Approaches to Tuberculosis Diagnostics

Marco Schito, Scientific Director, Critical Path to TB Drug Regimens

19 July 2017

Critical Path to TB Drug Regimens

CRITICAL PATH INSTITUTE

OVERVIEW

Critical Path to TB Drug Regimens

1. Available diagnostic tools
2. Culture: the gold standard?
3. Molecular tools in development
4. Molecular diagnostic utilization
5. Diagnostic discrepancies
6. Sequence-based assays
7. Clinical trial applications

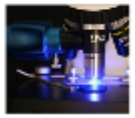
ADVANCES IN AVAILABLE DIAGNOSTIC TOOLS

Critical Path to TB Drug Regimens

Tuberculin

IGRAs

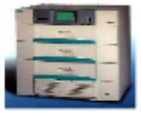
Conventional microscopy



LED/FM microscopy

Urine LAM

Solid Cultures



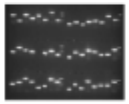
Liquid Culture

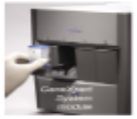
MIC Sensititer plate

Conventional, phenotypic DST

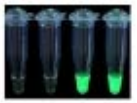
Molecular DST (LPAs)

Conventional PCR





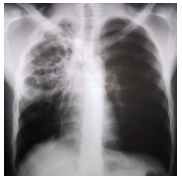
Xpert MTB/RIF & Ultra



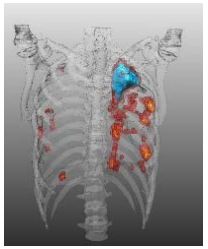
TB LAMP

Strip speciation

Conventional chest X-ray



Portable X-ray

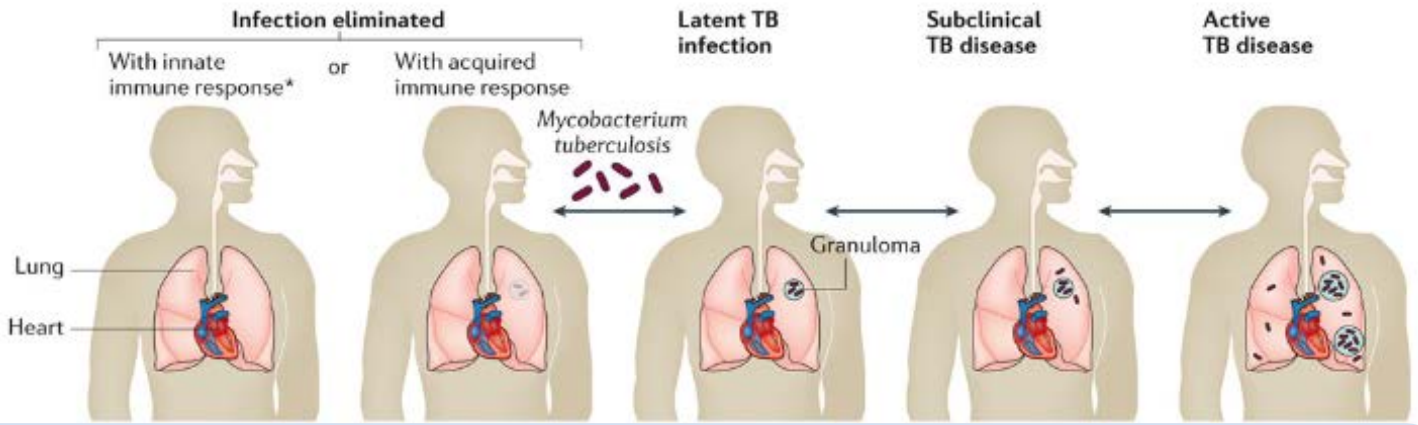


PET-CT

DIAGNOSTIC TESTS ACROSS TUBERCULOSIS DISEASE SPECTRUM

Critical Path to TB Drug Regimens

- Over 30% of the world's population is infected (2.2 B)
- Only ~5–10% will develop clinical disease (110 M)



TST/IGRA	-	+	+	+	(+)
Smear	-	-	-	(-)	+/-
Culture	-	-	-	(+)	+
Molecular	-	(-)	-	(+)	+
Symptoms	-	-	-	+/-	+/++

- Researchers understand little about what distinguishes individuals whose infection progresses to active tuberculosis (TB) from those whose infection remains latent for decades

CULTURE: GOLD STANDARD

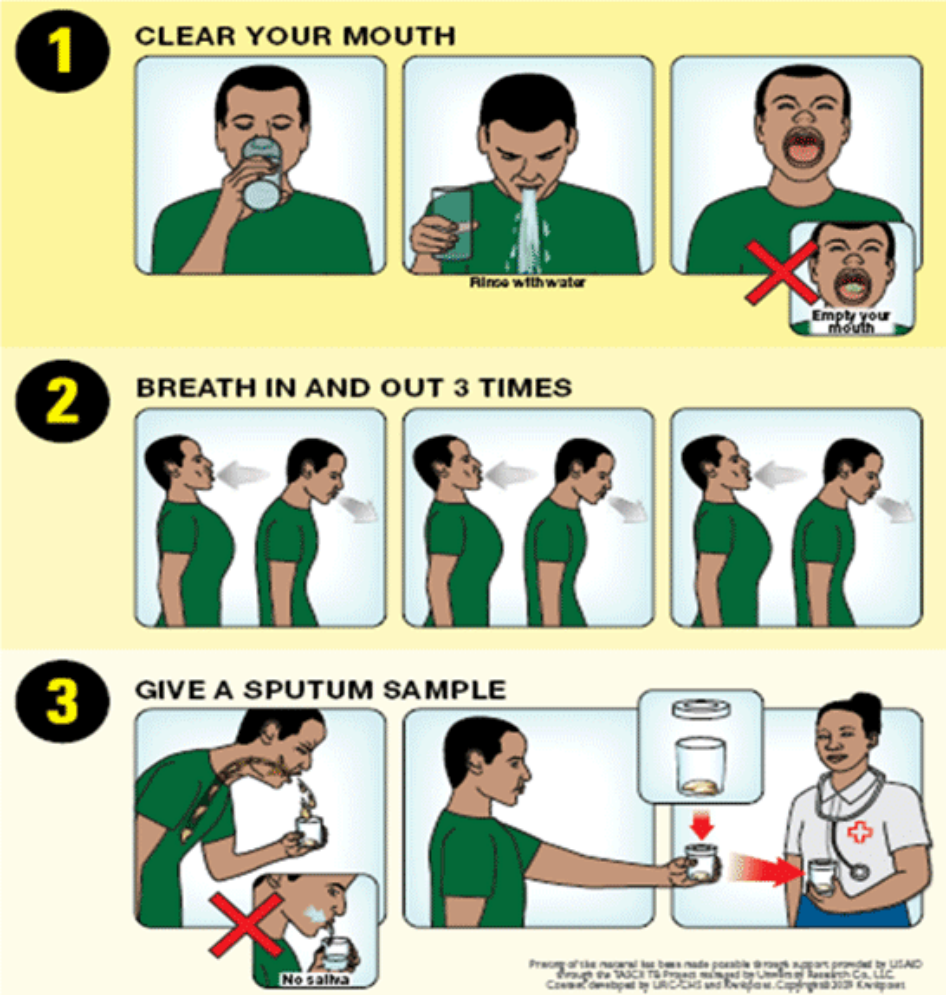
Critical Path to TB Drug Regimens

Pathogen-specific challenges

- TB grows slowly (3-4 weeks)
- Contamination issues
- Laboratory delays
  - Poor sample quality
  - Batch runs
  - Adjudication
  - Results back to patient

