Johns Hopkins Engineering

Immunoengineering

Immunoengineering—Pathogens

Diagnostics

JOHNS HOPKINS
WHITING SCHOOL
of ENGINEERING

The Need for Diagnostics

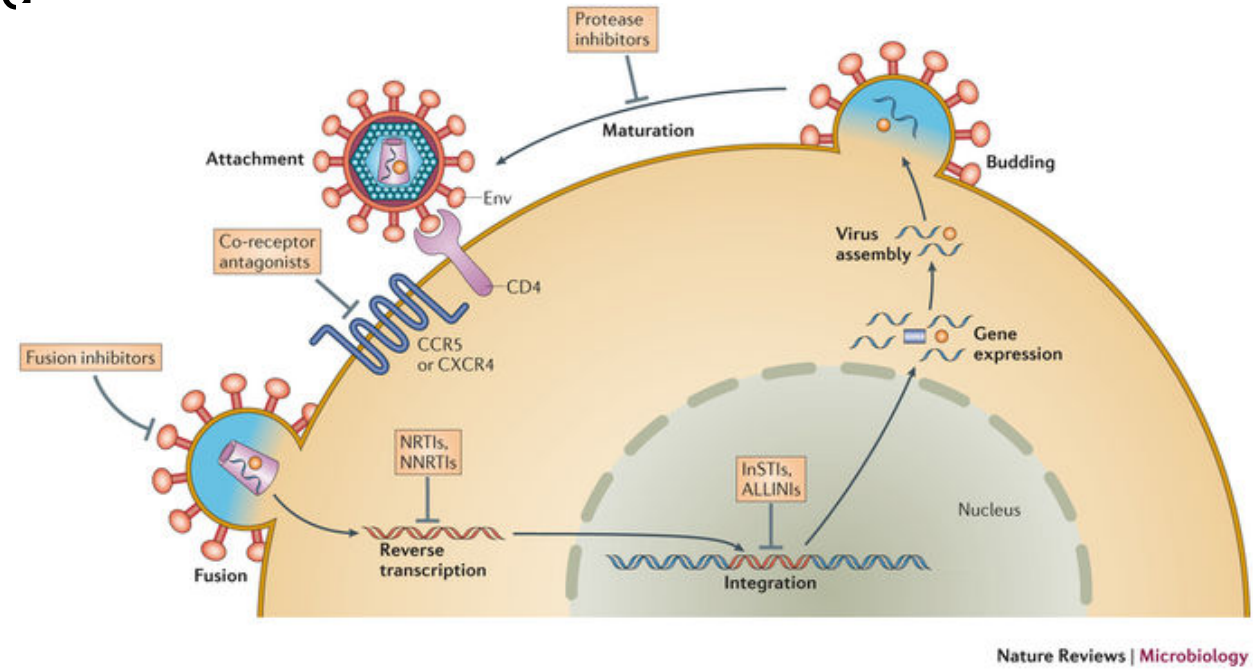
The Need for Diagnostics

- Limit/prevent Spread

https://www.flickr.com/photos/121483302@N02/14632566347

The Need for Diagnostics

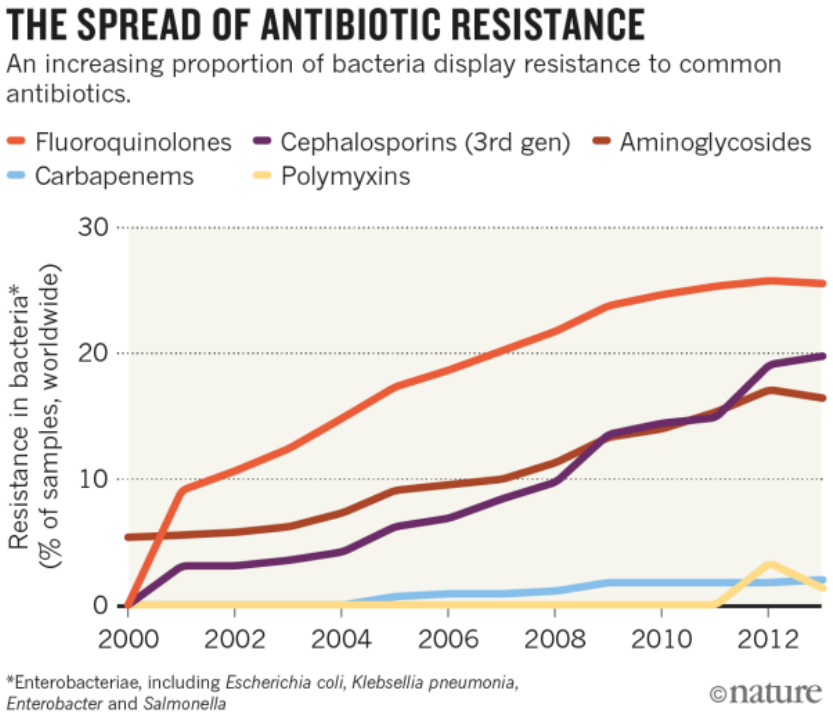
- Limit/prevent Spread
- Faster Treatment



Laskey, Sarah B., and Robert F. Siliciano. "A mechanistic theory to explain the efficacy of antiretroviral therapy." *Nature Reviews Microbiology* 12.11 (2014): 772.

