Biorepositories for the Development of In Vitro Diagnostics in Microbiology: A Longer-term Perspective

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Summary (BLUF)

- Prospective clinical trials are ideal but not be most efficient (or possible) for clinical validation.
- Retrospectively archived open biorepositories may aid in 'expeditious' clinical validation.
- This is an area where FDA has actively engaged.
- Partnering with other interested groups (e.g., IDSA) may be valuable.
- This is not unique (nor intuitive) for Infectious Diseases but ID is somewhat unique for the need (in certain cases) to monitor effectiveness on an ongoing basis

IDSA PUBLIC POLICY SUPPLEMENT ARTICLE

Combating Antimicrobial Resistance: Policy Recommendations to Save Lives

Infectious Diseases Society of America (IDSA)*

Table 1. Summary of Legislative Recommendations for Congress

- VII.3 A clinical specimen repository should be established by the National Institute of Allergy and Infectious Diseases and FDA to support R&D of novel molecular diagnostic tests as part of the GAIN Act or other legislation.

Clinical Infectious Diseases, 2011:52 (Supplement 5)

Ongoing Examples: Tuberculosis

FDA NEWS RELEASE
For Immediate Release: Oct. 4, 2010

FDA awards nearly $3 million for TB research
Awards support critical public health need for TB drug development

The U.S. Food and Drug Administration today announced the award of $2.9 million to support six research projects that will help with the diagnosis, treatment, and prevention of tuberculosis (TB).

TB remains a major public health challenge with an increasing prevalence worldwide. Two recent articles published by FDA's Office of Critical Path Programs note that advances are urgently needed in TB drug development to shorten therapy and to treat drug-resistant disease.

"FDA recognized an urgent need for the engagement and leadership of public health institutions to promote this critical, but neglected, area of medical therapeutics," said FDA Commissioner Margaret A. Hamburg, M.D.

Funded with congressional support in FY2010, the following six grantees were chosen from among 30 applications:

Ann Ginsberg, M.D., Ph.D., Global Alliance for TB Drug Development – Frozen trials, developing a repository of clinical trial specimens

Ongoing Examples: Aspergillosis

"The Clinical Laboratory Diagnostics for Invasive Aspergillosis contract was created to support the establishment and maintenance of a tissue repository of prospectively collected clinical samples from patients at high risk for invasive aspergillosis (IA) and from subjects at high risk for IA with potentially interfering medical conditions. Other prominent goals include the performance of comparison studies between Food and Drug Administration (FDA)-cleared tests for IA and experimental IA diagnostic tests.

……. The tissue repository will be located at the University of Florida and should be a valuable resource comprising well characterized, sequential samples spanning from pre-symptomatic through to proven disease."

http://www.astecdiagnostics.org

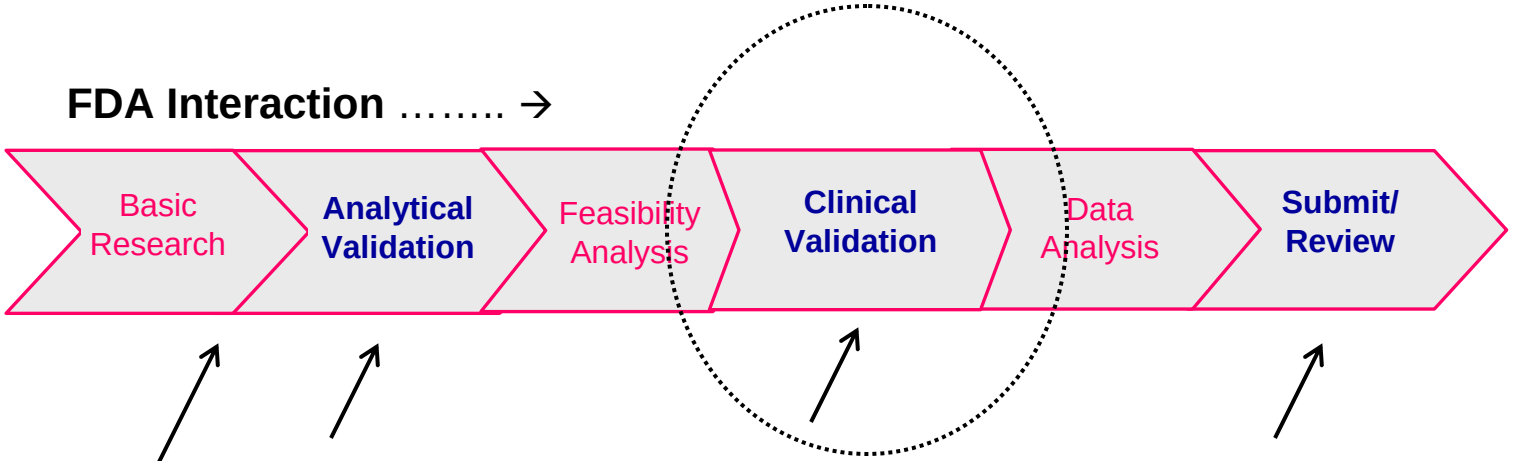
“It is hoped that the development of new diagnostic tests for IA will be facilitated through this contract to advance the field of contemporary clinical laboratory diagnostics for IA and improve the standard of care for patients at high risk of developing IA. …... The investigators will then perform studies to compare the IA diagnostic test that has been replicated with an FDA-cleared IA diagnostic test.”

