Developing Human Diagnostics in an Emergency Situation

What is the expected need and how do we get what we need?

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Jean B Patel, PhD, D(ABMM)

BECKMAN COULTER

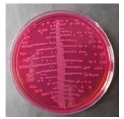
TYPES OF DIAGNOSTICS THAT WOULD HELP

Category	Diagnostic Need	Status Today	Future
 **Infection Diagnostics**	A pathogen needs to be identified and therapy decisions need to be made.	These diagnostics exist today but are slow.	Rapid tests can suffer from accuracy gaps that need to be closed for impact on antibiotic use. All tests need to be updated when new antimicrobial resistance emerges.
 **Prevention Diagnostics**	The patient is not infected but may harbor detectable characteristics that identify them as high risk for acquiring a healthcare associated infection (HAI) or at high risk for transmitting multi-drug resistant organisms (MDROs) to other patients.	Interventions today are limited to infection prevention decisions including contact precautions, isolation or patient cohorting.	New interventions are in development & diagnostics can determine when an intervention should be used.

FASTER INFECTION DIAGNOSTICS

Conventional Testing for blood cultures can take between 4 to 70+ hours

Sample collection | Incubation | Gram Stain | Streaking & Subculture | Incubation | Plate reading & colony picking | Assay Set Up | ID/AST | Results



One test on market

Multiple high-plexed tests on market.

One test on market

Many tests in development.

Diagnostic & TTR	Pathogen ID <2h	Molecular Identification of Resistance Mechanisms <2h	Phenotypic AST <8h
Antibiotic Adjustment	Direct from specimen can have the most impact but requires high sensitivity.	Biggest impact is for Gram-positive pathogens	Has the potential for a definitive therapy decision if results are accurate and the menu is sufficient

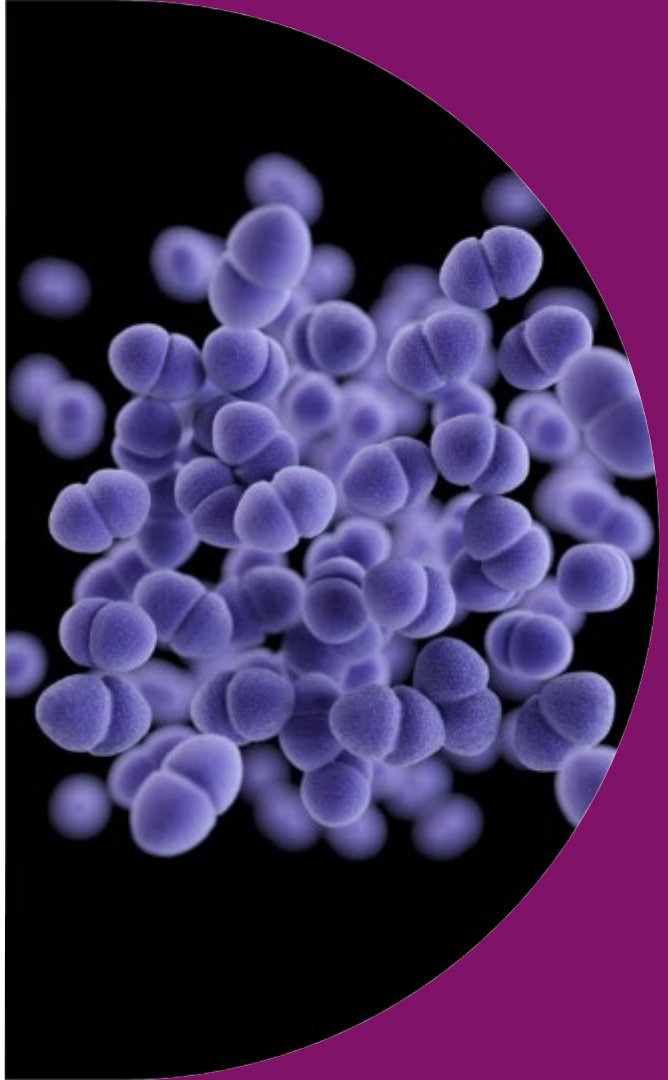
Rapid diagnostics have come a long way. Increased sensitivity (ID) and accuracy/test menu (rapid phenotypic AST) are needed for improved clinical decision making.