Phenotypic DST

- Additional 4-6 weeks (1st line)
- Additional 4-6 weeks (2nd line)
  - Limited capacity

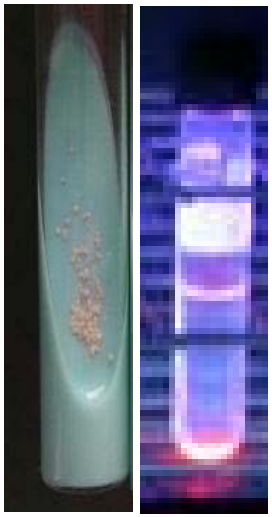


PHENOTYPIC DRUG SUSCEPTIBILITY TESTS (DST)

Critical Path to TB Drug Regimens

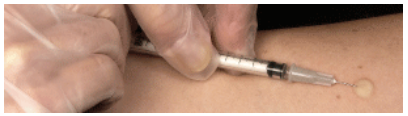
Established challenges

- Huge investment in past decade
- Technical capacity and retention
- Infrastructure and biosafety
- Quality issues and contamination rates



Emerging challenges

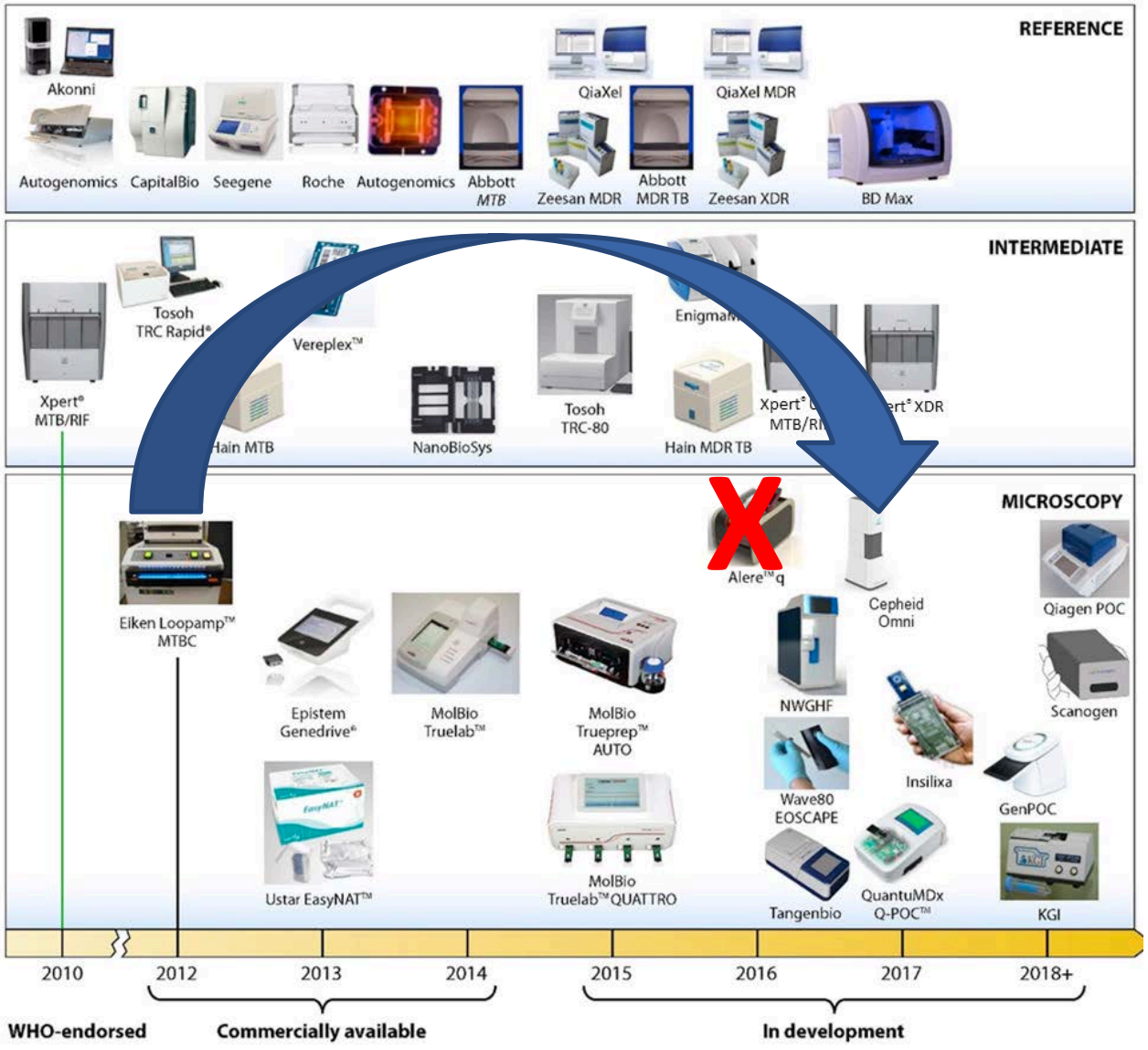
- Maintenance of infrastructure and capacity
- Appropriate infection control measures and programs for staff screening
- New costs and legislation for international transfer



Need for rapid POC tests

MOLECULAR GENOMIC REVOLUTION

Critical Path to TB Drug Regimens



Tech in development

- Phage-based
- Breath detection
- Biomarkers

NEW TOOLS: PROBE-BASED GENEXPERT MTB/RIF ASSAY

Critical Path to TB Drug Regimens

- WHO endorsed in 2010 & FDA cleared in 2013
- Provide result from sputum in 2 hours
  - Identify TB and determine resistance to Rifampicin (Rif)
    - Ultra-cartridge as sensitive as culture but lower specificity
    - New “Omni” form factor for point-of-care applications
    - New XDR cartridge will expand the drug menu

