European Federation of Pharmaceutical Industries and Associations

Diagnostics: A focus on use in development of drugs for MDR pathogens

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Key ideas in advance

- New diagnostics are hard work
  - Speed & simplicity are key
  - Validation can be a challenge
- Diagnostics could change the game
  - Surprisingly, a diagnosis is not required
  - By enriching, a predictive diagnostic could have great power

Preface: Overlapping problems

- Classical culture techniques have low sensitivity
  - Community-acquired pneumonia: at best 30% culture positive
- Refining culture techniques will not fix this
  - Organisms die en route to the lab
  - Organisms may be present only briefly (esp. in the blood)
- A positive culture doesn't always have meaning
  - Some pathogens are also colonizers (*S. pneumoniae*)
- Thus, diagnostics are part of an overall approach
  - Culture-positive patients are preferred, but
  - Bayesian prior needs to be high: Right syndrome, right setting
  - Culture-negative patients are part of the way a drug is used

Diagnostic Disambiguation

“We need a diagnostic” can have several meanings

- Definitive diagnostic: Makes a diagnosis
  - A positive blood culture is usually taken as definitive
- Predictive diagnostic: Predicts result of another test
  - Organisms on Gram-stain → growth in culture is more likely
- A diagnostic strategy: Systematic use of tests
  - Serial antigen testing and chest CT when at risk for aspergillosis

Speed also matters

To influence initial decisions, must match disease

- (Chronic) HCV infection: OK if test takes days
- Pneumonia: Result needed in at most a few hours

This has a big impact in clinical trial work

- Must minimize use of prior effective antibiotics
- Care algorithms may set timelines that effectively mandate initial empirical therapy
- Global development programs require tools that can be implemented in many different care settings

Speed and certainty may diverge

- Speed is gained by moving to molecular detection
  - Positive PCR for *S. pneumoniae* DNA in blood
  - PCR could be fast and surely has predictive diagnostic value
- But, not routinely accepted alone as definitive. **Why?**
  - When we grow bacteria from the blood, we know that the host defenses are overwhelmed
  - If no organism from the blood, might the patient be biologically different from those with a positive culture?
  - Perhaps the DNA is from dead bacteria!

Putting it together

When one says “We need a diagnostic,” do you mean

- A really rapid *predictive* diagnostic
  - A (near) bed-side tests that predicts high-risk of subsequent growth of *P. aeruginosa*?
  - That’s probably possible and would be useful both in clinical trial work and in routine care
- A really rapid *definitive* diagnostic?
  - We have this for a only few things (e.g., influenza)
- A slow *definitive* diagnostic?
  - We already have that: Culture!

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Key idea

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The power of rapid prediction

- We always want to maximize culture-based proof
  - If only 30%[1] are positive…
  - Then 70% (~3/4th!) lack microbiologic results
- If a test moves us from 30 to 50% evaluable...
  - Test need not make a diagnosis, it only needs to increase likelihood of a positive definitive test result
  - Test might rule in or rule out – doesn't matter
- **Study size goes down 40%:** we save cost & time[2]

1. 30% is typical for community-acquired bacterial pneumonia.
2. Another example: If we can take the typical 50% culture-proven rate of hospital-associated bacterial pneumonia studies to 75%, the study size shrinks by a third.

Rapid prediction has value both for clinical trials and in routine care

- Benefit in clinical trials is evident: more efficient trials
  - Might even help with problem of needing to enroll before effective empiric therapy is given
- There is also a long-term value: The same diagnostic that supported the trial could has routine care value
  - Who would most benefit from this new (expensive) therapy?
  - The same efficiency gain applies as for the trials
  - Even more subtle: A diagnostic that guides drug selection based on likely resistance mechanism would be very interesting

Diagnostics and drugs are (and face) separate problems

- Problem of the diagnostic device manufacturer
  - Our regulatory pathways hand reimbursement patterns are geared towards definitive diagnostics
  - The topic merits further discussion
- Problem of the drug developer
  - Efficient trials are sought, but use of a predictive tool should not lead to a drug-device linkage in the marketing authorization
  - The predictive diagnostic is one of many ways to select patients at high-risk for the relevant organism

What is happening in this area?

- This is very hard work, but there is a lot of activity
  - Intersection of physical and biological science: microfluidics, novel surface chemistries, and more
- EU is active via IMI[1] and FP7[2]. Examples:
  - E.g. Rapp-ID,[1] (www.rapp-id.eu)
  - TheraEDGE,[2] https://www.theraedge.org/
  - These programs seek point-of-care (POCT) diagnostic tools
- In the United States…
  - NIAID and DARPA have active programs
  - IDSA has called for further US investment

1. IMI = Innovative Medicines Initiative, a joint initiative of EFPIA (European Federation of Pharmaceutical Industries and Associations) and the EU Commission;
2. FP7 = Framework Program 7, an EU Commission funding program

My wish list for the perfect test

- Specimen (whole blood, urine, sputum, CSF)
  - No specimen processing! Take it as it is.
- Applied to a dipstick-like device
  - I'm willing to apply a drop or two of fluid
  - Room temperature stable, no batteries
- Color change or line appearance in 2 minutes
- Immediate uses of this test to detect / predict
  - *P. aeruginosa* or metallo-beta-lactamases
  - Bacterial pneumonia (hospital or community)
- **Does not have to be definitive**

In closing

- Diagnostics could have dramatic effects
  - Stewardship: Guiding use in practice
  - The difficult economics of antibiotics: In part as a result, the global pipeline is frighteningly thin
  - Efficient development: Selecting and validating patients for clinical trials
- A perfect diagnostic is not required
  - Speed is as valuable as a specific diagnosis
- To make this real, many hands are needed