The Relationship between Antimicrobial Susceptibility Testing Devices and Antibiotic Markets

COMMITTEE ON THE LONG-TERM MEDICAL AND ECONOMIC EFFECTS OF ANTIMICROBIAL RESISTANCE
NATIONAL ACADEMY OF SCIENCE, MEDICINE AND ENGINEERING

January 6, 2021

Disclosures and Disclaimer

- Kevin Krause is the V.P. Clinical Sciences and Development Operations, and a shareholder in AN2 Therapeutics, Inc.
- He is a former employee of Achaogen, Cerexa (Forest Laboratories/Actavis, Allergan, now Abbvie) and Theravance
- He played various roles in the clinical development, approval and/or launch of Zemdri® (plazomicin), Avycaz® (ceftazidime-avibactam), Teflaro® (ceftaroline fosamil), Vibativ® (telavancin), Colobreathe® (inhaled colistin) and Quinsair® (inhaled levofloxacin)
- He has accepted consulting fees from Achaogen, Inc., Cipla USA, Spero Therapeutics, Felix Biotechnology, ID Biologics, Genentech/Roche, SMAC, and F-prime Capital
- He is an advisor to and shareholder in BioAmp Diagnostics
- The views and opinions expressed in this presentation are those of the author

AST Devices are a Broad Group of Medical Diagnostics

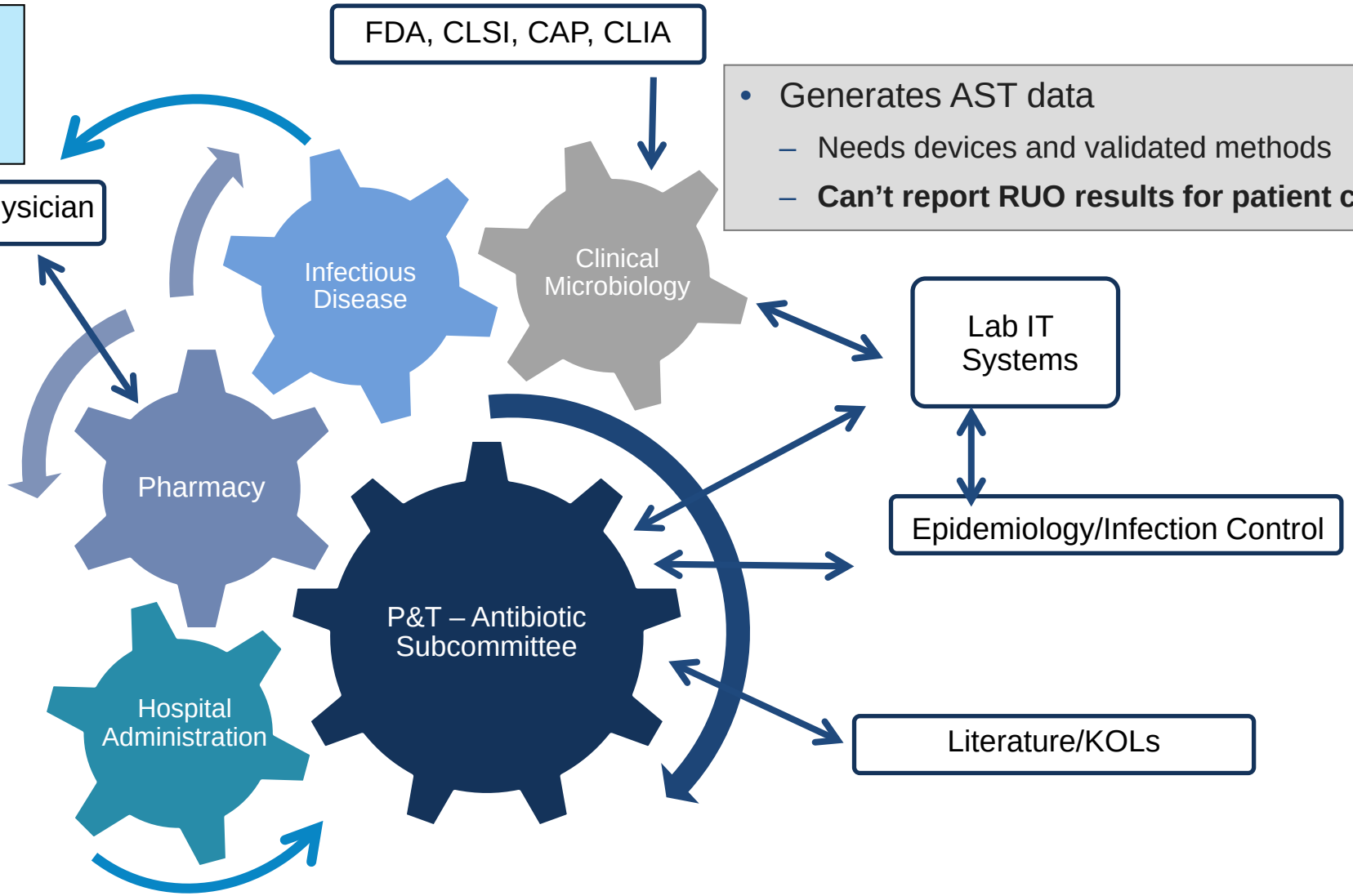
- Commercial Antimicrobial Susceptibility Testing (AST) devices include:
  - Kirby-Bauer disks and Gradient strips
  - Dry-form MIC panels
  - Automated AST systems
- Used to determine susceptibility of a patient's isolate to a given drug
- AST platforms are owned and commercialized by device companies
  - Symbiotic relationship between drug companies that need AST results for sales and AST companies that need pharma to bring new drugs to them
- These are not companion diagnostics
  - Simultaneous approval of both drug and device is not strictly required