The Need for Diagnostics

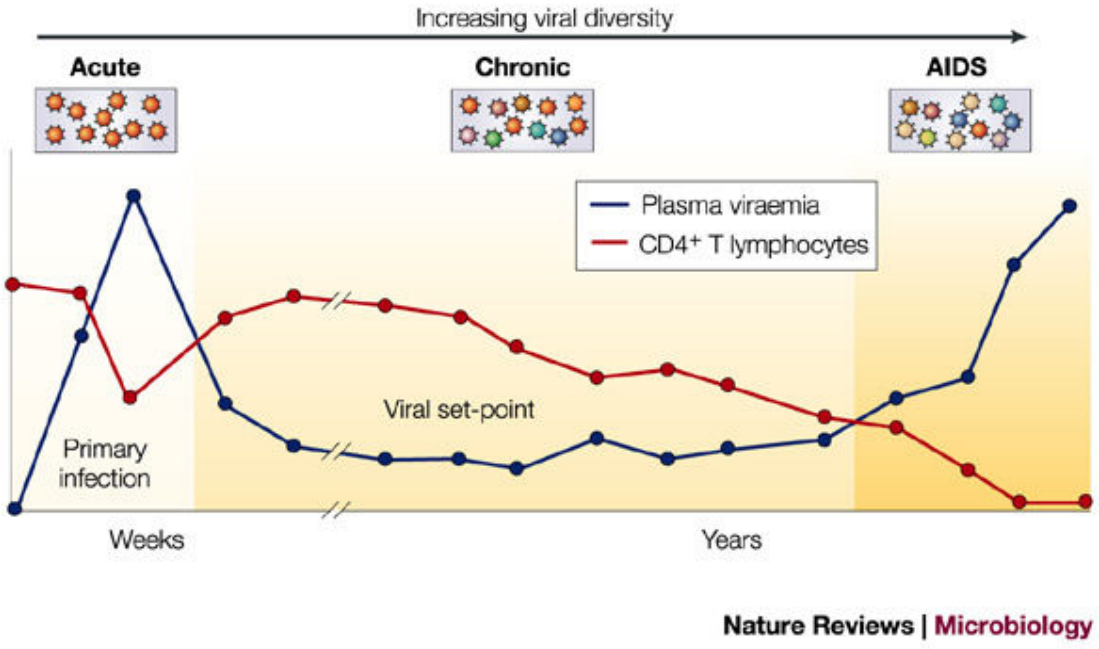
- Limit/prevent Spread
- Faster Treatment
- Correct Treatment



Reardon, Sara. "Spread of antibiotic-resistance gene does not spell bacterial apocalypse—yet." *Nature News* (2015).

The Need for Diagnostics

- Limit/prevent Spread
- Faster Treatment
- Correct Treatment
- Patient Management



Simon, Viviana, and David D. Ho. "HIV-1 dynamics in vivo: implications for therapy." *Nature Reviews Microbiology* 1.3 (2003): 181.

Case Study

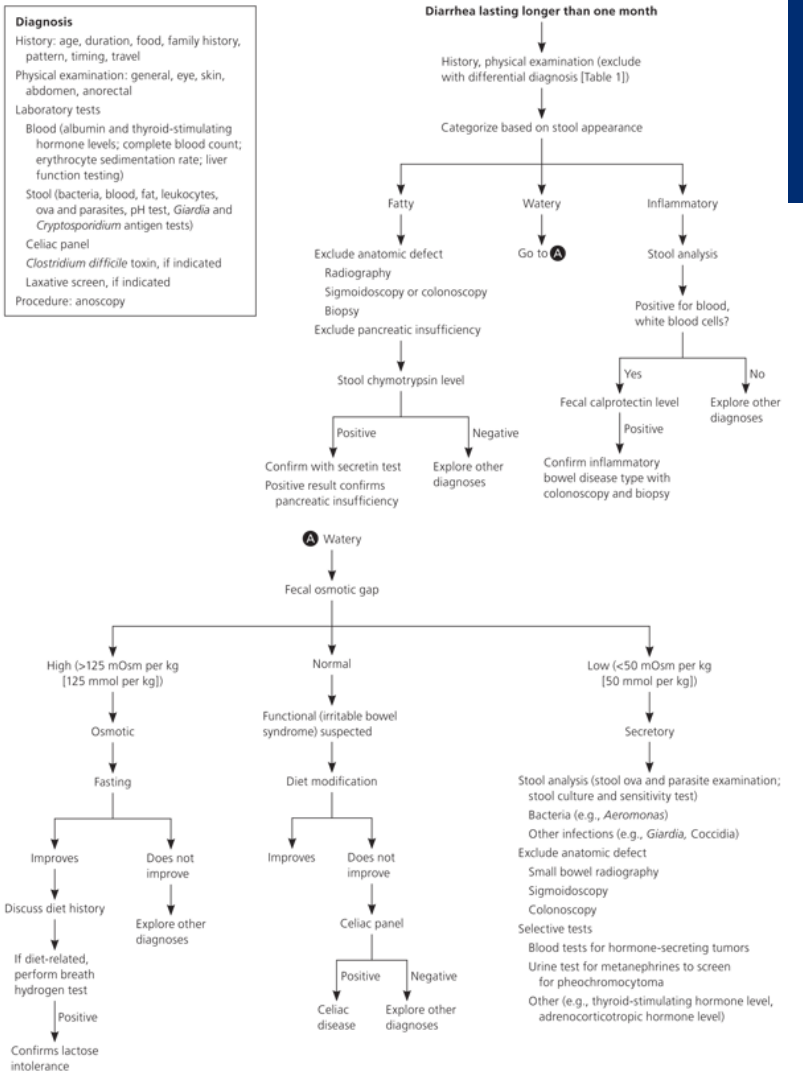
A 10 year old girl comes to the clinic after 6 days of watery diarrhea. Her parents do not know what to do and are worried because she has lost a lot of energy since getting sick.

What should you do?

First Take a History

- What is the frequency of your stools?
- How long you have been experiencing diarrhea?
- What are the consistency, color, and approximate volume of the stools?
- Is there blood or mucus in the stool?
- What other symptoms are you having: abdominal pain, nausea, fever, headache, fatigue?
- What and where have you eaten recently?
- Have you been camping? Have you traveled outside of the U.S.? Where?
- Are any of your family members, close acquaintances, or co-workers ill?
- Have you been on antibiotics lately?

