Emerging Bacterial Pathogens Unit

OSPEDALE SAN RAFFAELE

NGS for diagnosis and management of drug resistant tuberculosis

Microbial Pathogenesis Symposium, 28-29 May 2019, Institut Pasteur, Paris

Daniela M Cirillo, MD PhD

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WHO Collaborating Centre in TB Laboratory Strengthening
IRCCS San Raffaele Scientific Institute, Milan, Italy

The roadmap to new TB diagnostics
to achieve End TB and Global Plan targets

Improve TB case detection

1. Triage test (high NPV)

Or **ideally**

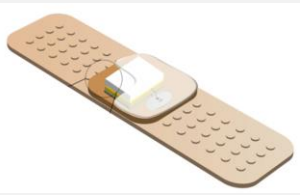
2. Highly sensitive stand-alone detection test

Universal access to DST

1. TB confirmation with rapid integrated DST for critical drugs
2. Test for cure
3. Comprehensive DST to cover the extended portfolio of drugs
4. DR surveillance
5. Control transmission

Support TB elimination

1. LTBI: Test to identify high risk of progression to active disease
2. Incipient TB test: to identify early subclinical TB

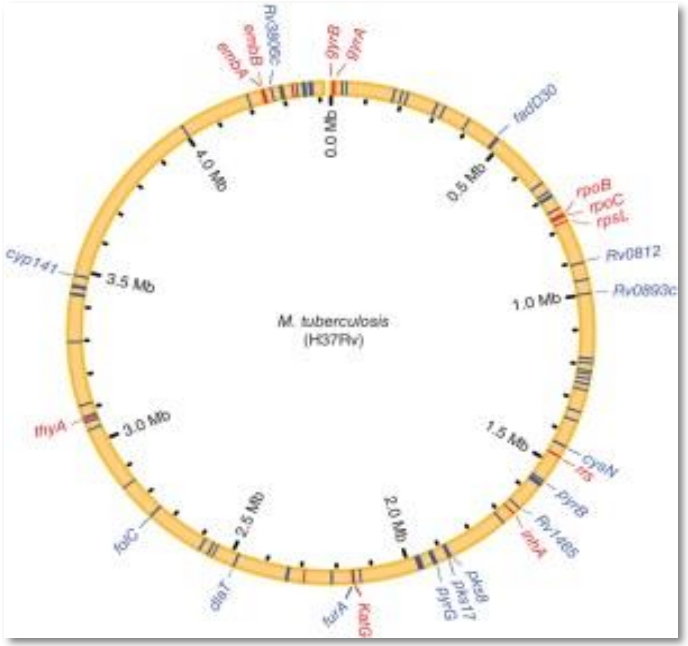


Whole genome sequencing

Species and lineage ID
Evolution studies

Resistance to first-, second-line and new drugs

Epidemiological and transmission analysis



Public health: anti-TB Drug Resistance Surveys and Surveillance

Development and evaluation of user-friendly tools

KNOWLEDGE INCREASE

NGS have *measurable* parameters that can be used for QC

- ✓ Diagnosis of DR TB
- ✓ Transmission analysis
- ✓ Drug resistance survey and routine surveillance
- ✓ Approaching new MDR TB drugs

Prevalence of resistance estimated through sequencing compared with phenotypic testing

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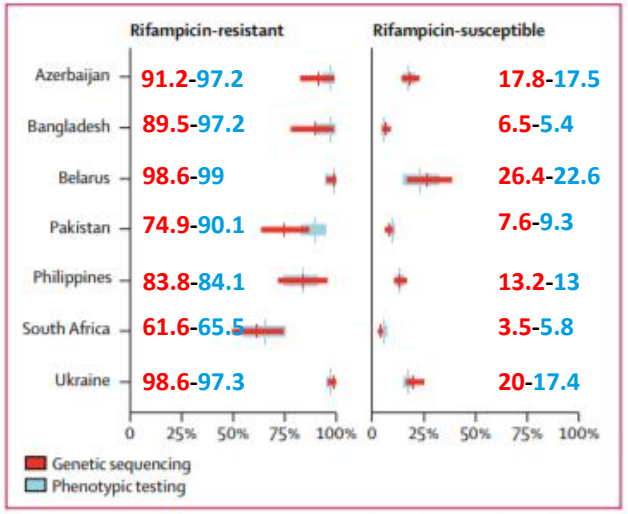

Figure 2: Prevalence of isoniazid resistance, estimated through genetic sequencing compared with phenotypic testing