Drug Sponsors typically do not revenue-share on AST devices but profit indirectly because drugs are rarely used if AST devices are not available

Network of Stakeholders Apply and Evaluate AST Results in Different Ways

- Uses AST to:
  - Prescribe a new drug
  - Advocate for formulary addition

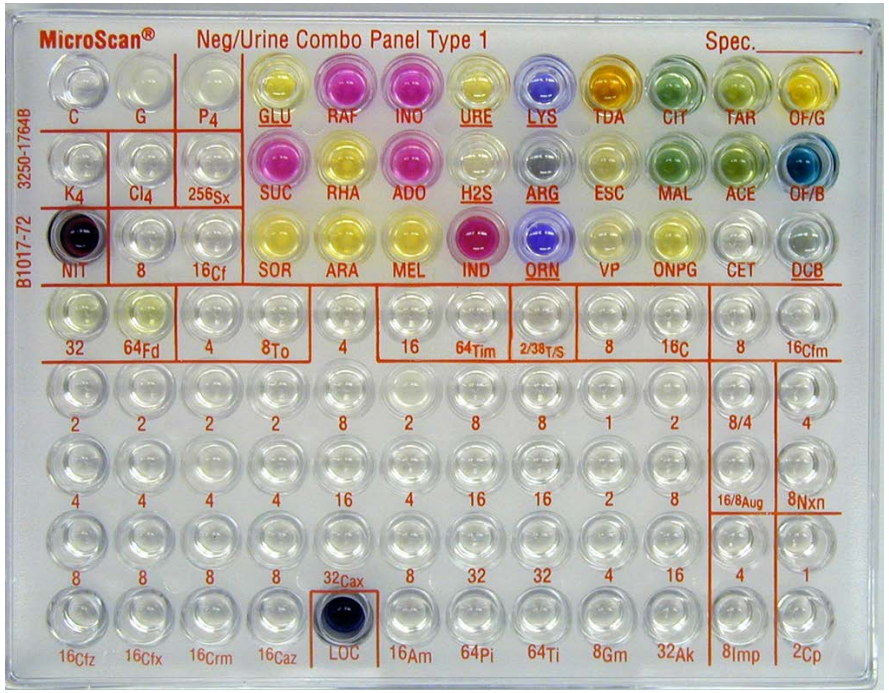
- Uses AST to:
  - Integrate a new drug into stewardship program
  - Make dose recommendations



- Generates AST data
  - Needs devices and validated methods
  - **Can't report RUO results for patient care**

AST Device Development – Financial Implications for Drug Developers

- The sponsor funds all development of AST devices (~$7M in total)
  - Little financial incentive for AST companies to add most new drugs to a panel
  - Strong customer demand to use limited space AST panels for a new drug
    - An addition of a new drug requires a removal of something else
- No-cost supply of GMP grade powder from sponsor
- Technical input during development
- Handling Med Info requests or concerns from the field



Drug Sponsors must make significant financial and technical investments in AST diagnostics during clinical development

