Biomarkers for Pediatric TB and Update on Standardized SOPs for Pediatric Sample Collection

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Pediatric TB Diagnosis

- Diagnosis of TB challenging
 - Symptoms non-specific
- Microbiological diagnosis uncommon
 - Difficult to obtain sputum specimens
 - Children with paucibacillary disease
 - Low culture yield: 2-30%
 - In low-resource settings: limited access to hospitals, specimen collection rarely attempted
- Diagnostic accuracy using clinical criteria poor
- Strong interest in discovery and validation of biomarkers for pediatric TB diagnosis

Pediatric TB Diagnosis



Cuevas CID 2012

Pediatric TB Diagnosis with Xpert MTB/RIF



Pooled sensitivity of induced sputum, expectorated sputum and gastric aspirate against TB culture:

– 66% (single Xpert MTB/RIF)

Cuevas CID 2012; WHO 2013

The "Ideal" Pediatric TB Biomarker

A Blueprint to Address Research Gaps in the Development of Biomarkers for Pediatric Tuberculosis

Mark Patrick Nicol,^{1,a} Devasena Gnanashanmugam,^{2,a} Renee Browning,² Eleanor S. Click,³ Luis E. Cuevas,⁴ Anne Detjen,⁵ Steve M. Graham,^{5,6,7} Michael Levin,⁸ Mamodikoe Makhene,² Payam Nahid,⁹ Carlos M. Perez-Velez,¹⁰ Klaus Reither,¹¹ Rinn Song,^{12,13} Hans M. L. Spiegel,¹⁴ Carol Worrell,² Heather J. Zar,¹⁵ and Gerhard Walzl¹⁶

- Based on easily obtainable specimen (urine, blood, exhaled air, saliva, stool), not respiratory specimens
- Can distinguish between latent TB (also with non-TB associated symptoms) and active disease

Diagnose both pulmonary and extrapulmonary TB

 Meet TPP sensitivity and specificity targets for diagnostic or triage test

Independent of age, nutritional or HIV status

 Can be integrated into a point-of-care or close to point-of care platform with rapid results
 Nicol CID 2015

TPP: Diagnostic Biomarker



Identify novel biomarker-based diagnostic test [TPP1]:

- Optimal sensitivity: ≥ 66% (=Xpert), no minimal sensitivity defined
- Optimal specificity: 98%

Cuevas CID 2012, WHO 2014

TPP: Triage Biomarker



Identify novel biomarker-based triage test [TPP2]:

- Sensitivity: optimal > 95%, minimal 90%
- Specificity: optimal > 80%, minimal 70%

Triage for Pediatric TB?



Triage for Pediatric TB?



Current Pediatric Biomarker Evidence



Limited pediatric literature

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- Mainly proofof-principle or exploratory studies
- Few studies with independent validation cohorts

s – sputum u – urine b –whole blood

Current Pediatric Biomarker Evidence



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Transcriptomics (1)

- Micro-array based genomwide RNA host expression analysis using whole blood
- Included both discovery (S. Africa, Malawi) and validation cohorts (Kenya)

Derived 51 transcript signature TB vs. other disease and 42 transcript signature TB vs. LTBI

- Developed single risk score from signature to distinguish confirmed TB vs. other diseases
- Results: Sensitivity 83% (95% CI 69-94%); Specificity 84% (95% CI 75-93%)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Diagnosis of Childhood Tuberculosis and Host RNA Expression in Africa

Suzanne T. Anderson, Ph.D., M.R.C.P.C.H., Myrsini Kaforou, M.Phil.,
Andrew J. Brent, Ph.D., M.R.C.P., Victoria J. Wright, Ph.D., Claire M. Banwell, Ph.D.,
George Chagaluka, M.B., B.S., Amelia C. Crampin, F.F.P.H.M., Hazel M. Dockrell, Ph.D.,
Neil French, F.R.C.P., Ph.D., Melissa S. Hamilton, Ph.D., Martin L. Hibberd, Ph.D.,
Florian Kern, M.D., Paul R. Langford, Ph.D., F.S.B., Ling Ling, M.B., B.S.,
Rachel Mlotha, F.C.P. (Paeds) (SA), Tom H.M. Ottenhoff, M.D., Ph.D.,
Sandy Pienaar, M.Sc., Vashini Pillay, M.B., Ch.B., J. Anthony G. Scott, F.R.C.P.,
Hemed Twahir, M.Med., Robert J. Wilkinson, F.R.C.P., Ph.D., Lachlan J. Coin, Ph.D.,
Robert S. Heyderman, F.R.C.P., Ph.D., Michael Levin, Ph.D., and
Brian Eley, F.C.P. (Paeds) (SA), for the ILULU Consortium and KIDS TB Study Group*