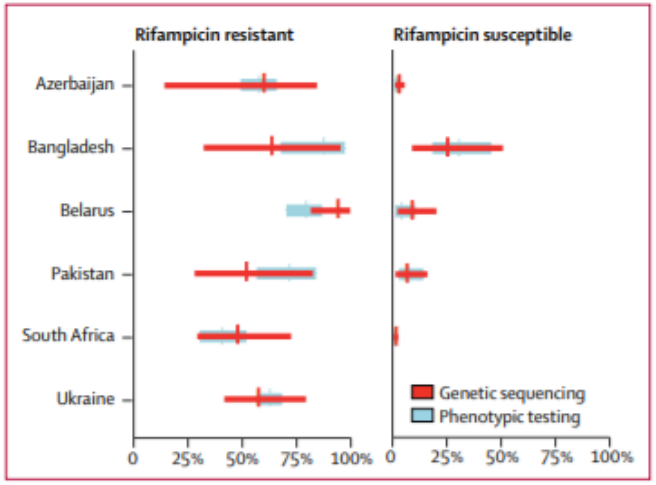

Figure 4: Prevalence of pyrazinamide resistance, estimated through genetic sequencing compared with phenotypic testing

blue as means and 95% confidence intervals
red as means and 95% credible intervals from the Bayesian model

Population-based resistance of *Mycobacterium tuberculosis* isolates to pyrazinamide and fluoroquinolones: results from a multicountry surveillance project

Matteo Zignol, Anna S Dean, Natavan Alikhanova, Sönke Andres, Andrea Maurizio Cabibbe, Daniela Maria Cirillo, Andrei Dadu, Andries Dreyer, Michèle Driesen, Christopher Gilpin, Rumina Hasan, Zahra Hasan, Sven Hoffner, Ashaque Husain, Alamdar Hussain, Nazir Ismail, Mostofa Kamal, Mikael Mansjö, Lindiwe Mvusi, Stefan Niemann, Shaheed V Omar, Ejaz Qadeer, Leen Rigouts, Sabine Ruesch-Gerdes, Marco Schito, Mehriban Seyfaddinova, Alena Skrahina, Sabira Tahseen, William A Wells, Ya Diul Mukadi, Michael Kimerling, Katherine Floyd, Karin Weyer, Mario C Raviglione

Genetic sequencing for surveillance of drug resistance in tuberculosis in highly endemic countries: a multi-country population-based surveillance study

Matteo Zignol, Andrea Maurizio Cabibbe*, Anna S Dean*, Philippe Glaziou, Natavan Alikhanova, Cecilia Ama, Sönke Andres, Anna Barbova, Angeli Borbe-Reyes, Daniel P Chin, Daniela Maria Cirillo, Charlotte Colvin, Andrei Dadu, Andries Dreyer, Michèle Driesen, Christopher Gilpin, Rumina Hasan, Zahra Hasan, Sven Hoffner, Alamdar Hussain, Nazir Ismail, S M Mostofa Kamal, Faisal Masood Khanzada, Michael Kimerling, Thomas Andreas Kohl, Mikael Mansjö, Paolo Miotto, Ya Diul Mukadi, Lindiwe Mvusi, Stefan Niemann, Shaheed V Omar, Leen Rigouts, Marco Schito, Ivita Sela, Mehriban Seyfaddinova, Girts Skenders, Alena Skrahina, Sabira Tahseen, William A Wells, Alexander Zhurilo, Karin Weyer, Katherine Floyd, Mario C Raviglione*

EVIDENCE

Large overlap between resistance determined by genetic sequencing, after adjustment for sensitivity, and the true prevalence of drug resistance

- ✓ Accuracy of genetic sequencing is very good at predicting phenotypic resistance to rifampicin, isoniazid, the fluoroquinolones, and (among rifampicin-resistant cases) injectable drugs

Whole genome sequencing

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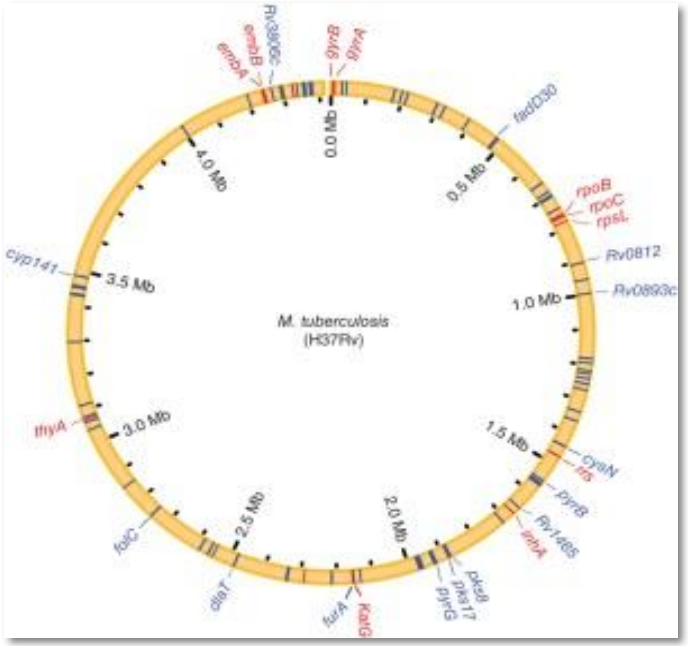