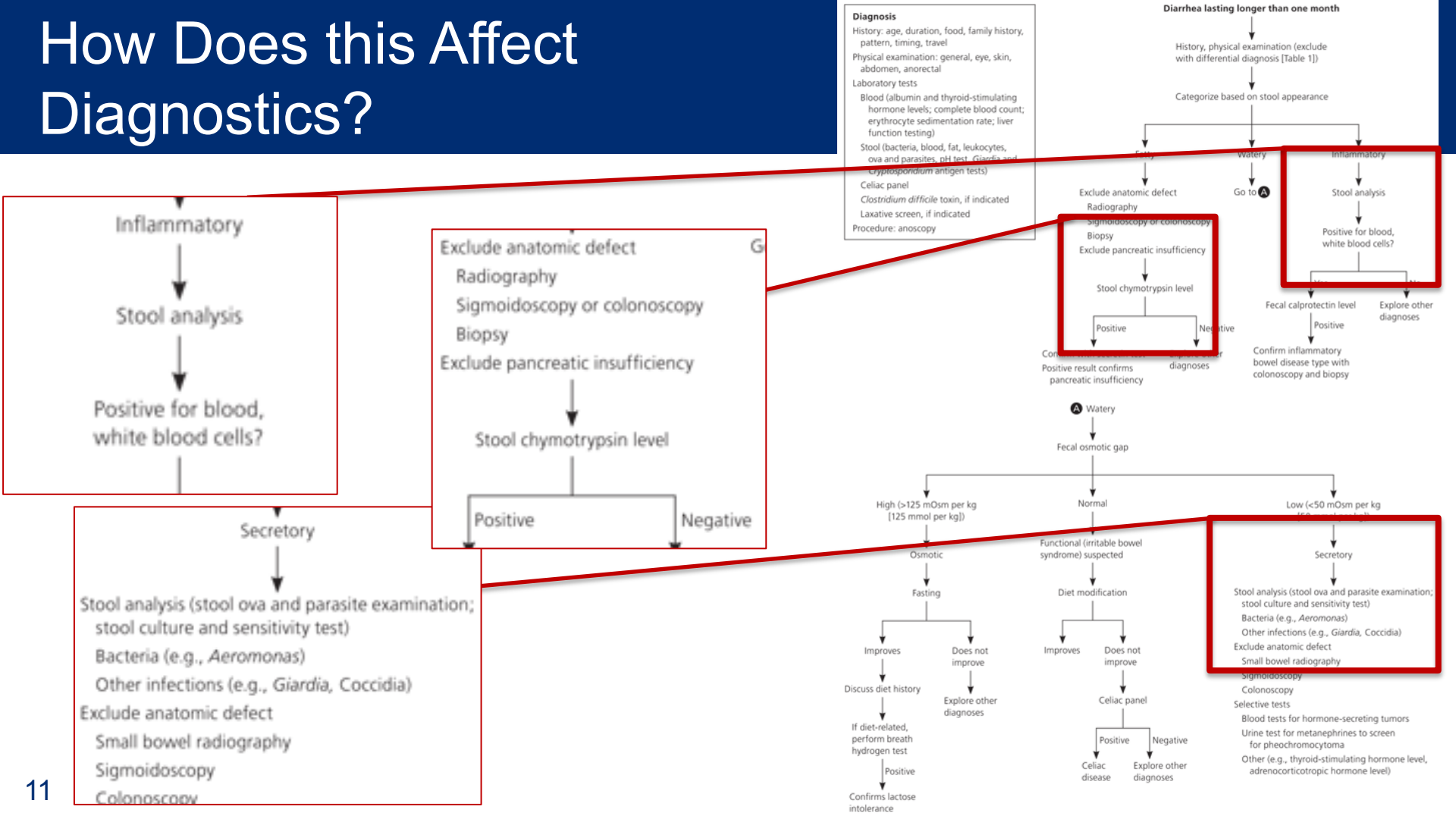
How Does this Affect Diagnostics?



Potential Diseases and Diagnostic Tests

- White blood cell count
- Microscopy
- Stool Culture
- Antigen tests – ELISA
- GI panel – PCR detects DNA/RNA
- Blood samples
- Imaging – Colonoscopy, CT scan, MRI scan

How Does this Affect Diagnostics?