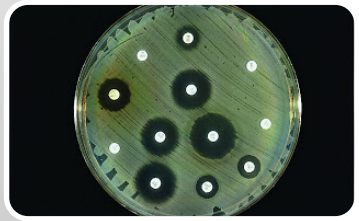
AST Device Development – Technical Input Needed from Drug Developers

AST Development Requires Significant Pharma Resources:

- Need dedicated and experienced personnel to work with various AST partners
- Match development timelines to cyclic development of AST devices
- Limited spots available for AST development for new drugs at each device company

Defined in Early Development

- Drug powder handling
- QC ranges
- Disk mass
- Target organisms
- MIC testing methods
- MIC – agar dilution correlation
- Preliminary Reference Testing Methods



Defined in Late Development

- Final Reference Testing Methods
- Tentative Breakpoints
- Timelines
- Launch plans
- Planned Markets
- MIC vs. dry-form panels

Timeline to AST Availability at Drug Launch is Challenging

- Regulatory changes have accelerated manual test clearance
  - Rapid FDA CDRH clearance of KB disks and dry-form MIC panels used in Phase 3
  - First device cleared sets performance expectations - secondary AST devices need equivalence
- Manual methods are problematic for clinical labs
  - Cumbersome, labor intensive, require extensive validation
  - Not integrated into hospital IT systems
  - Some hospitals no longer have SOPs for using these methods
- Automated devices are coming to market faster, but there is still a several year lag between drug launch and broad AST availability

The legislative proposals designed to fix the antibiotic industry need to include diagnostics or we won't have the tools to effectively use new drugs

AST Device Development – What Can Go Wrong?

- The final list of pathogens narrows at drug approval
  - Data from non-label pathogens not usable in a 510k
  - May need to test more isolates to meet min. numbers
- The breakpoint is lower than anticipated
  - May require redevelopment if incorrect MIC range was developed
- AST development stops to address challenges or breakpoint changes that effect existing panels
  - Telavancin AST development effected by emergence of VISA/VRSA
  - Ceftaroline AST development effected by problems with piperacillin-tazobactam reporting

Antimicrobial Activity

AVYCAZ has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections [*see Indications and Usage (1.1), (1.2) and (1.3)*].

Complicated Intra-abdominal Infections (cIAI)

Aerobic Bacteria

Gram-negative Bacteria

- *Citrobacter freundii* complex
- *Enterobacter cloacae*
- *Escherichia coli*
- *Klebsiella oxytoca*
- *Klebsiella pneumoniae*
- *Proteus mirabilis*
- *Pseudomonas aeruginosa*

Complicated Urinary Tract Infections (cUTI), including Pyelonephritis

Aerobic Bacteria

Gram-negative Bacteria

- *Citrobacter freundii* complex
- *Enterobacter cloacae*
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Proteus mirabilis*
- *Pseudomonas aeruginosa*

Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP)

Aerobic Bacteria

Gram-negative Bacteria

- *Enterobacter cloacae*
- *Escherichia coli*
- *Haemophilus influenzae*
- *Klebsiella pneumoniae*
- *Proteus mirabilis*
- *Pseudomonas aeruginosa*
- *Serratia marcescens*

Table 8. Susceptibility Interpretive Criteria for Ceftazidime/Avibactam

Pathogen	*Minimum Inhibitory Concentration (mg/L)*		*Disk Diffusion Zone Diameter (mm)*	
	S	*R*	*S*	*R*
Enterobacteriaceae	≤ 8/4	≥ 16/4	≥ 21	≤ 20
Pseudomonas aeruginosa	≤ 8/4	≥ 16/4	≥ 21	≤ 20

Making Changes to AST Devices is Slow and Can Hamper Development of AST for New Drugs

- Outdated breakpoints for approved drugs leads to poorly informed treatment decisions and the potential for worse clinical outcomes
- Updates for existing drugs are therefore prioritized over new drug development
- However, these changes take a lot of time and money
  - Significant lag time between breakpoint change and implementation
  - Takes too long to collect required data
  - Strains limited resources at AST companies and limits their capacity to make AST available for new drugs
- Slow implementation leads to a non-level playing field for new drugs launching with updated breakpoints
  - Plazomicin breakpoints vs. other aminoglycosides
  - Beta-lactam/beta-lactamase inhibitor breakpoints vs. those of the underlying beta-lactam

There Are Public Health Implications for Slow Implementation of New Breakpoints

- The FDA and CLSI lowered the carbapenem breakpoints for Enterobacteriaceae in 2010, but these changes took years to implement on most AST systems
- Bartsch, et al JCM (2016) modeled the impact of this delay on CRE carriage rates in the U.S.
- Results - immediate use of new breakpoints in 2010 could have decreased incidence of CRE carriage by ~8,500 patients over 5 years