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- ✓ Approaching new MDR TB drugs

A cluster of multidrug-resistant *Mycobacterium tuberculosis* among patients arriving in Europe from the Horn of Africa: a molecular epidemiological study

Timothy M Walker, Matthias Merker*, Astrid M Knoblauch*, Peter Helbling, Otto D Schoch, Marieke J van der Werf, Katharina Kranzer, Lena Fiebig, Stefan Kröger, Walter Haas, Harald Hoffmann, Alexander Indra, Adrian Egli, Daniela M Cirillo, Jérôme Robert, Thomas R Rogers, Ramona Groenheit, Anne T Mengshoel, Vanessa Mathys, Marjo Haanperä, Dick van Soolingen, Stefan Niemann†, Erik C Böttger†, Peter M Keller†, and the MDR-TB Cluster Consortium‡*

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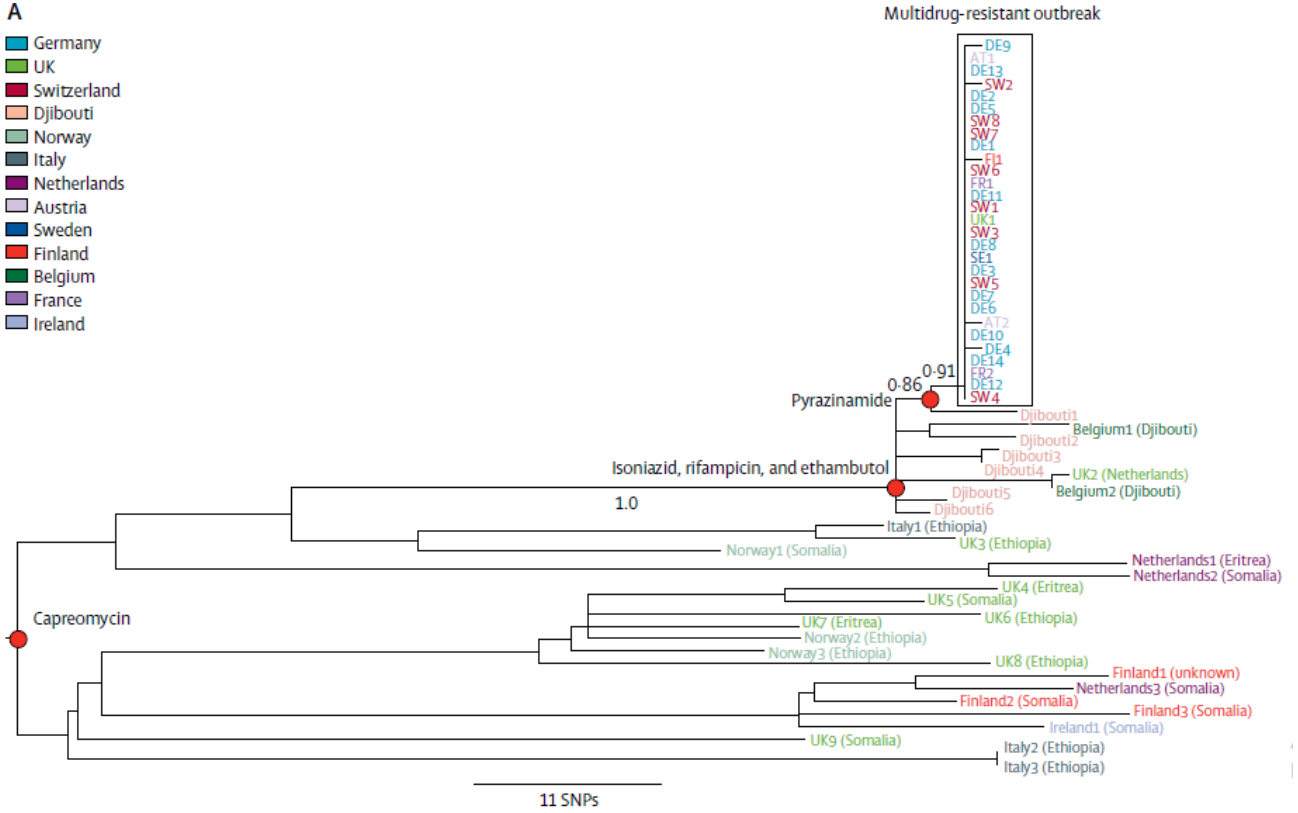
Case Definition Proposal

