Diagnostics for pediatric TB and harmonization of research on pediatric biomarkers

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Overview

• Background
• Prioritizing research questions
• Designing the Repository: Pediatric TB Diagnostics biobank consortium
• Sample/ Specimen Collection
• Data Harmonization
• Funding & Sustainability
• Regulatory Challenges
• Operations and Implementation
Challenges in Diagnosing Pediatric TB

- **Clinical**
  - Low sputum production
  - More difficult to diagnose in young, malnourished, and HIV infected children
  - Young age likely have a significant disease burden
  - Acute severe pneumonia
  - MDR TB
  - Extra-pulmonary disease is more common in children

- **Microbiologic**
  - Pauci-bacillary disease
  - Low sensitivity and low specificity of existing tests
  - Unable to distinguish LTBI vs. TB disease
  - Lack of POC tests
  - Poor timeliness of results

Graham 2014, Cuevas 2014
Epidemiologic Challenges

Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates

Helen E Jenkins, Arielle W Tolan, Courtney M Yuen, Jonathan B Par, Salman Keehney, Carlos M Perez-Velez, Marcello Pagano, Marcolos C Bacino, "Tud Cahn"

- 32,000 children with MDR TB in 2010
- Nearly 1 million children with TB disease in 2010
- Risk of MDR TB same in children as in adults reflecting transmission of MDR TB strains
- Many cases of MDR TB and TB are not reported in children

Jenkin 2014, Dodd 2014
Optimal Pediatric TB Diagnostics

• Optimal POC test would be:
  – Affordable
  – Patient-friendly and user-friendly
  – Accurate in people with any form of TB
  – Result in treatment decisions in one visit

• A rapid biomarker-based instrument-free test for non-sputum samples
• A rapid sputum-based molecular test for microscopy centers
Assessment of the novel T-cell activation marker—tuberculosis assay for diagnosis of active tuberculosis in children: a prospective proof-of-concept study

- TAM TB: T cell activation marker TB
- Measures CD27 phenotype of CD4 T cells producing IFN gamma in response to TB antigens
- Sputum independent blood test providing results within 1 day of blood collection
- Conducted at 2 sites in Tanzania
- Results: 15/18 culture confirmed TB cases were detected
- Sensitivity 83.3% (95% CI 58.6-96.4%)
- Specificity 96.8% (95% CI 89.9-99.6%)

- TB disease distinguished from other diseases and from LTBI by genome wide analysis of host RNA expression in blood
- Conducted at sites in Malawi, South Africa (discovery cohort), and Kenya (validation cohort)
- 51 transcript signature distinguished TB vs. other disease; 42 transcript signature distinguished TB disease vs. LTBI
- Signatures translated into a single risk score for use in resource poor settings
- Results: Risk score (based on RNA signature) identified culture confirmed TB vs. other disease
  - Sensitivity 82.9% (95% CI 68.6-94.3%)
  - Specificity 83.6% (95% CI 74.6-92.7%)

Portevin 2014, Anderson 2014
Attendees (50+)
• University/ Academia
• Non-profit
• US Government
• PIs with ongoing TB repositories
• Chaired by Mark Nicol and Gerhard Walzl

Goals:
• Facilitate diagnosing TB in children through promoting biomarker research
• Define key scientific and operational research gaps and needs
• Promote collaboration among stakeholders and interested organizations
• Pursue harmonized research and development of pediatric TB diagnostic biomarkers
• Coordinate and streamline the long and challenging process to validated and qualified diagnostic biomarkers
Defining priority Pediatric TB biomarker research question(s)

• Identify a new biomarker(s) for diagnosis of TB disease in children who are symptomatic
  – Biomarker for treatment response secondary

• Prioritized study population:
  – Children between 0-5 yrs
    » Group in which there is greatest difficulty in confirming Dx
    » Large burden of TB disease
    » Most severe disease, highest mortality
  – Secondary priority to include children aged 0 - 15yrs
  – Include HIV-infected children
  – Include symptomatic disease for pulmonary and extrapulmonary TB

• Prioritize prospective cohort design that includes adequate follow up
Designing the Repository

• Three options, none mutually exclusive:
  – Development of a de novo, collaborative, federally-funded, globally accessible, centralized biorepository
  – Expansion of existing adult TB repositories, already with vetted approaches, to include pediatric populations
  – Establish a biorepository consortium/network - A Pediatric TB Shared Biorepository Resource

• Continue raise awareness/educate major funding agencies on the importance of establishing pediatric TB repositories
Pediatric TB Diagnostic Biomarker Consortium

• Maximize leverage of existing cohorts and biorepositories
  – Pool existing repositories globally
• Establish governance framework
  – Define missions, goals, and development pipeline
  – Oversight and maintenance of the agreed upon principles of ownership, collection, storage, distribution and use of samples.
• Encourage sharing of information and SOPs across investigators
  – Objective to maximize harmonization prior to implementation of studies
  – Minor differences in SOPs should be acceptable
• Develop roadmap
• Include external consultants to advise/guide on the repository formation.
• Regular ongoing meetings
Sample/ Specimen Collection

• Lab working group to create harmonization of methodology across research units and sites

• Develop standardized SOPs
  – Prioritization of specimen types
    • Blood is a priority specimen but need adherence to stringent blood volume collection guidelines for pediatric research
    • Respiratory specimens: remain important due to ongoing biomarker research activities on sputum samples among adults

• Ideal specimen volume, number of aliquots, volume of aliquots
  – Insufficient sample volume is the norm with difficulties in aliquoting; needs to look at having multiple repositories.
Data Harmonization

• Need for a data sharing framework (database interoperability)
• Revisit standard definitions in Pediatric TB
• Reach consensus on required metadata
• Reach consensus on characterization of cohort (mycobacterial evaluation, # of cultures)
• Obtain endorsements (WHO, etc., if possible).
Funding and Sustainability

• Limited interest by major funding agencies due to challenges
  • Substantial investments to build cohort and infrastructure
  • Pediatric funding requirements can be up to 10 times higher compared to adult studies
  • No dedicated funding source for banking so research groups bearing funding
  • Sustainability of repositories questioned leading to even less funding interest

• Involve industry partners early & continue to target major funding agencies

• Consider mandating banking in expensive cohort studies
  • Stipulate/ include certain funding level for biobanking in RFAs

• Consider training/education (e.g. IRBs etc.)

• Establish cost recovery mechanisms
  • Consider different levels based on funding needs, available funds, scientific promise of proposed studies
Regulatory issues and custodianship

• Catalog general principles around biobanking and shipping abroad
  – Develop based on international PI experiences at existing pediatric research sites
• Access: develop clear, flexible, transparent, amenable “Guidelines for Access” for specimens and participant clinical data sharing
• Establish responsibility to curate/maintain these repositories (the individual investigators and specified repositories within networks)
• Specific regulations may vary by country/by sample/by target patient population
  – Consider IP issues and future use consent early
  – Exporting samples may be easier with element of capacity building
• Maintenance of participant confidentiality and de-identification
Operations and Implementation

- Link to mandated tiered pricing of any tools developed such that they are affordable in low and middle income countries
- Include cost recovery mechanisms for the biobank
- Consider implementation of the proposed diagnostic test
- Location of the patient and the diagnostic platform
- Time required for...
  - Sample to reach the lab
  - Results to reach the patient
  - Clinician to meet the child
- Perception of the test
- Anticipating bottlenecks and planning to avoid these