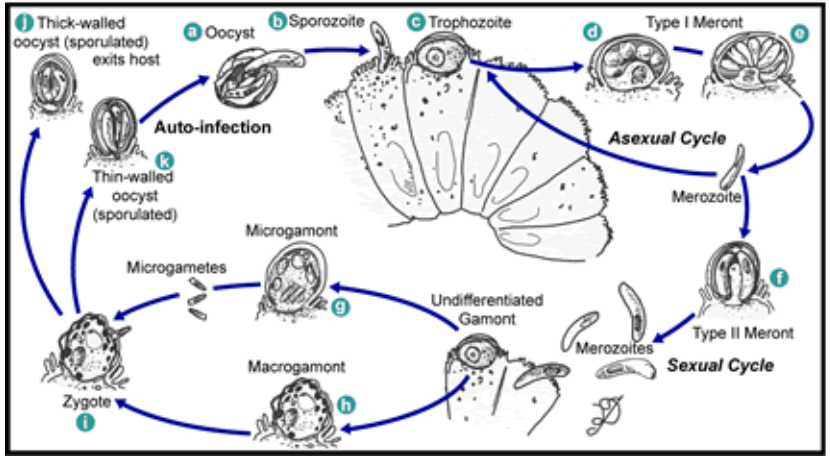
Case Study

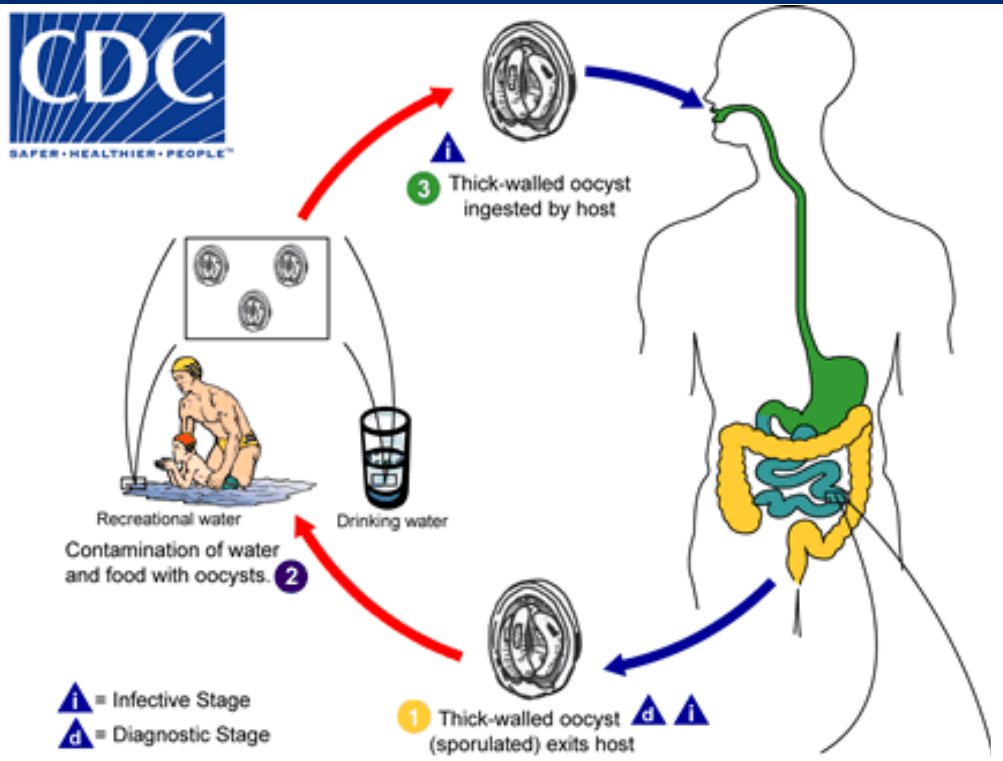
A 10 year old girl comes to the clinic after 6 days of watery diarrhea. Her parents do not know what to do and are worried because she has lost a lot of energy since getting sick.

You follow up with a quick history and learn she has been on summer break and has been swimming a lot in the local lake.

Based on this you do a microscopy test for parasites

Cryptosporidium





https://www.cdc.gov/dpdx/cryptosporidiosis/index.html

Design Criteria of Diagnostics

- What design principles of diagnostics development should be considered?

Design Criteria of Diagnostics

- Accurate
  - Specificity
  - Sensitivity
- Simple
- Affordable
- Timely
- Broadly applicable
  - Diverse population
  - Disease states
- Reproducibility
- Diagnosis impacts therapy and improves outcomes
- Funding

Sensitivity and Specificity

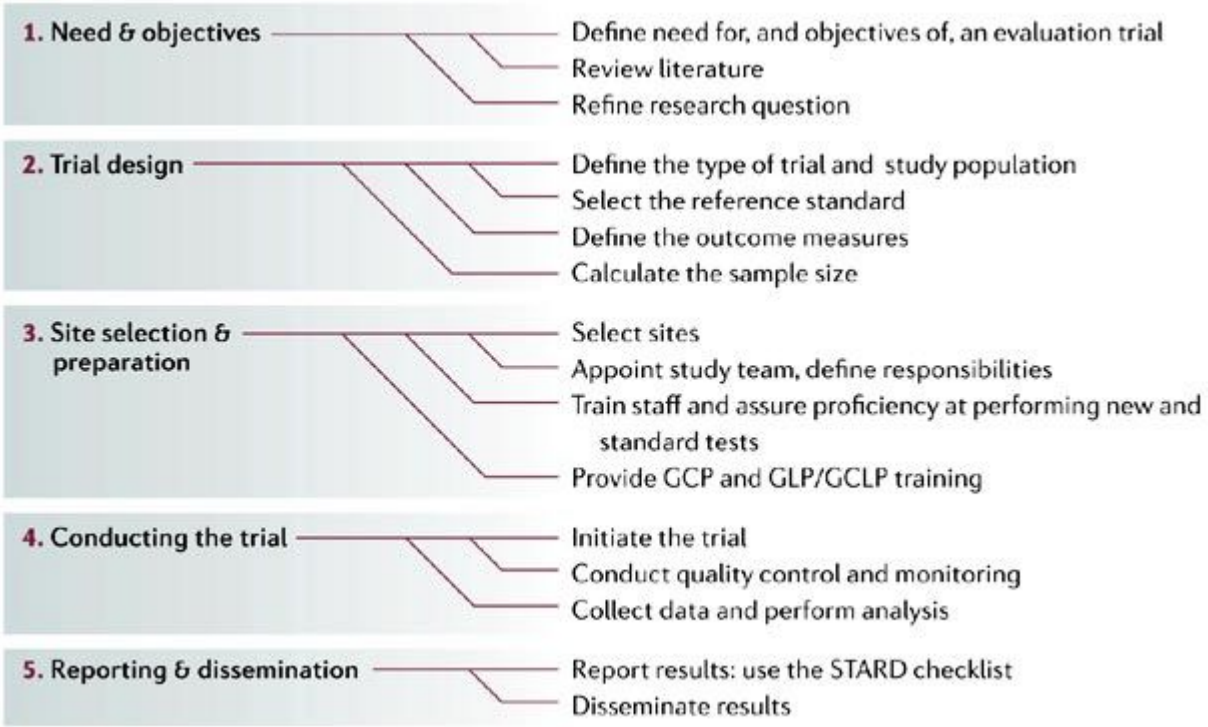
- Sensitivity: Probability that infected person will test positive
- Specificity: Probability that health person will test negative
- Need gold standard

	Disorder	No Disorder
Positive Test Result	True Positive (TP)	False Positive (FP)
Negative Test Result	False Negative (FN)	True Negative (TN)

Sensitivity = TP/(TP+FN)
Specificity = TN/(TN+FP)
PPV = TP/(TP+FP)
NPV = TN/(FN+TN)

Carvajal, Diana N., and Peter C. Rowe. "Sensitivity, specificity, predictive values, and likelihood ratios." *Pediatr Rev* 31.12 (2010): 511-513.