http://www.astecdiagnostics.org

Obvious Examples

- Resistant pathogens
- Differential diagnosis for diseases with multiple etiologies, e.g., pneumonia, UTI, bacteremia, gastroeneteritis, etc….

The (Annotated) Prototype Development Pathway….



Clinical Validation of New Diagnostic Assays – Current Status

- Prospective studies
  - Clinical sites
- Purchase archived specimens from vendor/other source
  - Commercial vendor
  - Pharmaceutical company trial
  - Clinical investigator
- CDC/‘Public Health’ source
- Company specimen bank

Why Is The Need for Repositories Self-Evident…..

- Prospective clinical trials are difficult to begin with….
- A prospective clinical trial for a low-incidence disease is particularly difficult….
- A prospective clinical trial for a low-incidence disease when the incentives are low could be a perfect storm….

One (Potential) Way Out of This Box…..

- Prospectively Archived Repositories:
  - Prospectively collected archived specimens as an essential component of clinical validation for new diagnostics
  - Specimens are entered into repository by predefined protocols
  - Repositories ‘available’ to assay developers

Prospectively Archived Repositories

- Neither a traditional “bank” or “repository,” ‘perhaps’ serving needs of both
- Limited to specimens obtained according to rigorous study protocols that may be across clinical studies
- Each specimen linked to protocol specified clinical data collected with established (e.g., CDISC) data standards
- The number and nature of specimens in each “collection” can be ‘estimated’ based on likely utility
- Could be integrated with clinical care, ‘case control’ studies via statistical matching….
- **‘Ongoing’ collection**

What Specimens Could be Added

- Any (defined by the protocol/clinical needs)
  - 'genotypic' isolates
  - 'phenotypic' isolates
  - 'rare' isolates
- Different matrices
  - Some matrices more difficult than others (e.g., sputum)
  - Some may be difficult to aliquot

Potential Repository Uses

- 'Traditional use': 'classic' specimen bank for diverse samples
  - May be particularly useful for multiplex assays
- 'Training' sets: less 'controlled' samples for preliminary test development/evaluation.
- '**Validation sets**': rigorously collected sample sets for clinical validation, e.g., sequential specimens collected from a pre-defined protocol study (such as a clinical drug study or diagnostic protocol)
- 'Unique studies': protocols defined across repository collections, sampling for a new diagnostic test for assessing durable cure/relapse

Is This Possible – Yes!

- Aspergillus Technology Consortium (AsTeC)
- Tuberculosis
  - Global Alliance for Tuberculosis (ReMox Trial/others)
  - Clinical Diagnostics Research Consortium (CDRC)
- 'Influenza'
- Others (? Companion diagnostics)

Caveats

- Added complexity, i.e., specimens captured as part of another study, e.g., a drug trial
- Specimens ‘unaffected’ by storage
- Limited sample volume, especially if aliquoted
- Concomitant standardized clinical data captured
- Statistical input regarding repository design, sampling, data collection: work to be done
- **Not the whole nine yards, other regulatory requirements remain**
  - **Some prospective samples will be necessary, including specificity**
  - **fresh/frozen bridging study (essential to show equivalence for all specimen types)**

Advantages

- 'Well characterized' reference samples
  - Particularly valuable for multiplex instruments
- Reduction in clinical validation time
- Rigorous, scientifically valid results
- 'Potential' for direct comparison between assays
- Permit studies of targeted populations by separate 'sampling' protocols from within the repository

Thank-you