenMark Diagnostics, Carlsbad, CA).

The assays are performed directly on positive blood culture specimens detected by a continuous monitoring blood culture system. The turnaround time and pathogen targets in each panel are shown in Table 1. While FilmArray BCID and PhenoTest BC include targets for both Gram positive and Gram negative organisms in one test kit, Verigene and ePlex have Gram-positive and Gram-negative panels separately and Gram staining results determines selection of the appropriate test panels. Of note the PhenoTest BC is currently the only assay that enables rapid antimicrobial susceptibility testing in addition to pathogen identification. The antimicrobial susceptibility panel of the PhenoTest BC includes amikacin, ampicillin, ampicillin/sulbactam, aztreonam, ceftazidime, ceftaroline, cefepime, ceftriaxone, ciprofloxacin, daptomycin, erythromycin, ertapenem, gentamicin, linezolid, meropenem, piperacillin/tazobactam, tobramycin, and vancomycin. There have been no major differences in the performance of those multiplex blood culture panels to support superiority one over another.[7–22] In general, their performance is lower with polymicrobial blood culture specimens than monomicrobial ones.[7,8,13,14,19,20,22] Improvement of clinical outcomes such as length of stay, time to optimal antibiotic therapy, and 30-day mortality rate with antimicrobial stewardship interventions based on the results of rapid blood culture identification have been demonstrated.[23–34]

Meningitis and Encephalitis

Meningitis and encephalitis are potentially life-threatening infections and could leave severe neurological sequela. Rapid pathogen detection to guide appropriate treatment is critically important to improve clinical outcomes. Currently FilmArray Meningitis/Encephalitis (ME) panel (bioMérieux, Marcy l'Etoile, France) is the only FDA-cleared assay available in the U.S. The pathogen targets included in the FilmArray ME panel are *Escherichia coli* K1, *Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis* (encapsulated), *Streptococcus agalactiae, Streptococcus pneumoniae*, Cytomegalovirus, Enterovirus, Herpes simplex virus 1, Herpes simplex virus 2, Human herpesvirus 6, Human parechovirus, Varicella zoster virus, and *Cryptococcus neoformans/gattii*. The advantages of the FilmArray ME panel compared to conventional cultures and individual molecular-based tests are rapid turnaround time (one hour) and a small amount of CSF (0.2mL) required for detection of 14 targets. In the meta-analysis of eight studies accounting for 3,059 patients met the inclusion criteria of the diagnostic accuracy test review of the FilmArray ME panel, mean sensitivity was 90% (95% CI 86 - 93%) and mean specificity was 97% (95% CI 94 - 99%).[35] The studies that specifically evaluated false positive and negative results were also analyzed, and it was found that 4% and 1.5% of specimens were determined as false positive and false negative respectively by the FilmArray ME panel compared with reference standard methods after implementing adjudication for discrepant results.[35] The highest proportion of false positive was observed for *Streptococcus pneumoniae* followed by *Streptococcus agalactiae*, and the highest proportion of false negative was observed for Herpes simplex virus 1 and 2, enterovirus, and *Cryptococcus neoformans/gattii*.[35] Most of the false negative *Cryptococcus neoformans/gattii* cases were those who were on antifungal treatment.[35]

Respiratory Tract Infections

There are currently five FDA-cleared multiplex panels for respiratory pathogens: NxTAG Respiratory Pathogen Panel (Luminex Molecular Diagnostics, Toronto, Canada), FilmArray Respiratory Panel (bioMérieux, Marcy l'Etoile, France), Verigene

Table 1. Turnaround time and pathogen targets of FDA-cleared multiplex blood culture identification panels