LOW UTILIZATION OF NEW TOOLS

Critical Path to TB Drug Regimens

Country (WHO classification)	Cartridges Procured [B] (n)	Modules Procured [B] (n)	Initial Smears [C] (n)	Smear/ Xpert Cartridge Ratio[J]	% change in smear/Xpert ratio 2014-2015	Algorithm[H]	Smear/Xpert Ratio (0.1 1 10 100 1000 10000)
Thailand	45,190	120	192,585	4.26	-96.56	HIV+, DR, Children, EPTB	
South Africa	2,777,190	9	164,735	0.06	-96.29	All, HIV+, DR, Children, EPTB	
Nigeria	152,450	377	165,968	1.09	-96.08	HIV+, DR, Children, EPTB	
Kenya	199,150	252	570,000	2.86	-93.99	HIV+, DR, Children, EPTB	
Ethiopia	165,300	36	4,600,000	27.83	-92.65	HIV+, DR, Children, EPTB	
India	766,860	140	7,028,841	9.16	-87.18	HIV+, DR, Children, EPTB	
Philippines	169,200	516	1,628,642	9.63	-77.03	HIV+, DR, Children, EPTB	
Pakistan	181,800	106	1,384,621	7.62	-75.43	HIV+, DR, Children, EPTB	
Vietnam	88,400	84	1,651,749	18.68	-70.15	HIV+, DR, Children, EPTB	
China	220,000[##]	3600[##]	5,079,636	23.09	-68.92	DR	
Myanmar	110,800	132	850,000	7.67	-66.93	HIV+, DR, EPTB[U]	
Cambodia	38,300	135	344,345	8.99	-57.39	HIV+, DR, EPTB	
Mozambique	66,550	128	207,441	3.12	-49.72	HIV+, DR, Children, EPTB	
Russia	4,550	N/A	6,096,500	1,339.89	-43.85	All, Children, HIV+, DR, EPTB	
Brazil	207,350	280	820,000	3.95	-36.22	All, HIV+, DR, Children, EPTB	
United Rep. of Tanzania	33,990	64	362,054[^]	10.65	-11.24	All, HIV+, DR, Children, EPTB	
Uganda	84,280	24	309,068	3.67	-10.56	HIV+, DR, Children	
Bangladesh	116,800	2	3,615,109	30.95[¶]	-8.97	HIV+, DR, EPTB	
Indonesia	70,000	88	2,678,829	38.27	-2.62	HIV+, DR, Children, EPTB	
Afghanistan	4,450	20	437,688	98.36	165.83	HIV+, DR [^]	
Zimbabwe	75,570	180	224,284	2.97	394.65	HIV+, DR, Children, EPTB	
DR Congo	12,800	46	2,760,000	215.63	591.11	DR	

Cazabon et al. ERJ in press

RESEARCH ARTICLE

Low implementation of Xpert MTB/RIF among HIV/TB co-infected adults in the International epidemiologic Databases to Evaluate AIDS (IeDEA) program

Kate Clouse[1,2,3], Meridith Blevins[1,4], Mary Lou Lindegren[1,2], Marcel Yotebieng[5], Dung Thi Nguyen[6], Alfred Omondi[7], Denna Michael[8], Djimon Marcel Zannou[9], Gabriela Carriquiry[10], April Pettit[2,3]*, International Epidemiologic Databases to Evaluate AIDS (IeDEA) collaboration[¶]

Table 3. TB testing utilization and outcomes among 2722 adult patients.

	n (%)
TB test utilization (n = 2722)	
Received at least one TB test	2070 (76%)
Received no TB test	650 (24%)
Missing	2 (<1%)
Type of TB test performed (n = 2555)*	
AFB smear	2025 (79%)
Culture	333 (13%)
Xpert	118 (5%)
Other NAAT	79 (3%)

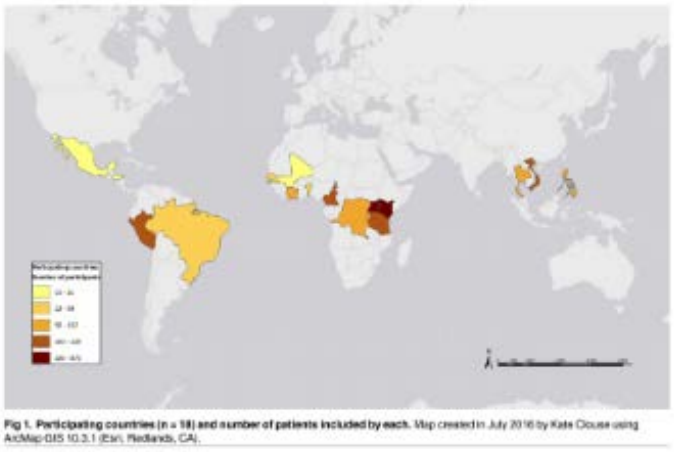


Fig 1. Participating countries (n = 18) and number of patients included by each. Map created in July 2016 by Kate Clouse using ArcMap GIS 10.3.1 (Esri, Redlands, CA).

"Xpert utilization was low even though the majority of sites had access to the test"