Transcriptomics (2)

Genome-wide expression for diagnosis of pulmonary tuberculosis: a multicohort analysis

Timothy E Sweeney, Lindsay Braviak, Cristina M Tato, Purvesh Khatri

- Re-analyzed microarray data from Anderson study (491 children) and from RNA host expression study conducted in Venezuela (27 children)
- Discovered signature of three genes to distinguish TB vs. LTBI and TB vs. other diseases
 - Divided combined data set into discovery and validation cohorts
- Distinction between children with confirmed TB and children with LTBI: sensitivity 87%, specificity 84%

Transcriptomics (3)

A blood RNA signature for tuberculosis disease risk: a prospective cohort study

Daniel E Zak*, Adam Penn-Nicholson*, Thomas J Scriba*, Ethan Thompson†, Sara Suliman†, Lynn M Amon, Hassan Mahomed, Mzwandile Erasmus, Wendy Whatney, Gregory D Hussey, Deborah Abrahams, Fazlin Kafaar, Tony Hawkridge, Suzanne Verver, E Jane Hughes, Martin Ota, Jayne Sutherland, Rawleigh Howe, Hazel M Dockrell, W Henry Boom, Bonnie Thiel, Tom H M Ottenhoff, Harriet Mayanja-Kizza, Amelia C Crampin, Katrina Downing, Mark Hatherill, Joe Valvo, Smitha Shankar, Shreemanta K Parida, Stefan H E Kaufmann, Gerhard Walzl, Alan Aderem, Willem A Hanekom, for the ACS and GC6-74 cohort study groups‡

- Prospective cohort study among adolescents (12-18 years)
- Followed adolescents with LTBI for two years to differentiate progressors from non-progressors
 - Used RNA sequencing to derive signature
- Validated signature using RT-PCR among adolescent household contacts in South Africa and Gambia
 - Sensitivity 54% and specificity of 83% in identifying progressors

Zak Lancet 2016

T Cell Markers

Assessment of the novel T-cell activation marker-tuberculosis assay for diagnosis of active tuberculosis in children: a prospective proof-of-concept study

Damien Portevin, Felicien Moukambi, Petra Clowes, Asli Bauer, Mkunde Chachage, Nyanda E Ntinginya, Elirehema Mfinanga, Khadija Said, Frederick Haraka, Andrea Rachow, Elmar Saathoff, Maximilian Mpina, Levan Jugheli, Fred Lwilla, Ben J Marais, Michael Hoelscher, Claudia Daubenberger, Klaus Reither*, Christof Geldmacher*

- T-cell activation marker_TB (TAM-TB) assay
 - Measures the frequency of CD27 phenotype of CD4⁺ T cells producing IFN-gamma in response to TB antigens
 - Loss of CD27 likely indication of TB-antigenmediated T cell activation and differentiation
- Prospective cohort study in Tanzania
- TAM-TB: Sensitivity of 83% and specificity of 97%

Current Pediatric Biomarker Evidence



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Lateral Flow Urine LAM Assay

- Cochrane: only available biomarker-focused metaanalysis
 - Included adult studies
- Recent published pediatric studies: one from South Africa, one from Tanzania
- South Africa:
 - Sensitivity 48%, specificity 61%
 - AUC children with HIV 0.64, children without HIV 0.53
- Tanzania:
 - Sensitivity 50% children with HIV, 0% among children without HIV
 - Specificity 97%

Shah Cochrane 2016, Nicol Lancet GH 2014; Kroidl Eur Resp Journal 2015

Current Pediatric Biomarker Evidence



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Update on Standardized SOPs for Pediatric Sample Collection

- Initiative following NIH Workshop to:
- Promote collaboration among organizations and stakeholders
- Foster harmonized research and development of pediatric TB diagnostic biomarkers
- Develop standardized SOPs for sample collection



PEDIATRIC TUBERCULOSIS: ADDRESSING RESEARCH GAPS IN DIAGNOSTIC TB BIOMARKERS

MAY 5-6, 2014 | BETHESDA, MD



SOP Development

- Frequent conference calls since 2014
- Expert group of scientists, physicians and laboratory specialists
- Developed SOPs to guide collection of the following specimens:
 - Induced sputum
 - Gastric aspirate
 - Nasopharyngeal aspirate
 - Combined nasogastric-string test
 - Urine
 - Blood
- Guidance on required supplies, safety measures, volume considerations, transport of specimens, with detailed step-by-step instructions

Sharing and Availability

- Available to any interested organization
- Contact:
 - Devasena Gnanashanmugam (NIH/NIAID): devasena.gnanashanmugam@nih.gov
 - Renee Browning (NIH/NIAID): browningr@niaid.nih.gov

Thank you!



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