	FilmArray	Verigene	PhenoTest	ePlex
Turnaround time	1 hour	2-2.5 hours	7 hours[a]	1.5 hours
Pathogen targets				
Gram positive bacteria				
Staphylococcus species	X	X		X
S. aureus	X	X	X	X
Coagulase-negative *Staphylococcus* spp.			X	
S. epidermidis		X		X
S. lugdunensis		X	X	X
Streptococcus species	X	X	X	X
S. pneumoniae	X	X		X
S. pyogenes	X	X		X
S. agalactiae	X	X		X
S. anginosus group		X		X
Enterococcus species	X			X
E. faecalis		X	X	X
E. faecium		X	X	X
Listeria species		X		X
L. monocytogenes	X			X
Lactobacillus species				X
Micrococcus species				X
Bacillus cereus group				X
Bacillus subtilis group				X
Corynebacterium species				X
Cutibacterium acnes				X
Gram negative bacteria				
Enterobacteriaceae	X			
Escherichia coli	X	X	X	X
Klebsiella species			X	
Klebsiella pneumoniae	X	X		X
Klebsiella oxytoca	X	X		X
Proteus species	X	X	X	X
Proteus mirabilis				X
Enterobacter species		X	X	
Enterobacter (non-*cloacae* complex)				X
Enterobacter cloacae complex	X			X
Citrobacter species		X	X	X
Serratia species				X
Serratia marcescens	X		X	X
Pseudomonas aeruginosa	X	X	X	X
Acinetobacter species		X		
Acinetobacter baumanii	X		X	X
Haemophilus influenzae	X			X
Neisseria meningitidis	X			X
Bacteroides fragilis				X
Fusobacterium necropholum				X
Fusobacterium nucleatum				X
Morganella morganii				X
Coronobacter sakazakii				X
Salmonella species				X
Stenotrophomonas maltophilia				X
Yeast				
Candida species				X
Candida albicans	X		X	
Candida glabrata	X		X	
Candida krusei	X			
Candida parapsilosis	X			
Candida tropicalis	X			
Antimicrobial resistance markers				
mecA	X	X		X
mecC				X
VanA/B	X			
VanA		X		X
VanB		X		X
KPC (*bla*$_{KPC}$)	X	X		X
OXA (*bla*$_{oxa}$)		X		X
VIM (*bla*$_{VIM}$)		X		X
IMP (*bla*$_{IMP}$)		X		X
CTX-M (*bla*$_{CTX-M}$)		X		X
NDM (*bla*$_{NDM}$)		X		X

[a] Including antimicrobial susceptibility testing for amikacin, ampicillin, ampicillin/sulbactam, aztreonam, ceftazidime, ceftaroline, cefepime, ceftriaxone, ciprofloxacin, daptomycin, erythromycin, ertapenem, gentamicin, linezolid, meropenem, piperacillin/tazobactam, tobramycin, and vancomycin.

Respiratory Pathogens Flex Nucleic Acid Test (RP Flex) (Luminex Molecular Diagnostics, Toronto, Canada), eSensor Respiratory Viral Panel (RVP) (GenMark Diagnostics, Carlsbad, CA), and ePlex Respiratory Pathogen (RP) Panel (GenMark Diagnostics, Carlsbad, CA). The assays are performed on nasopharyngeal swab specimens collected from individuals who are suspected to have respiratory tract infections. NxTAG Respiratory Pathogen Panel and Verigene RP Flex allow panel customization to avoid detection of unnecessary targets and minimize the cost. The turnaround time and pathogen targets included in each panel are shown in Table 2. The assay performance generally demonstrated high concordance rates with positive percent agreement 84.5 - 98.8% and negative percent agreement 99.2 - 100% when compared between different multiplex panels or with a laboratory-developed polymerase chain reaction (PCR) assay as a reference method.[36–40] However, more frequent discrepancies have been reported for adenovirus,[36,40] influenza B virus,[36] human metapneumovirus,[39] parainfluenza 3,[39] coronavirus,[40] and rhinovirus/enterovirus.[40] It is important to keep in mind that detection of a certain virus does not necessarily mean that the virus is a causative pathogen of respiratory symptoms that a patient has because viruses can be colonized in the respiratory tract asymptomatically. In addition, detection of multiple targets is not uncommon.[36,37] Although immunocompromised patients can develop severe viral respiratory infections and are more likely to benefit from the multiplex panel testing than immunocompetent individuals, they can shed viruses for a prolonged period of time without clinical symptoms. The results of the multiplex respiratory panel testing need to be interpreted carefully in a clinical context. Further work up may be indicated as there are many respiratory pathogens that are not included in multiplex respiratory panels.