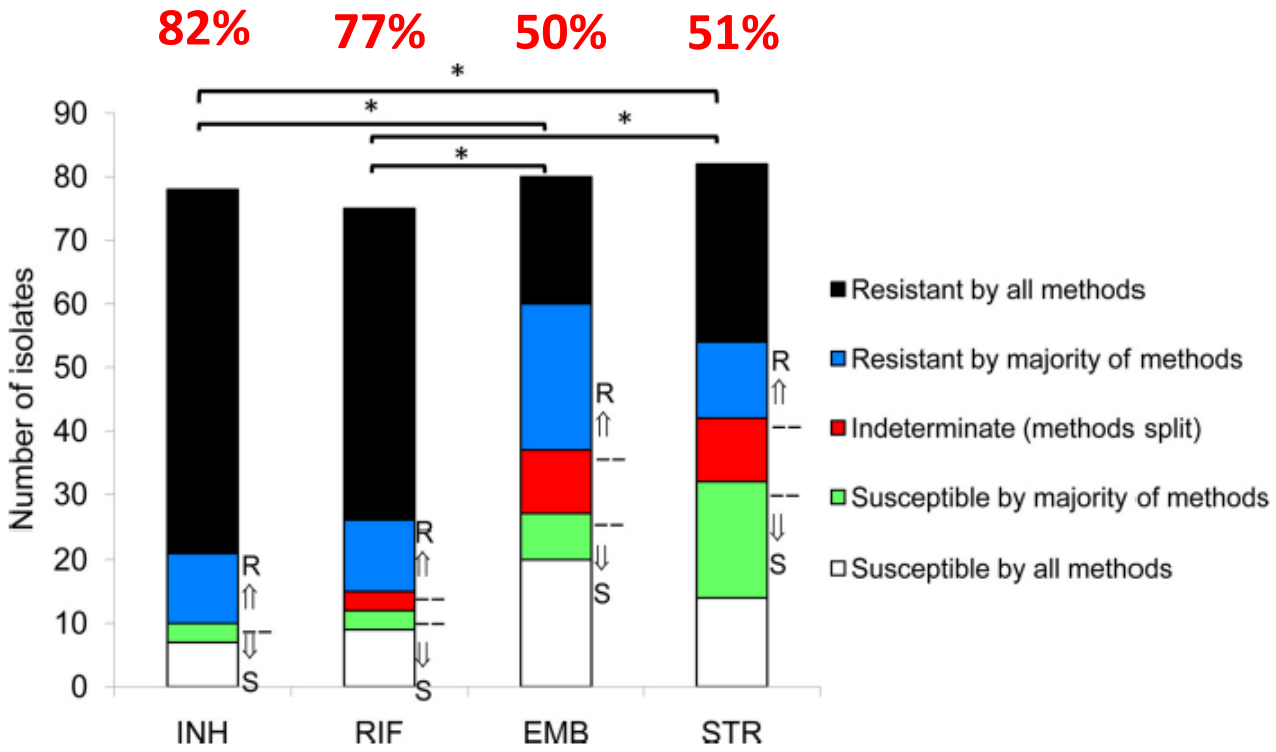
Clouse et al. 2017 PLoS One

CONCORDANCE AMONG DIFFERENT DST ASSAYS

Critical Path to TB Drug Regimens

DST methods evaluated

- L-J proportion
- MGIT 960
- GeneXpert MTB/RIF
- HAIN MTBDR*plus*
- MycoTB Sensititre
- Phage lab-based qPCR



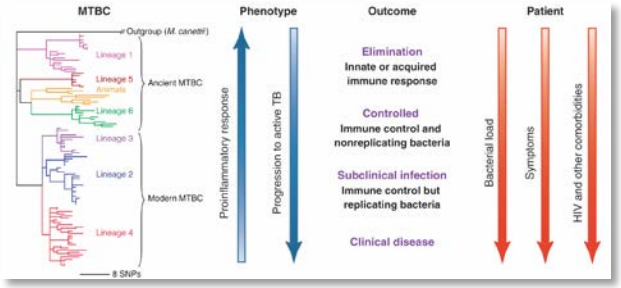
Why the discrepancies?

- Phenotypic test issues for some drugs
- Unknown, rare or unique Single Nucleotide Polymorphisms (SNPs)
- Epidemiological cut-off and critical concentrations poorly characterized
- Low-level mixed populations (hetero-resistance)

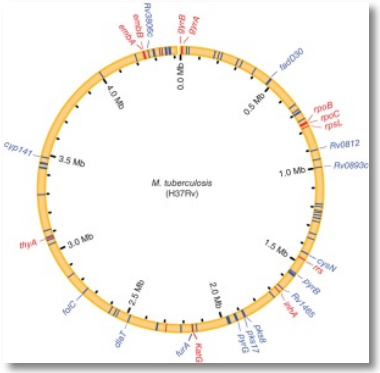
Banu S *et al*, 2014. JCM

NEXT GENERATION SEQUENCING

Critical Path to TB Drug Regimens



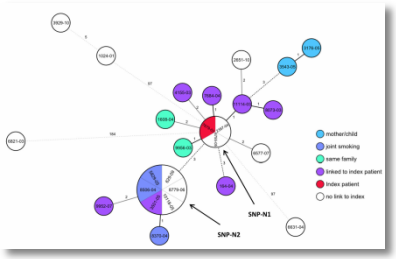
Virulence determinants



Drug-resistance

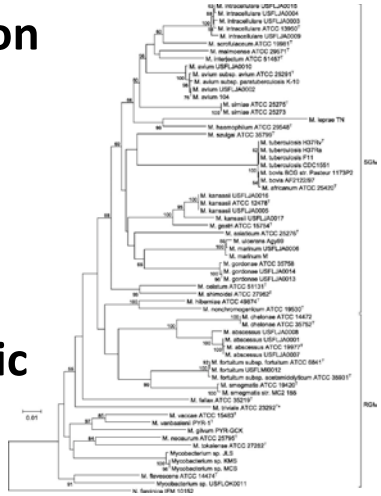
Identification

Genotyping

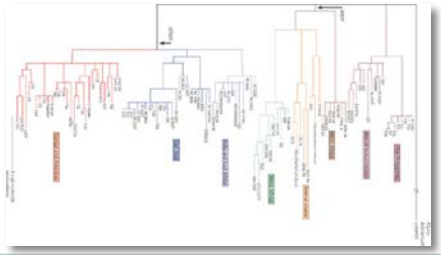


All-in-one

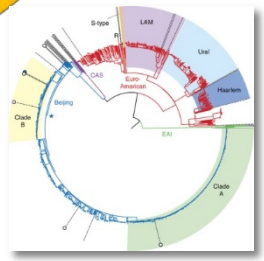
Phylogenetic



Evolution



Population structure



NEXT GENERATION SEQUENCING FOR DRUG RESISTANCE

Critical Path to TB Drug Regimens

Whole Genome

- Strengths
  - Full genome
  - Comprehensive
- Weaknesses
  - Slow
  - Culture dependent
  - Expensive
  - Bioinformatics

Targeted Amplicon

- Strengths
  - Sequence direct from sputum
  - Simpler and faster
  - Deeper sequencing
  - Up to several hundred loci
- Weaknesses
  - Less information
  - Prior knowledge of targets
  - Optimization

Need for a comprehensive database to provide a priori information regarding *Mtb* drug loci and mutations associated with drug resistance