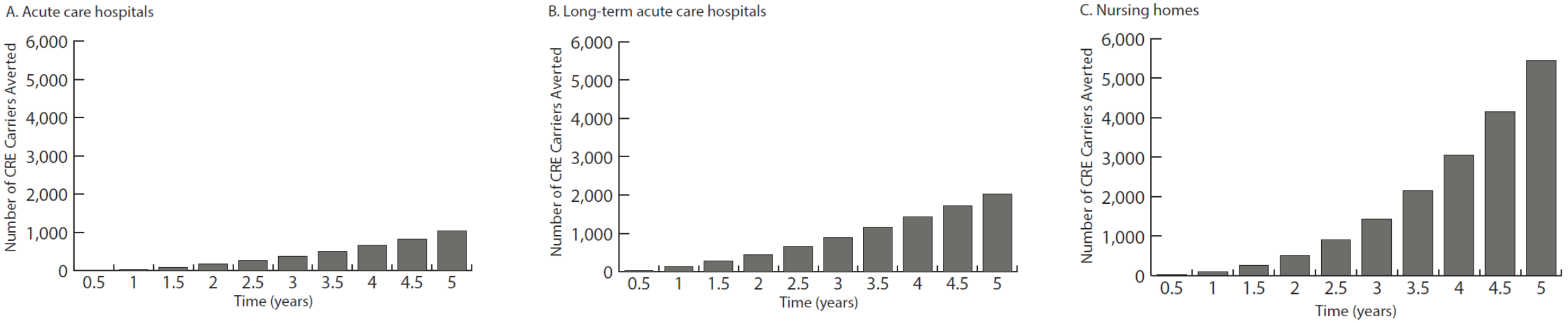


Figure 1 from Bartsch et al. Impact of Delays between the Clinical and Laboratory Standards Institute (CLSI) and the Food and Drug Administration (FDA) Revising Interpretive Criteria for Carbapenem-Resistant *Enterobacteriaceae* (CRE). J Clin Microbiol. 2016 Nov;54(11):2757-2762. Epub 2016 Aug 31

A Less Than Ideal and Expensive Fix - Fulfillment Programs

- Distribution of Research Use Only (RUO) Kirby-Bauer disks and gradient strips for distribution to requesting investigators
  - Bridges the gap until diagnostics are commercially available
  - Allows hospitals to establish baseline product characteristics with minimal expense
  - Results can not be used to direct patient care
  - Significant annual cost to the company but necessary for a successful launch
- May also supply stocks of drug powder for shipment to support pre-clinical contract labs, investigators, IIT investigators and for shipment to clinical microbiology laboratories that would like to test your drug in their own lab

May cost >$1M to implement per drug, which cuts directly into low expected launch revenue for a new antibiotic

Next-Generation and Rapid Diagnostics
Identifying Patients for Treatment Faster than AST Results?

- Can we leverage intersecting DX and RX motivations during clinical trials?
  - Faster and more accurate identification of potential patients for drug trials
  - Diagnostic companies need real world usage data
  - Example – use of a rapid diagnostic in a CABP study
    - Reduce numbers of non-evaluable patients (big problem!) while generate data that accelerates diagnostic development
- Diagnostics that identify resistance markers are not tied to an antibiotic
  - Useful in outpatient setting or where culture is becoming less common
  - Circumvent many of the challenges with traditional AST
- Considerations:
  - Price per test and reimbursement challenges
  - Space considerations in the lab for a new instrument
  - Presence of a gene vs. MICs

We Need to Bring AST Devices Along with New Antibiotics

- Simultaneous approval of drugs and automated AST devices for new antibiotics is ideal
- We need to enable Pharma, AST companies and the FDA to work together on ways to bring drugs and AST devices to market faster
- Regulatory flexibility on data requirements would expedite this process
  - Streamlining of data requirements
  - Increased flexibility in the types of isolates used for 510(k) studies
  - New avenues for AST device labeling to allow for limited used statements like with new drugs
- Congress/HHS should be encouraged to continue creating financial incentives for AST
- We have made great progress on streamlining antibiotic drug development, but we still need to fix the timelines for AST availability

<u>Call to Action</u> - Simultaneous approval of drugs and AST devices for new antibiotics is optimal for providers and patients alike