Gastrointestinal Infections

Infectious diarrheal illness is very common worldwide. Since 1990, diarrhea has been ranked among the top ten causes of death and disability-adjusted life-years (DALYs) among all ages, and one of the top five causes of death and DALYs for children younger than five years.[41] Conventional methods for diarrheal pathogen detections include microscopic examination, culture, and enzyme-linked immunosorbent assays (ELISA). Microscopic examination for parasite detection requires specific expertise and the results are operator dependent which causes variability in sensitivity. Stool culture is labor intensive and takes two to three days to result. ELISA assays are generally less sensitive than PCR.[42–44] There are currently three FDA-cleared multiplex gastrointestinal pathogen panels in one kit available in the U.S. FilmArray Gastrointestinal (GI) Panel (bioMérieux, Marcy l'Etoile, France), Verigene Enteric Pathogen Test (Luminex Molecular Diagnostics, Toronto, Canada), and xTAG Gastrointestinal Pathogen Panel (Luminex Molecular Diagnostics, Toronto, Canada). BD MAX (BD Diagnostics, Sparks, Maryland, USA) is also a FDA-cleared multiplex assay, but has 4 separate panels for gastrointestinal pathogens: Enteric Bacterial Panel, Extended Enteric Bacterial Panel, Enteric Parasite Panel, and Enteric Viral Panel. The turnaround time and pathogen targets included in those assays are shown in Table 3. Overall multiplex panel tests had higher positivity rates compared to conventional methods in performance evaluation studies.[45–52] Simultaneous detection of multiple pathogens is not uncommon as well as detection of pathogens in asymptomatic patients which can make interpretation of the test results and management challenging for clinicians.[53,54]

Point-of-care Molecular Based Tests

There are a variety of FDA-cleared nucleic acid amplification tests available for one to several targets for surveillance as well as diagnosis of specific infections. Examples include methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, Carbapenem resistance genes (bla_{KPC}, bla_{NDM}, bla_{VIM}, bla_{OXA-48}, and bla_{IMP}), Group A *Streptococcus*, Group B *Streptococcus*, Influenza virus A & B/RSV, *Clostridium difficile* with or without NAP 027, Norovirus, Human simplex virus 1 & 2, *Mycobacterium tuberculosis* with rifampin resistance, *Trichomonas vaginalis, Chlamydia trachomatis/Neisseria gonorrhea*, and *Bordetella pertussis/Bordetella parapertussis*.

T2 System

Candidemia is associated with high mortality rates. Although the rates are variable depending on the clinical setting, mortality rates range from 20% to 60%.[55,56] Blood culture is the gold standard for diagnosis of Candidemia. However, sensitivity of blood culture is as low as 50%.[57,58] T2Candida

Table 2. Turnaround time and pathogen targets of FDA-cleared multiplex respiratory panels

	FilmArray	Verigene	NxTAG	eSensor	ePlex
Turnaround time	1 hour	2 hours	5 hours[a]	6 hours	1.5 hours
Pathogen targets					
Viruses					
Influenza A	X	X	X	X	X
Influenza A H1	X	X	X	X	X
Influenza A H3	X	X	X	X	X
Influenza 2009 H1N1	X			X	X
Influenza B	X	X	X	X	X
Respiratory Syncytial Virus	X				
Respiratory Syncytial Virus A		X	X	X	X
Respiratory Syncytial Virus B		X	X	X	X
Parainfluenza virus 1	X	X	X	X	X
Parainfluenza virus 2	X	X	X	X	X
Parainfluenza virus 3	X	X	X	X	X
Parainfluenza virus 4	X	X	X		X
Coronavirus (229E/HKU1/NL63/OC43)					X
Coronavirus HKU1	X	X	X		
Coronavirus NL63	X		X		
Coronavirus 229E	X		X		
Coronavirus OC43	X		X		
Adenovirus	X		X		X
Adenovirus B/E				X	
Adenovirus C				X	
Rhinovirus		X		X	
Rhinovirus/Enterovirus	X		X		X
Human Metapneumovirus			X	X	X
Human Bocavirus			X		
Bacteria					
Mycoplasma pneumoniae	X		X		X
Chlamydophila pneumoniae	X		X		X
Bordetella pertussis	X	X			
Bordetella parapertussis/ Bordetella bronchiseptica		X			
Bordetella holmesii		X			