ReSeqTB
Relational Sequencing TB Data Platform

RESEQTB SEQUENCE INTERPRETATION

Critical Path to TB Drug Regimens

Defined Criteria

1) Statistical
2) Homoplasy
3) MIC
4) Clin outcome
5) Functional Genetics

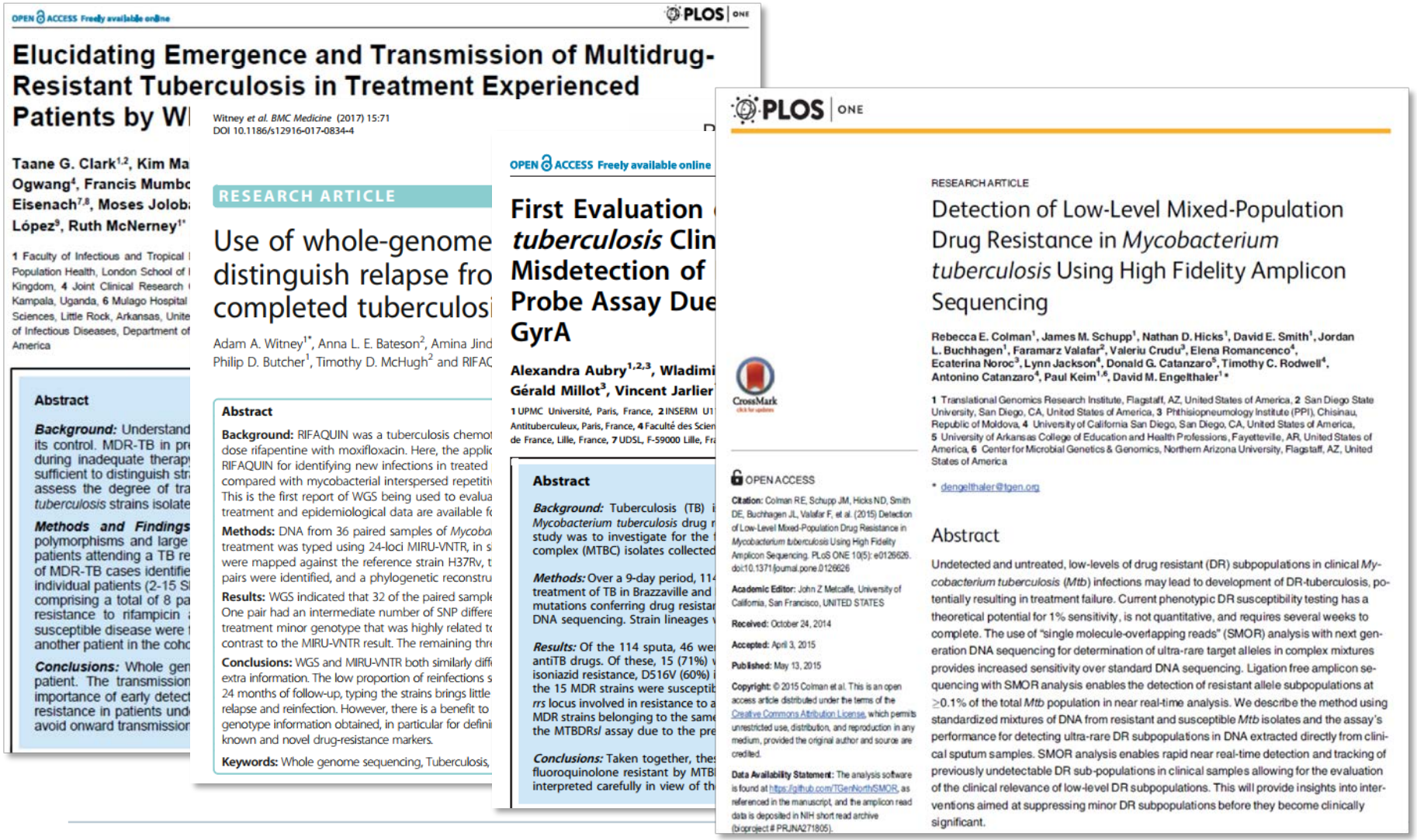
Drug	Gene	AA Change	NUC Change	Res w/ Mutation	Susc w/ Mutation	Sens	Spec	LR+	p-value	
AMI	rrs	NA	1401A>G	202	13	0.759	0.988	>10	0.000	●
AMI	rrs	NA	1402C>T	1	2	0.004	0.998	2.10	0.474	○
AMI	rrs	NA	1484G>T	2	0	0.008	1.000	>10	0.037	●
CAP	rrs	NA	1401A>G	129	38	0.713	0.960	>10	0.000	●
CAP	rrs	NA	1402C>T	2	2	0.011	0.998	5.31	0.120	○
CAP	rrs	NA	1484G>T	2	0	0.011	1.000	>10	0.025	●
KAN	rrs	NA	1401A>G	112	6	0.569	0.992	>10	0.000	●
KAN	rrs	NA	1402C>T	0	1	0.000	0.999	0.00	0.797	○
KAN	rrs	NA	1484G>T	1	0	0.005	1.000	>10	0.203	○
MFX	gyrA	Ala90Val	269C>T	7	5	0.104	0.993	>10	0.000	●
MFX	gyrA	Asp94Ala	281A>C	5	5	0.075	0.993	>10	0.001	●
MFX	gyrA	Asp94Asn	280G>A	2	1	0.030	0.999	>10	0.021	●
MFX	gyrA	Asp94Gly	281A>G	21	13	0.313	0.982	>10	0.000	●
MFX	gyrA	Asp94His	280G>C	3	1	0.045	0.999	>10	0.002	●
MFX	gyrA	Gly88Ala	263G>C	0	1	0.000	0.999	0.00	0.914	○
MFX	gyrA	Gly88Cys	262G>T	1	0	0.015	1.000	>10	0.086	○
MFX	gyrA	Ser91Pro	271T>C	6	2	0.090	0.997	>10	0.000	●
MFX	gyrA	Ser95Thr	284G>C	64	658	0.955	0.075	1.03	0.268	○

- LR>10 – ● High confidence that the mutation confers drug or is associated with resistance.
- LR <10 or >5 - ● Additional data desirable for improving evidence that the mutation confers or is associated with drug resistance (include data that is available such as numerator, denominator, and lineage).
- LR<5 or >1 - ● Inconclusive evidence that the mutation confers or is associated with drug resistance. Substantial additional data required (suggest additional clinical test to follow up).
- LR<1 - ● No evidence of association between mutation and drug resistance.