Diagnostic Trial Design

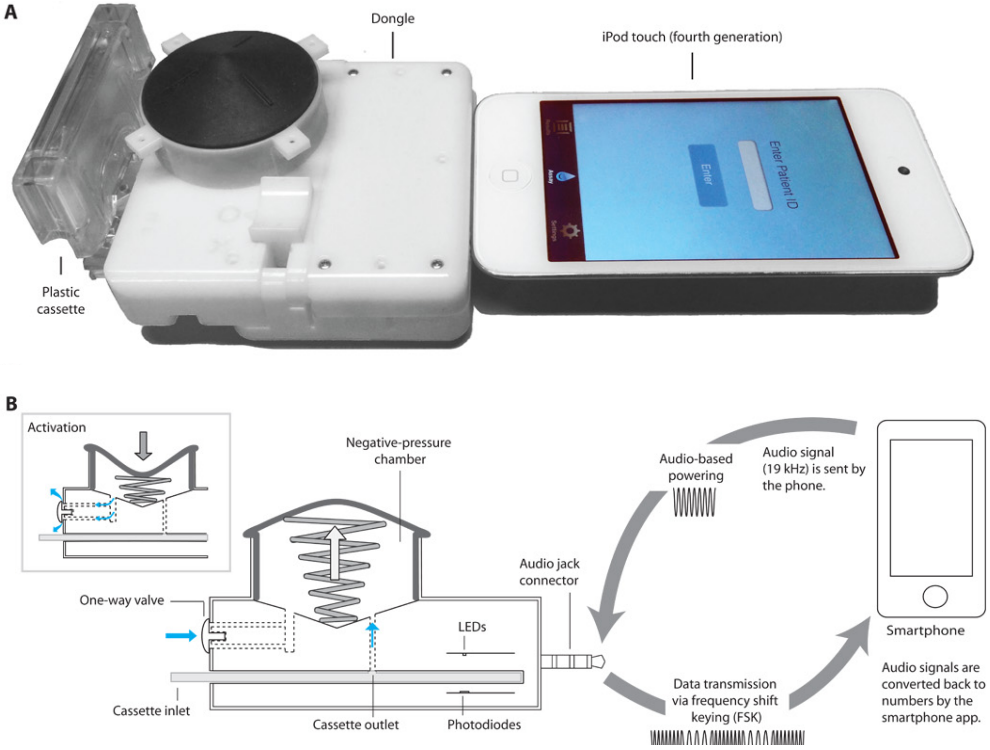


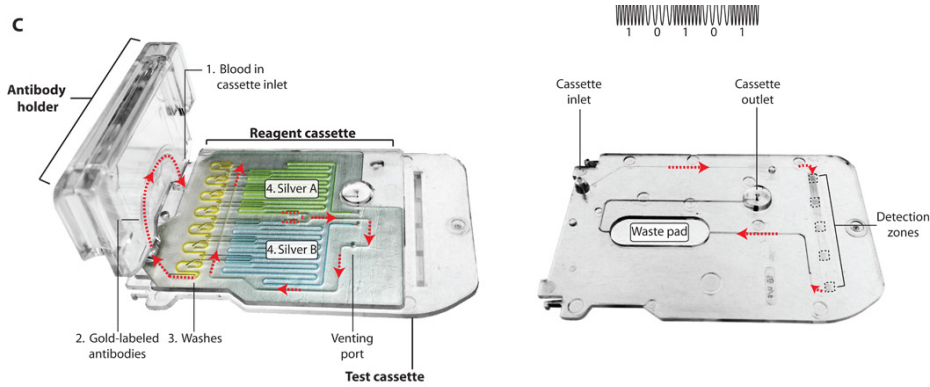
Banoo, Shabir, et al. "Evaluation of diagnostic tests for infectious diseases: general principles." *Nature Reviews Microbiology* 6 (2008): S16-S28.

Diagnostic Examples

- Point-of-care diagnostics – Identifying HIV and syphilis
- Treatment Decisions – Antibiotic susceptibility
- Disease management – HIV patients with tuberculosis

Point-of-Care Diagnostics – HIV + Syphilis





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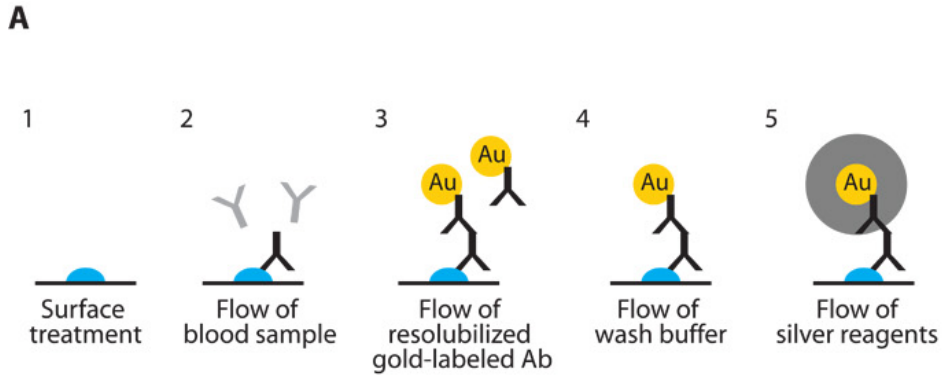
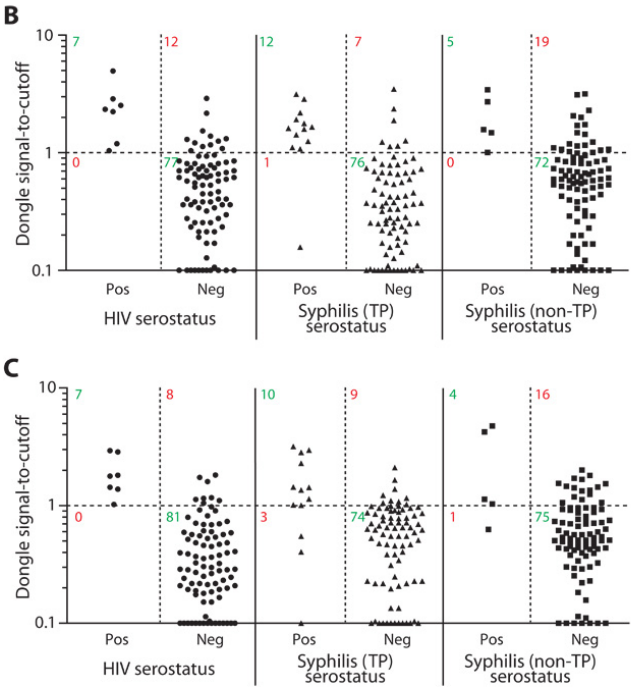
	ELISA		Smartphone dongle	
	Method	Cost (USD)	Method	Cost (USD)
Electronics	Plate reader	$8,850	Custom PCB (outsource manufacturing in China)	$31
Communication	Data acquisition cable	—	FSK via audio jack	—
Mechanical	Plate washer	$9,600	Power-free vacuum pump (injection moldable case)	$3
Total		$18,450 *+ computer*		$34 *+ smartphone*