[a] *For 96 samples*

Panel (T2 Biosystems, Lexington, Massachusetts, USA) is an FDA-cleared qualitative T2 Magnetic Resonance (T2MR) assay for detection of Candida species directly from whole blood specimens. In T2 system blood-compatible polymerase chain reaction is followed by hybridization of the amplified pathogen DNA to capture probe–decorated nanoparticles. Hybridization yields nanoparticle micro-clusters that cause large changes in the sample's T2MR signal.[59] T2Candida Panel identifies five species of Candida by categorizing them in three groups: Candida albicans/ Candida tropicalis, Candida parapsilosis, and Candida glabrata /Candida krusei. Time to result is three to four hours. In a multicenter clinical trial including 14 centers, the assay sensitivity was 89%.[60] In patients receiving antifungal therapy, T2Candida Panel identified bloodstream infections that were missed by conventional blood cultures.[60] In another multicenter clinical trial including 12 centers, the overall sensitivity was 91.1% and specificity was 99.4%. [61] The pooled analysis including eight studies conducted to evaluate accuracy of T2Candida Panel demonstrated the pooled sensitivity of 91% and specificity of 94%.[62] T2 system also has FDA-cleared Bacterial Panel which can detect *Enterococcus faecium*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* directly from whole blood samples. In a diagnostic accuracy study T2Bacterial Panel sensitivity and specificity for proven blood stream infections were 90% and 90% respectively.[63] Mean time to identification was 3.61 hours (SD, 0.2) for one sample and 7.70 hours (SD, 1.38) for seven samples.[63]

MALDI-TOF MS

Matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry (MS) is a rapid, accurate, and cost-effective identification

method for bacterial and fungal culture isolates with direct smear. In mass spectrometry analysis, sample protein molecules are converted into ions in the gas phase by laser ablation. The ionized molecules are subsequently accelerated by a potential difference and fly through the flight tube towards the detector, and the system measures the analytes' time of flight to the detector which produces a characteristic spectrum. The advantages of MALDI-TOF MS are ability to identify broad range of pathogens and low cost. Turnaround time for the MALDI-TOF MS assay itself is short, but it takes one to two days until the culture isolate for direct smear becomes available. In an effort to shorten time to pathogen identification in blood culture, various sample preparation procedures including Sepsityper kit (Bruker Daltonics, Bremen, Germany) and in-house methods were developed to perform MALDI-TOF MS directly from positive blood culture bottles without subculture. Overall correct identification rates to species level and genus level range 39.9 - 89.7% and 76.4 -100% respectively, and the rates were higher in Gram negative organisms compared to Gram positive organisms.[64–79] Performance was poor in polymicrobial cultures[65,67–69,71–73,75–78] and yeast identifications.[66,70,71,79] Recently, an alternative method with subculture has been developed. The positive blood culture specimens are plated on solid media. After short incubation (four to six hours) 1 - 2 mm of the bacterial lawn is transferred with a 1 µL inoculation loop for direct smear. Using short incubation overall correct identification rates to species level range 69.7 - 99.5%.[80–83]

Table 3. Turnaround time and pathogen targets of FDA-cleared multiplex gastrointestinal panels

	FilmArray	Verigene	xTAG	BD Max[a]
Turnaround time	1 hour	2 hours	6 hours[b]	3-4 hours[b]
Pathogen targets				
Bacteria				
Campylobacter	X	X	X	X
Salmonella	X	X	X	X
Shigella		X	X	
Shigella/Enteroinvasive E. coli	X			X
Shiga-like toxin producing E. coli St1/St2	X		X	X
Shiga Toxin 1		X		
Shiga Toxin 2		X		
Vibrio	X	X		X
Vibrio cholerae	X		X	
Yersinia enterocolitica	X	X	X	X
Plesiomonas shigelloides	X			X
Enteroaggregative E. coli	X			
Enteropathogenic E. coli	X			
Enterotoxigenic E. coli LT/ST	X		X	X
E. coli O 157	X		X	
Clostridium difficile (toxinA/B)	X		X	
Viruses				
Adenovirus F40/41	X		X	X
Astrovirus	X			X
Norovirus GI/GII	X	X	X	X
Rotavirus A	X	X	X	X
Sapovirus (I, II, IV and V)	X			X
Parasites				
Cryptosporidium			X	X
Cyclospora cayetanensis	X			
Entamoeba histolytica	X		X	X
Giardia lamblia	X		X	X

[a] Consists of 4 separate panels (Enteric Bacterial Panel, Extended Enteric Bacterial Panel, Enteric Viral Panel and Enteric Parasite Panel)
[b] For 24 samples

Conclusions

Rapid diagnostic tests are powerful tools for the timely optimization of antimicrobial use. However, interpretations of the results such as potential false positive or negative and detection of colonized microorganisms require careful evaluation of the clinical settings and background of the patients. Cost-effectiveness also needs to be considered to determine indications for expensive rapid diagnostic tests to prevent overutilization of those tests.