SEQUENCING IN CLINICAL TRIALS

Critical Path to TB Drug Regimens

- **Transmission**
- **Relapse vs. re-infection**
- **Drug resistance**
- **Hetero-resistance**



OPEN ACCESS Freely available online PLOS ONE

Elucidating Emergence and Transmission of Multidrug-Resistant Tuberculosis in Treatment Experienced Patients by W

Taane G. Clark[1,2], Kim Ma
Ogwang[4], Francis Mumbo
Eisenach[7,8], Moses Joloba
López[9], Ruth McNerney[1*]

1 Faculty of Infectious and Tropical
Population Health, London School of
Kingdom, 4 Joint Clinical Research
Kampala, Uganda, 6 Mulago Hospital
Sciences, Little Rock, Arkansas, Unite
of Infectious Diseases, Department of
America

Abstract

Background: Understand
its control. MDR-TB in pr
during inadequate therap
sufficient to distinguish str
assess the degree of tra
tuberculosis strains isolate

Methods and Findings
polymorphisms and large
patients attending a TB re
of MDR-TB cases identifie
individual patients (2-15 S
comprising a total of 8 pa
resistance to rifampicin
susceptible disease were
another patient in the coho

Conclusions: Whole ge
patient. The transmissio
importance of early detec
resistance in patients und
avoid onward transmissio

Witney *et al. BMC Medicine* (2017) 15:71
DOI 10.1186/s12916-017-0834-4

RESEARCH ARTICLE

Use of whole-genome distinguish relapse fro completed tuberculosi

Adam A. Witney[1*], Anna L. E. Bateson[2], Amina Jind
Philip D. Butcher[1], Timothy D. McHugh[2] and RIFAC

Abstract

Background: RIFAQUIN was a tuberculosis chemot
dose rifapentine with moxifloxacin. Here, the applic
RIFAQUIN for identifying new infections in treated
compared with mycobacterial interspersed repetiti
This is the first report of WGS being used to evalua
treatment and epidemiological data are available f

Methods: DNA from 36 paired samples of *Mycoba*
treatment was typed using 24-loci MIRU-VNTR, in s
were mapped against the reference strain H37Rv, t
pairs were identified, and a phylogenetic reconstru

Results: WGS indicated that 32 of the paired sampl
One pair had an intermediate number of SNP differe
treatment minor genotype that was highly related t
contrast to the MIRU-VNTR result. The remaining thr

Conclusions: WGS and MIRU-VNTR both similarly diff
extra information. The low proportion of reinfections s
24 months of follow-up, typing the strains brings little
relapse and reinfection. However, there is a benefit to
genotype information obtained, in particular for defini
known and novel drug-resistance markers.

Keywords: Whole genome sequencing, Tuberculosis,

OPEN ACCESS Freely available online

First Evaluation *tuberculosis* Clin Misdetection of Probe Assay Due GyrA

Alexandra Aubry[1,2,3], Wladimi Gérald Millot[3], Vincent Jarlier

1 UPMC Université, Paris, France, 2 INSERM U1
Antituberculeux, Paris, France, 4 Faculté des Scien
de France, Lille, France, 7 UDSL, F-59000 Lille, Fr

Abstract

Background: Tuberculosis (TB) i
Mycobacterium tuberculosis drug r
study was to investigate for the
complex (MTBC) isolates collected

Methods: Over a 9-day period, 114
treatment of TB in Brazzaville and
mutations conferring drug resistar
DNA sequencing. Strain lineages

Results: Of the 114 sputa, 46 we
antiTB drugs. Of these, 15 (71%)
isoniazid resistance, D516V (60%)
the 15 MDR strains were susceptib
rrs locus involved in resistance to a
MDR strains belonging to the same
the MTBDR*sl* assay due to the pre

Conclusions: Taken together, thes
fluoroquinolone resistant by MTB
interpreted carefully in view of th

PLOS ONE

RESEARCH ARTICLE

Detection of Low-Level Mixed-Population Drug Resistance in *Mycobacterium tuberculosis* Using High Fidelity Amplicon Sequencing

Rebecca E. Colman[1], James M. Schupp[1], Nathan D. Hicks[1], David E. Smith[1], Jordan L. Buchhagen[1], Faramarz Valafar[2], Valeriu Crudu[3], Elena Romancenco[4], Ecaterina Noroc[3], Lynn Jackson[4], Donald G. Catanzaro[5], Timothy C. Rodwell[4], Antonino Catanzaro[4], Paul Keim[1,6], David M. Engelthaler[1]*

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OPEN ACCESS

Citation: Colman RE, Schupp JM, Hicks ND, Smith DE, Buchhagen JL, Valafar F, et al. (2015) Detection of Low-Level Mixed-Population Drug Resistance in *Mycobacterium tuberculosis* Using High Fidelity Amplicon Sequencing. PLoS ONE 10(5): e0126626. doi:10.1371/journal.pone.0126626

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Data Availability Statement: The analysis software is found at https://github.com/TGenNorth/SMOR, as referenced in the manuscript, and the amplicon read data is deposited in NIH short read archive (bioproject # PRJNA271805).

Abstract

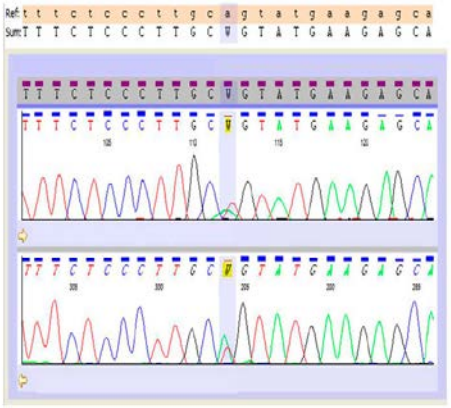
Undetected and untreated, low-levels of drug resistant (DR) subpopulations in clinical *Mycobacterium tuberculosis* (*Mtb*) infections may lead to development of DR-tuberculosis, potentially resulting in treatment failure. Current phenotypic DR susceptibility testing has a theoretical potential for 1% sensitivity, is not quantitative, and requires several weeks to complete. The use of "single molecule-overlapping reads" (SMOR) analysis with next generation DNA sequencing for determination of ultra-rare target alleles in complex mixtures provides increased sensitivity over standard DNA sequencing. Ligation free amplicon sequencing with SMOR analysis enables the detection of resistant allele subpopulations at ≥0.1% of the total *Mtb* population in near real-time analysis. We describe the method using standardized mixtures of DNA from resistant and susceptible *Mtb* isolates and the assay's performance for detecting ultra-rare DR subpopulations in DNA extracted directly from clinical sputum samples. SMOR analysis enables rapid near real-time detection and tracking of previously undetectable DR sub-populations in clinical samples allowing for the evaluation of the clinical relevance of low-level DR subpopulations. This will provide insights into interventions aimed at suppressing minor DR subpopulations before they become clinically significant.