Laksanasopin, Tassaneewan, et al. "A smartphone dongle for diagnosis of infectious diseases at the point of care." *Science translational medicine* 7.273 (2015): 273re1-273re1.

Point-of-Care Diagnostics – HIV + Syphilis





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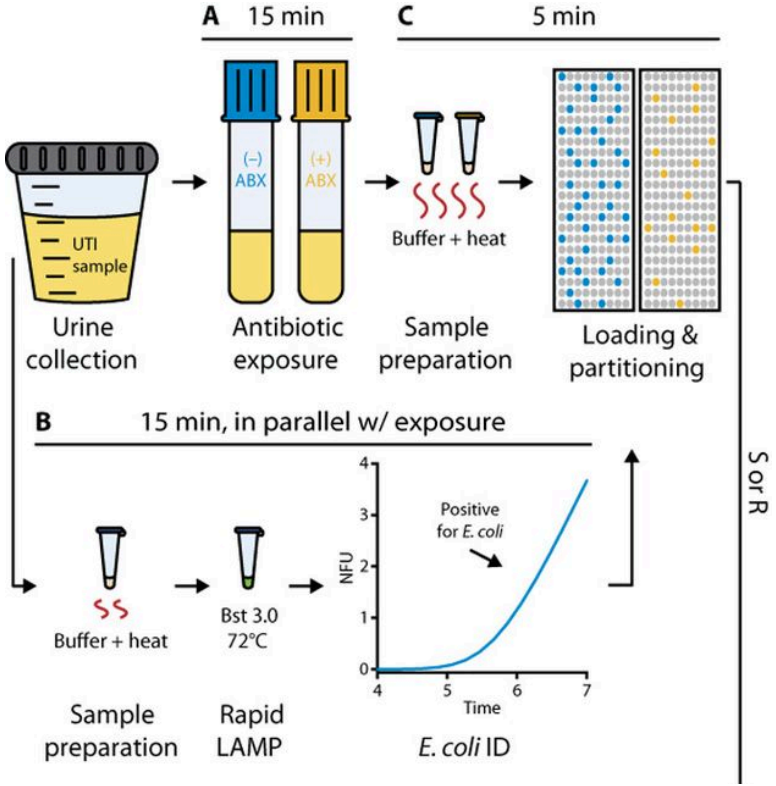
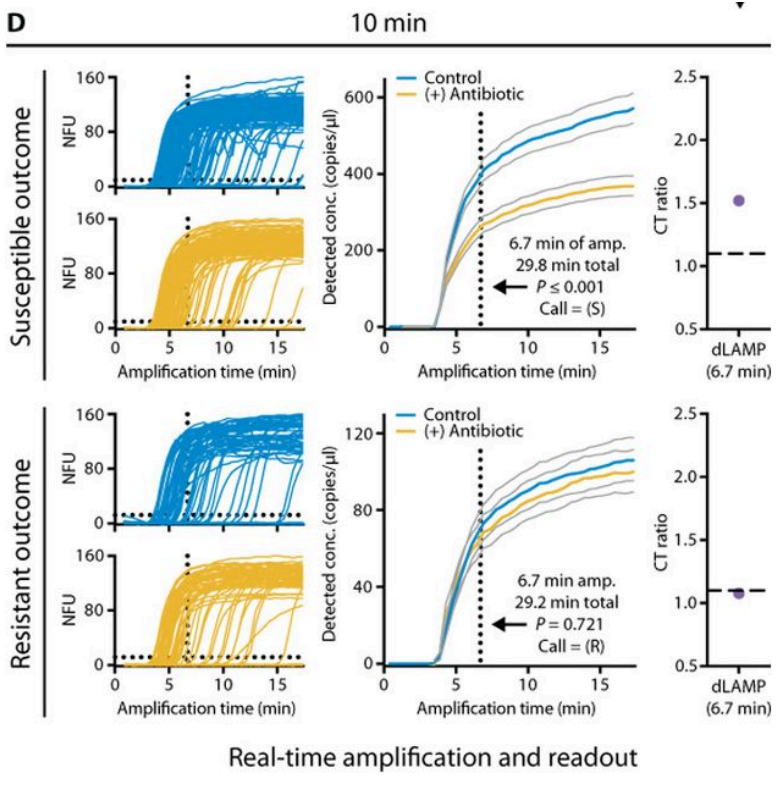
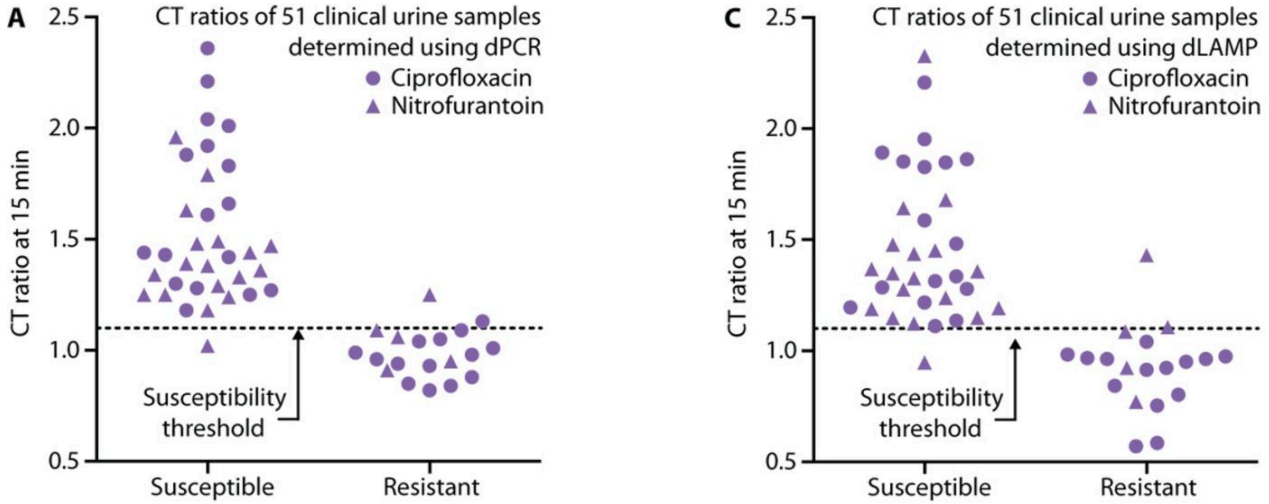
Antibiotic Susceptibility