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SARS-CoV-2 Serology Testing: An Epilogue

There are currently more than 200 SARS-CoV-2 commercial serology tests available in the U.S. Serology assays for SARS-CoV-2 initially did not require FDA emergency use authorization (EUA), and submission of assay validation data to Food and Drug Administration (FDA) was a voluntary process until May 4, 2020. Therefore, many laboratories notified FDA that they had validated their assays and started patient testing, but their assay performances were not reviewed by FDA prior to market release. A revised guidance from FDA has provided specific assay performance thresholds, and validation data submission for EUA has become manufacturers' requirements. A list of SARS-Co-V-2 serology tests that have been removed from the notification list due to manufacturers' voluntary withdrawal and lack of pending EUA request or issued EUA is available on the FDA website (https://www.fda.gov/medical-devices/emergency-situations-medical-devices/faqs-testing-sars-cov-2#nolonger). There is also a list of EUA authorized serology tests (https://www.fda.gov/medical-devices/emergency-situations-medical-devices/eua-authorized-serology-test-performance). It is advised to select an EUA authorized SARS-Co-V-2 serology test to assure the appropriate assay performance.

Commercial serology assays for SARS-CoV-2 are variable in different formats (lateral flow assays, enzyme immunosorbent assays, and chemiluminescent immunoassays) and antibody classes (IgM, IgA, IgG, and IgM/IgG total antibody) with using different antigens (nucleocapsid, S1 and/or S2 spike glycoproteins, and spike glycoprotein receptor binding protein).[1] The majority of patients seem to develop antibody response between seven and eleven

SARS-CoV-2 Serology Testing: An Epilogue, continued

days following exposure to SARS-CoV-2[2] although available data regarding timing of antibody appearance following disease onset are variable.[2–6] Wu et al. collected plasma samples from 175 COVID-19 recovered patients with mild symptoms and found that SARS-CoV-2 specific neutralizing antibodies were detected in patients from day 10-15 after the onset of disease.[7] They also found that elderly and middle-age patients had significantly higher plasma neutralizing antibody titers than young patients, and approximately 30% of recovered patients generated a very low level of neutralizing antibody titers (10 patients had undetectable levels).[7]

Antibody testing can be used for surveillance to identify how many people have been exposed to SARS-CoV-2 in the community as well as contact tracing. Another use of antibody testing is donor screening for convalescent plasma which is used to treat patients with SARS-CoV-2 infection. In the future, when a vaccine for SARS-CoV-2 becomes available, antibody testing would play a role in screening vaccine candidates and monitoring immune responses of vaccinated individuals.

Not all the antibodies produced are neutralizing antibodies that block viral entry to host cells.[8] Commercial serology assays do not distinguish between neutralizing antibodies and other antibodies. Therefore, detection of IgG antibodies by those assays does not mean that detectable levels of neutralizing antibodies are present, and antibody testing should not be used as a surrogate marker for protective immunity against SARS-CoV-2 infection. Even if a serology test that specifically detects neutralizing antibodies is developed, detection of neutralizing antibodies still does not equal to protective immunity because what levels of antibody titers would protect patients from SARS-CoV-2 infection is still unknown.

Antibody testing should not be used for diagnosing acute/recent SARS-Co-V-2 infection by itself because antibody may not be detected in the early days of the infection when the risk of transmission is the highest, and negative results do not rule out acute/recent SARS-CoV-2 infection. In general IgM suffers from false positivity more than other classes of antibodies,[9] and positive IgM results do not rule in acute/recent SARS-CoV-2 infection either. Grifoni et al. found SARS-CoV-2-reactive $CD4^+$ T cells in ~40%–60% of unexposed individuals, suggesting cross-reactive T cell recognition between circulating "common cold" coronaviruses (HCoV-OC43, HCoV-HKU1, HCoV-NL63, and HCoV-229E) and SARS-CoV-2,[10] and false positive results due to cross-reactivity with other coronaviruses are also possible. It is advised to check whether cross-reactivity with common cold coronaviruses has been validated or not prior to selection of antibody assays. It is also important to keep in mind that positive and negative predictive values of antibody assays depend on disease prevalence. When disease prevalence is low, false positivity rate is increased even with the excellent specificity.

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Disclosure

None reported. **MM**