Critical Path to TB Drug Regimens

Hetero-resistance (low-level mixed populations)

- The presence of a small number of organisms that are resistant to an antimicrobial drug within a population that are susceptible to the drug
- May explain why failure to eradicate an infection occurs in some patients treated with seemingly appropriate antibiotics

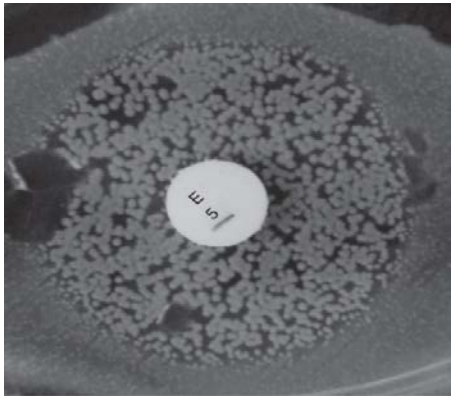
Sensitivity of detecting hetero-resistance



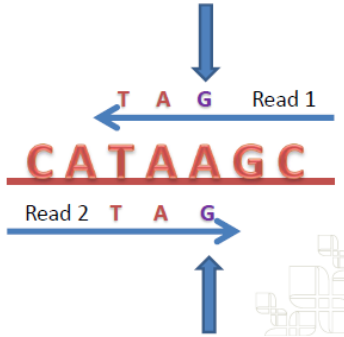
Sanger: 30-50%

…TTTCTCCCTTGCTTTATGAAGAGCA…
…TTTCTCCCTTGCTTTATGAAGAGCA…
…TTTCTCCCTTGCTTTATGAAGAGCA…
…TTTCTCCCTTGCATTATGAAGAGCA…
…TTTCTCCCTTGCTTTATGAAGAGCA…
…TTTCTCCCTTGCTTTATGAAGAGCA…
…TTTCTCCCTTGCTTTATGAAGAGCA…
…TTTCTCCCTTGCATTATGAAGAGCA…
…TTTCTCCCTTGCTTTATGAAGAGCA…
…TTTCTCCCTTGCTTTATGAAGAGCA…

WGS: 5-10%



Culture: 1-5%



Targeted: 0.01%

PREDICTING DRUG RESISTANCE

Critical Path to TB Drug Regimens

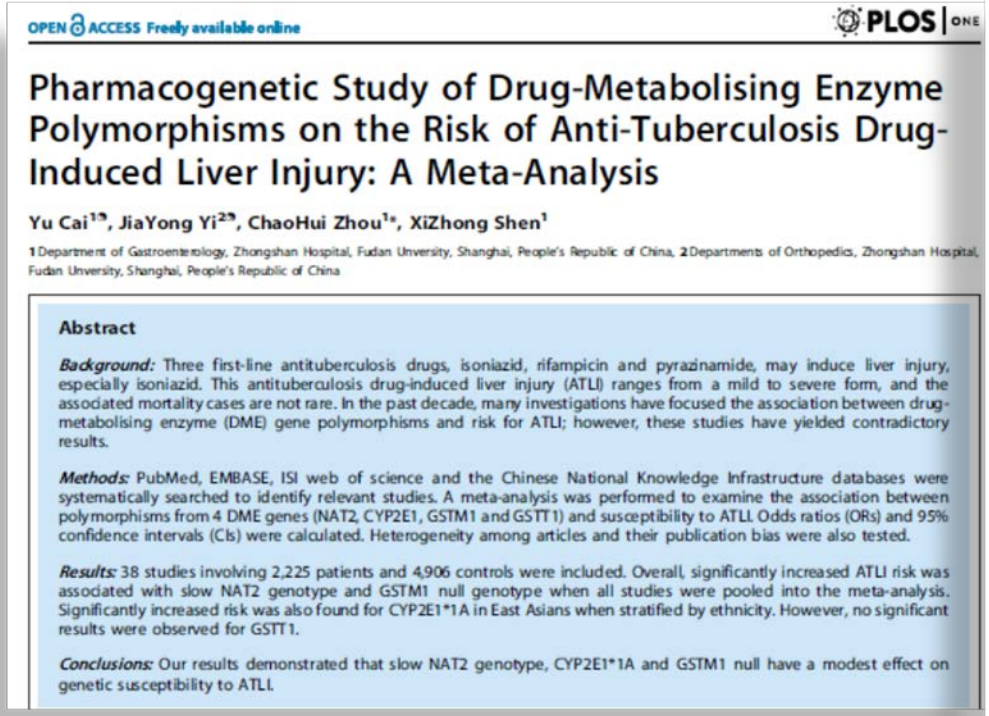
- Targeted amplicon sequencing such as the Single Molecule Overlapping Read (SMOR) assay can reduce the sequencing error rate from 1% to 0.01%
- Potential to identify populations of resistant bacteria with sensitivity that exceeds current gold standard methods

		AMK DST		SMOR
Sample Date	Resistance	Phenotypic	Genotypic	rrs SNP (% R Allele)
10/1/2008	MDR	S	S	none
11/19/2008	MDR	S	S	none
10/15/2009	unclassified	S	S	none
1/19/2010	MDR	S	S	none
7/20/2011	MDR	S	S	1401G (0.94%)
9/27/2011	pre-XDR	S	S	none
4/30/2012	pre-XDR	S	S	1401G (3.4%)
12/21/2012	XDR	R	R	1401G (29.6%)

Metcalfe et al. 2017. Am J Respir Crit Care Med

CAN NGS BE USED TO ASSESS HOST PHARMACOGENOMICS?

Critical Path to TB Drug Regimens



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PLOS ONE

Pharmacogenetic Study of Drug-Metabolising Enzyme Polymorphisms on the Risk of Anti-Tuberculosis Drug-Induced Liver Injury: A Meta-Analysis

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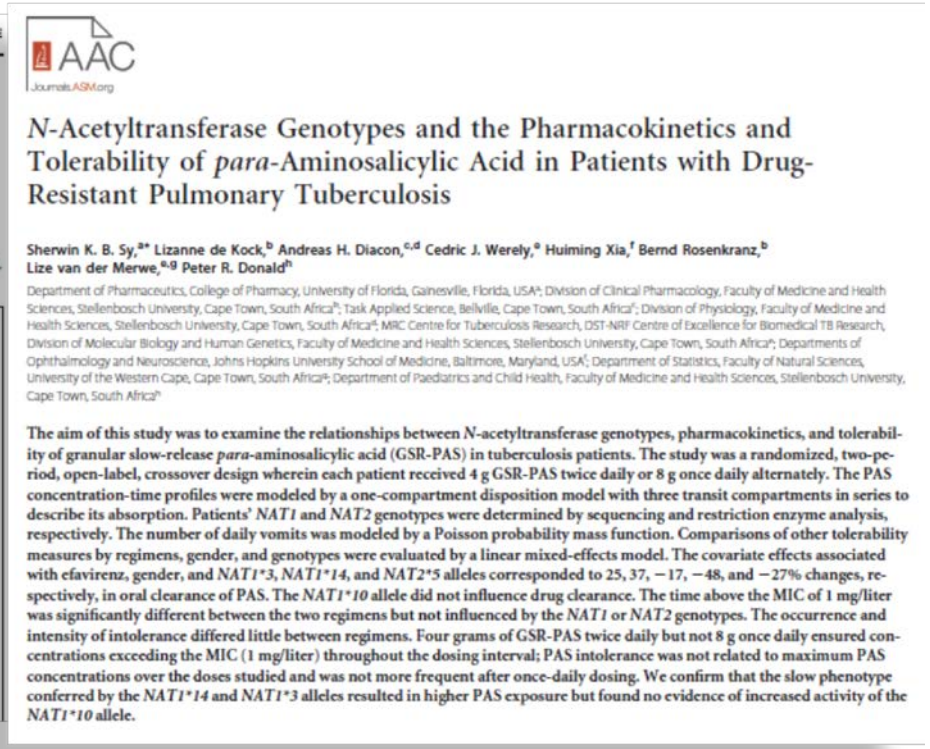
Abstract