Schoepp, Nathan G., et al. "Rapid pathogen-specific phenotypic antibiotic susceptibility testing using digital LAMP quantification in clinical samples." Science translational medicine 9.410 (2017): eaal3693.

Antibiotic Susceptibility



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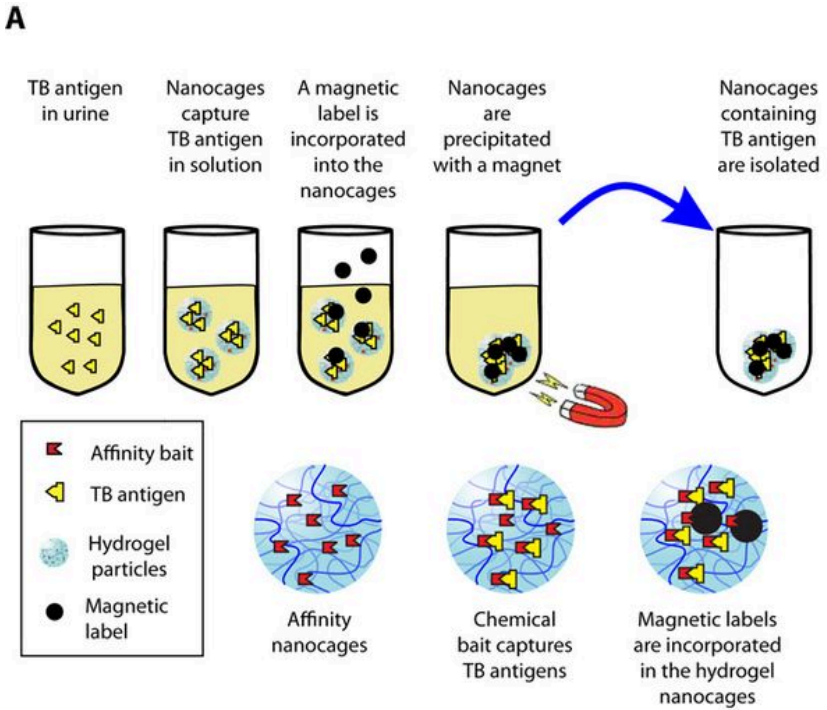
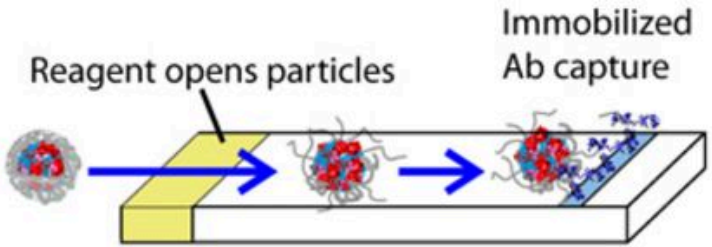
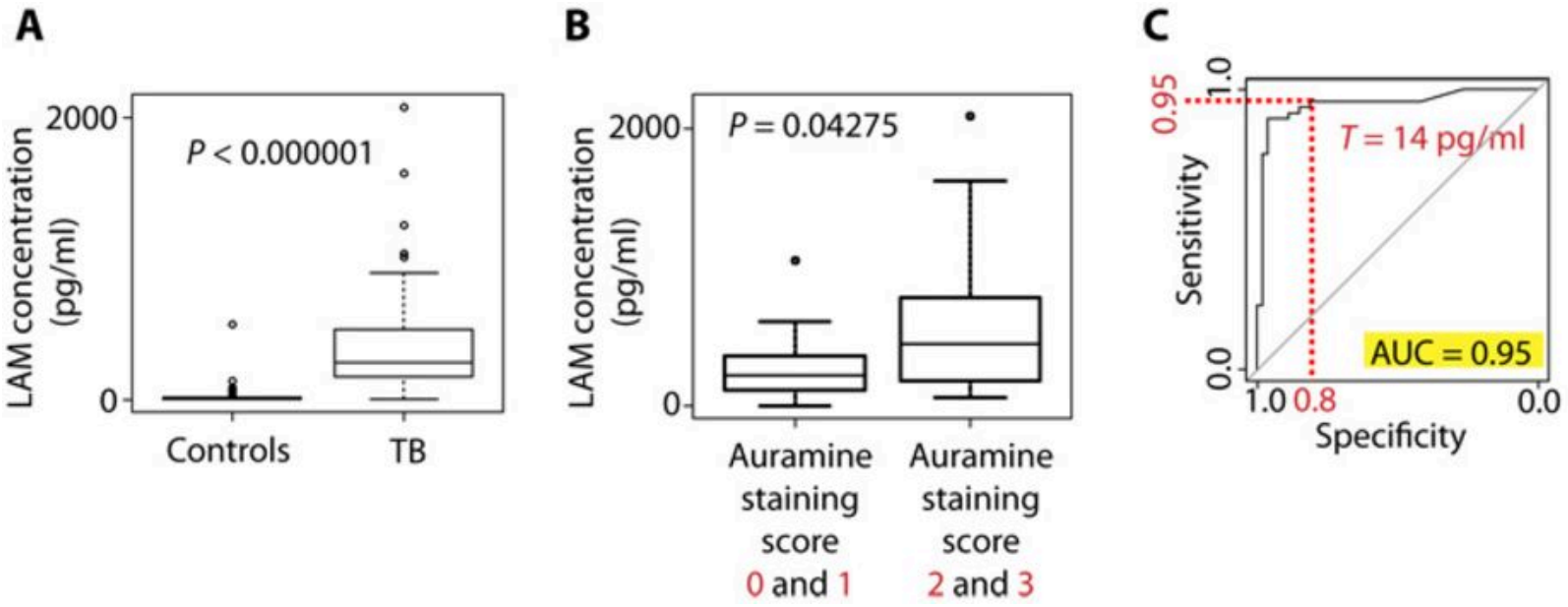
HIV- Patients with Tuberculosis