HOW TO IMPROVE UPON ID/AST TESTING FOR INFECTIONS

- Pathogen ID direct from blood – A technology breakthrough is needed to improve sensitivity

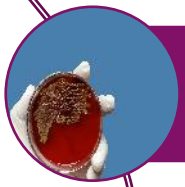
- Molecular testing for PBC – These are successful diagnostics. Work will be needed to keep these up-to-date.

- Rapid phenotypic AST – Customers want speed, accuracy, a test menu that replaces conventional AST and a price tag that rivals current costs.
  - This is a big lift but possible
  - Optimal clinical impact may mean a restructuring of when and how therapeutic decisions are made in a healthcare facility



RESPONDING TO NEW ANTIMICROBIAL RESISTANCE

The following resources are needed for test development:



Access to isolates

- Representative of the population
- Use for validation & verification

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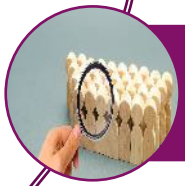
Knowledge of clinical epidemiology

- Who should be tested?
- What specimens should be tested?



Knowledge of the population size

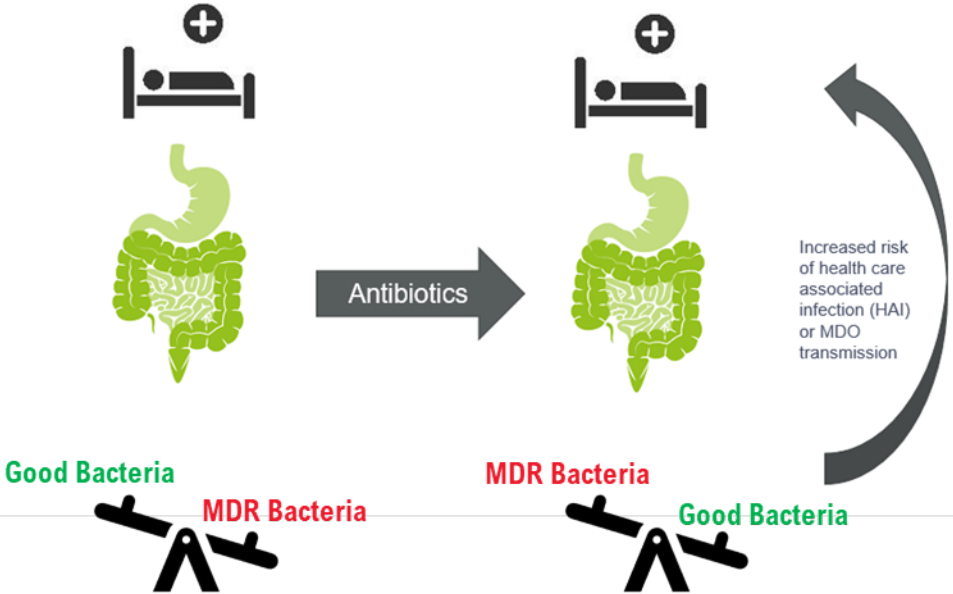
- Current
- Growth potential

Test development times:

Test	Time
Molecular detection of a new resistance gene	<1 year
Phenotypic susceptibility testing of existing drugs for a new type of resistance	<2 years
Phenotypic susceptibility testing of a new drug to multiple organism groups	2+ years

PREVENTION DIAGNOSTICS

Who is at high risk for an HAI or MDRO transmission?