Background: Three first-line antituberculosis drugs, isoniazid, rifampicin and pyrazinamide, may induce liver injury, especially isoniazid. This antituberculosis drug-induced liver injury (ATLI) ranges from a mild to severe form, and the associated mortality cases are not rare. In the past decade, many investigations have focused the association between drug-metabolising enzyme (DME) gene polymorphisms and risk for ATLI; however, these studies have yielded contradictory results.

Methods: PubMed, EMBASE, ISI web of science and the Chinese National Knowledge Infrastructure databases were systematically searched to identify relevant studies. A meta-analysis was performed to examine the association between polymorphisms from 4 DME genes (NAT2, CYP2E1, GSTM1 and GSTT1) and susceptibility to ATLI. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Heterogeneity among articles and their publication bias were also tested.

Results: 38 studies involving 2,225 patients and 4,906 controls were included. Overall, significantly increased ATLI risk was associated with slow NAT2 genotype and GSTM1 null genotype when all studies were pooled into the meta-analysis. Significantly increased risk was also found for CYP2E1*1A in East Asians when stratified by ethnicity. However, no significant results were observed for GSTT1.

Conclusions: Our results demonstrated that slow NAT2 genotype, CYP2E1*1A and GSTM1 null have a modest effect on genetic susceptibility to ATLI.



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N-Acetyltransferase Genotypes and the Pharmacokinetics and Tolerability of *para*-Aminosalicylic Acid in Patients with Drug-Resistant Pulmonary Tuberculosis

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The aim of this study was to examine the relationships between *N*-acetyltransferase genotypes, pharmacokinetics, and tolerability of granular slow-release *para*-aminosalicylic acid (GSR-PAS) in tuberculosis patients. The study was a randomized, two-period, open-label, crossover design wherein each patient received 4 g GSR-PAS twice daily or 8 g once daily alternately. The PAS concentration-time profiles were modeled by a one-compartment disposition model with three transit compartments in series to describe its absorption. Patients' *NAT1* and *NAT2* genotypes were determined by sequencing and restriction enzyme analysis, respectively. The number of daily vomits was modeled by a Poisson probability mass function. Comparisons of other tolerability measures by regimens, gender, and genotypes were evaluated by a linear mixed-effects model. The covariate effects associated with efavirenz, gender, and *NAT1*3*, *NAT1*14*, and *NAT2*5* alleles corresponded to 25, 37, −17, −48, and −27% changes, respectively, in oral clearance of PAS. The *NAT1*10* allele did not influence drug clearance. The time above the MIC of 1 mg/liter was significantly different between the two regimens but not influenced by the *NAT1* or *NAT2* genotypes. The occurrence and intensity of intolerance differed little between regimens. Four grams of GSR-PAS twice daily but not 8 g once daily ensured concentrations exceeding the MIC (1 mg/liter) throughout the dosing interval; PAS intolerance was not related to maximum PAS concentrations over the doses studied and was not more frequent after once-daily dosing. We confirm that the slow phenotype conferred by the *NAT1*14* and *NAT1*3* alleles resulted in higher PAS exposure but found no evidence of increased activity of the *NAT1*10* allele.

…our meta-analysis indicates that CYP2E1, NAT2 and GSTM1 genetic variation is significantly associated with anti-tuberculosis drug-induced liver injury. (PLoS One. 2012; 7(10): e47769.)

We observed the slow phenotype of NAT1*14 and NAT1*3 alleles was associated with greater PAS exposure. (Antimicrob Agents Chemother. 2015; 59(7): 4129-38)

HUMAN GENES ASSOCIATED WITH ANTI-TB DRUG-INDUCED ADVERSE EVENTS

Critical Path to TB Drug Regimens

Drug	Adverse Drug Reaction	Gene	Gene class	# SNPs *
RIF	Thrombocytopenia	*GPIX*	Receptor	2
INH	Hepatotoxicity	*NAT2*	DME-1	11
		CYP2E1	DME-1	10
		GSTM1	DME-2	3
		GSTT1	DME-2	2
PZA	Hepatotoxicity	*XDH*	DME	8
	Nephrotoxicity	*SLC22A12*	Transporter	10
EMB	Optic neuritis	*OPA1*	GTPase	12
AG	Nephrotoxicity	*LRP2*	Receptor	12
	Ototoxicity	*MYO7a*	Transporter	5

* SNP frequencies are population dependent

- If levels increase -> approach MTD and accumulation of **toxic** metabolites
- If levels decrease -> reduce treatment efficacy
  - Incomplete eradication of bacilli -> prolonged treatment and **relapse**
  - Increase chance of developing DR

Adapted from Sahu et al. 2015. Curr Drug Metabol. 16(7): 538-52

CONCLUSIONS

Critical Path to TB Drug Regimens

- **Culture remains challenging in high burden countries**
- **Poor uptake of new tools such as GeneXpert due to cost and political will**
- **Programmatic challenges of discordant results among diagnostic assays**
- **Optimization of sequencing tools in centralized labs can help address drug resistance crisis (PHE sequence-based DST; WHO and CDC surveillance)**

Sequencing assays currently available for scientific research and clinical trials

- Culture-free drug resistance assay (Pathogen DNA)
  - Hetero-resistance and resistance prediction
- Pharmacogenomic assay (Host DNA)
  - Predicting adverse events

Future biomarker assay tools in development

- Triage test to rule out TB at point-of-care
  - Systematic screening for active case finding (e.g. C-reactive protein)
- Rapid non-sputum instrument-free biomarker test for identifying TB disease
  - Special populations and EPTB (e.g. Nanodisk: blood-based TB test)
- Incipient assay
  - Biomarker(s) that predict disease progression (e.g. RNA signature assay)
- Treatment monitoring assay
  - Predict cure versus relapse (e.g. LAM biomarker)

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- Paolo Miotto

DTBE, CDC
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- Jamie Posey

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Bill & Melinda Gates Foundation
- Jim Gallarda

ReSeqTB expert members
- Stefan Niemann (Chair)

Thank you