Paris, Luisa, et al. "Urine lipoarabinomannan glycan in HIV-negative patients with pulmonary tuberculosis correlates with disease severity." *Science translational medicine* 9.420 (2017): eaal2807.

HIV- Patients with Tuberculosis



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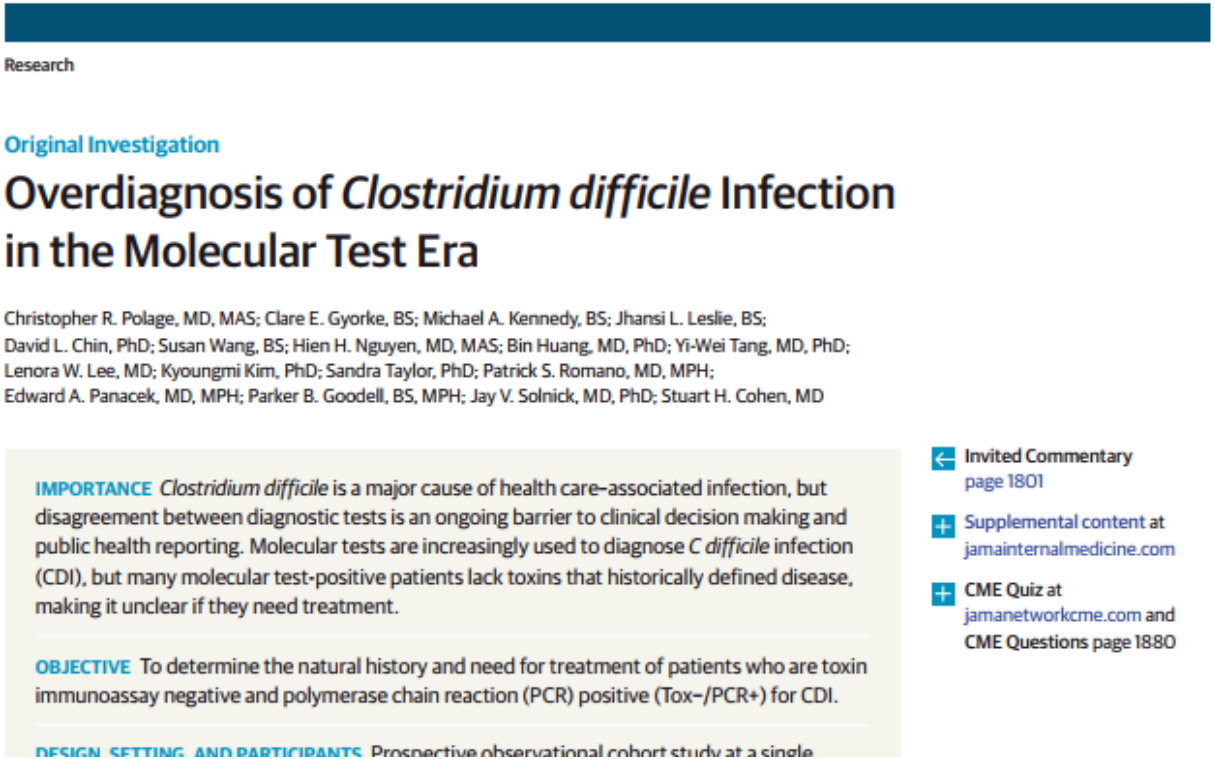
To Consider…



Research

Original Investigation

Overdiagnosis of *Clostridium difficile* Infection in the Molecular Test Era

Christopher R. Polage, MD, MAS; Clare E. Gyorke, BS; Michael A. Kennedy, BS; Jhansi L. Leslie, BS; David L. Chin, PhD; Susan Wang, BS; Hien H. Nguyen, MD, MAS; Bin Huang, MD, PhD; Yi-Wei Tang, MD, PhD; Lenora W. Lee, MD; Kyoungmi Kim, PhD; Sandra Taylor, PhD; Patrick S. Romano, MD, MPH; Edward A. Panacek, MD, MPH; Parker B. Goodell, BS, MPH; Jay V. Solnick, MD, PhD; Stuart H. Cohen, MD

IMPORTANCE *Clostridium difficile* is a major cause of health care–associated infection, but disagreement between diagnostic tests is an ongoing barrier to clinical decision making and public health reporting. Molecular tests are increasingly used to diagnose *C difficile* infection (CDI), but many molecular test-positive patients lack toxins that historically defined disease, making it unclear if they need treatment.

OBJECTIVE To determine the natural history and need for treatment of patients who are toxin immunoassay negative and polymerase chain reaction (PCR) positive (Tox−/PCR+) for CDI.

DESIGN, SETTING, AND PARTICIPANTS Prospective observational cohort study at a single

Invited Commentary page 1801

Supplemental content at jamainternalmedicine.com

CME Quiz at jamanetworkcme.com and CME Questions page 1880

Polage, Christopher R., et al. "Overdiagnosis of Clostridium difficile infection in the molecular test era." *JAMA Intern Med*175.11 (2015): 1792-1801.