Diagnostic Test	Information Generated	Decision Today	Decision Future
MDRO Colonization	Test a GI specimen for MDRO	Infection control precautions	Decolonization
Diagnostics to track transmission dynamics	Microbial relatedness assessment	Infection control precautions	
Microbiome diversity assessment	Test a GI specimen for the level of diversity present	No testing performed because of unproven value	Apply interventions to protect or restore the microbiome

WOULD PREVENTION DIAGNOSTICS IMPACT PATIENTS?

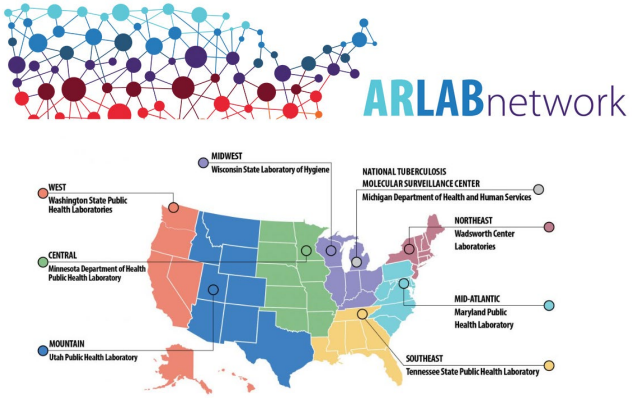
- **MDRO Colonization diagnostics can resolve an outbreak or predict a future HAI pathogen**
  - *"CRE surveillance at admission to the hospital were independently associated with lower new carrier prevalence."*
  - In a case-controlled study, a semi-quantitative PCR assay demonstrated that *Klebsiella colonization* density is associated with subsequent infection.
- **Transmission diagnostics can identify a common reservoir for transmission or elucidate transmission dynamics**
  - Conclusion from an outbreak of CR-Klebsiella at the NIH: "*Our analysis demonstrates that integration of genomic and epidemiological data can yield actionable insights and facilitate the control of nosocomial transmission.*"
- **Microbiome restoration works for *Clostridium difficile* infection. It could prevent HAIs for patients with high MDRO density in the GI tract**
  - "*Based on the findings from a large multi-center retrospective cohort, FMT is effective and safe for the treatment of CDI in children and young adults.*"

Is prevention diagnostics the future? If so, when and how should we invest in this?

- Ben-David D, et al. Infect Control Hosp Epidemio. 2014 Jul;35(7)
- Sun Y, et al. mSphere 6:e00500-21. https://doi.org/10.1128/mSphere.00500-21
- Snitkin ES, et al. Science. 2012; 4(148)
- Nicholson MR, et al.Clin Gastroenterol Hepatol. 2020 March ; 18(3): 612–619.

MARKET BARRIERS HINDER DEVELOPMENT OF PREVENTION DIAGNOSTICS

- **Example**: Carbapenem-Resistant GN Colonization Tests
- One FDA-cleared test on the market – Cepheid CARBA-R
- Available for testing in the AR Lab Network



- Slow test uptake of this testing in hospitals and the AR Lab Network
  - No specific reimbursement for infection control testing (test is primarily for inpatients)
  - No interventions outside of infection control precautions. If providers believe that these interventions are in-effective or too hard to implement, then testing is not desired.
  - This is not an everyday test for a laboratory so it may be easier to outsource. Outsourced testing is less likely to be utilized and turn-around times are slower.

If colonization testing is important, incentives for test utilization are needed.

SUMMARY

- **Important infection diagnostic tests are already available or in development.**
  - Direct from blood testing can be improved with technology breakthroughs.
  - Rapid phenotypic antimicrobial susceptibility testing needs innovative test development muscle. Uptake will require clinical impact studies.
  - Outside funding such BARDA enables industry to take on risky projects while continuing to invest in core products.

- **Prevention diagnostics is an undeveloped testing category that could significantly impact HAI rates.** Needs:
  - Overcoming barriers to test utilization
  - Developing new interventions (decolonization testing) to mitigate risk of infection and transmission
  - Demonstration studies evaluating if diagnostics help to apply these interventions

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