- Resistance phenotype as on table 3.; i.e. INH high-level R, RIF R, CAP R, PZA R, quinolones S, amikacin S.
- Specific set of resistance mutations: see table 3
- MIRU-VNTR: 2-2-4-2-4-3-3-3-2-4-2-4-2-2-5-1-4-3-3-3-4-3-2-2 and/or WGS core genome MLST with <4 SNP (to be discussed)



EUSeqMyTB

CORRESPONDENCE | VOLUME 18, ISSUE 4, P377, APRIL 01, 2018

EUSeqMyTB to set standards and build capacity for whole genome sequencing for tuberculosis in the EU

Elisa Tagliani • Daniela Maria Cirillo • Csaba Ködmön • Marieke J van der Werf and the EUSeqMyTB Consortium

Published: April, 2018 • DOI: https://doi.org/10.1016/S1473-3099(18)30132-4

PeerJ

MTBseq: a comprehensive pipeline for whole genome sequence analysis of *Mycobacterium tuberculosis* complex isolates

Thomas Andreas Kohl[1,*], Christian Utpatel[1,*], Viola Schleusener[1], Maria Rosaria De Filippo[2], Patrick Beckert[1,3], Daniela Maria Cirillo[2] and Stefan Niemann[1,3]

Whole genome sequencing

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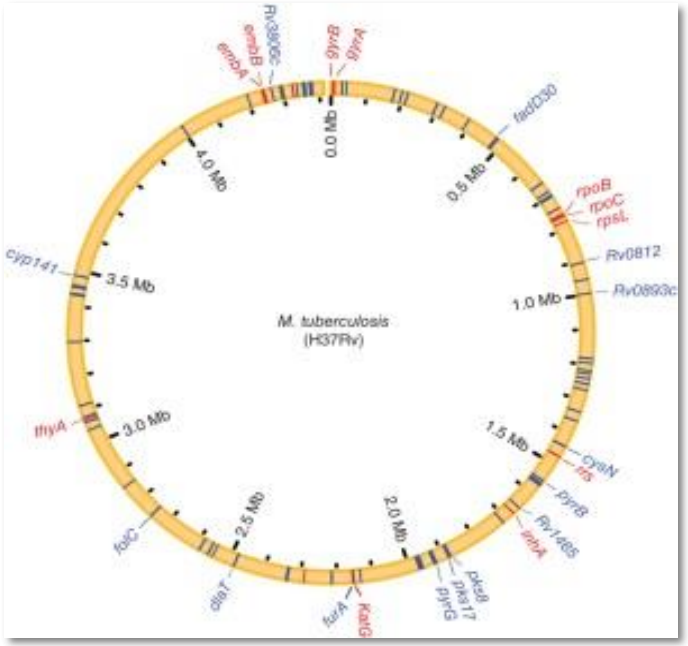
Evolution studies

Resistance to first-, second-line and new drugs

Epidemiological and transmission analysis



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WHO-recommended rapid diagnostics for DR-TB

Xpert ULTRA

- Integrated/automated qPCR
- Fully nested amplification
- Results in 1h17m
- Technical expertise: none
- TB detection by targeting two different multi-copy genes (IS6110 & IS1081)
- High-resolution melt curve analysis for rpoB detection
- Additional PCR modifications to improve sensitivity and specificity

MTBDRplus

- Reverse hybridization, colorimetric reaction
- Results in 6-7 h
- Technical expertise: some
- Biosafety lev 2
- Detect resistance in TB to Rifampicine (RpoB gene) and Isoniazide (InhA, KatG genes),

MTBDRsl

- Reverse hybridization, colorimetric reaction
- Results in 6-7 h
- Technical expertise: some
- Biosafety lev 2
- Detect resistance in TB to the fluoroquinolones (FQs; ofloxacin, moxifloxacin and levofloxacin) and the second-line injectable drugs (SLIDs; amikacin, kanamycin and capreomycin),

Suboptimal performance of rapid tests

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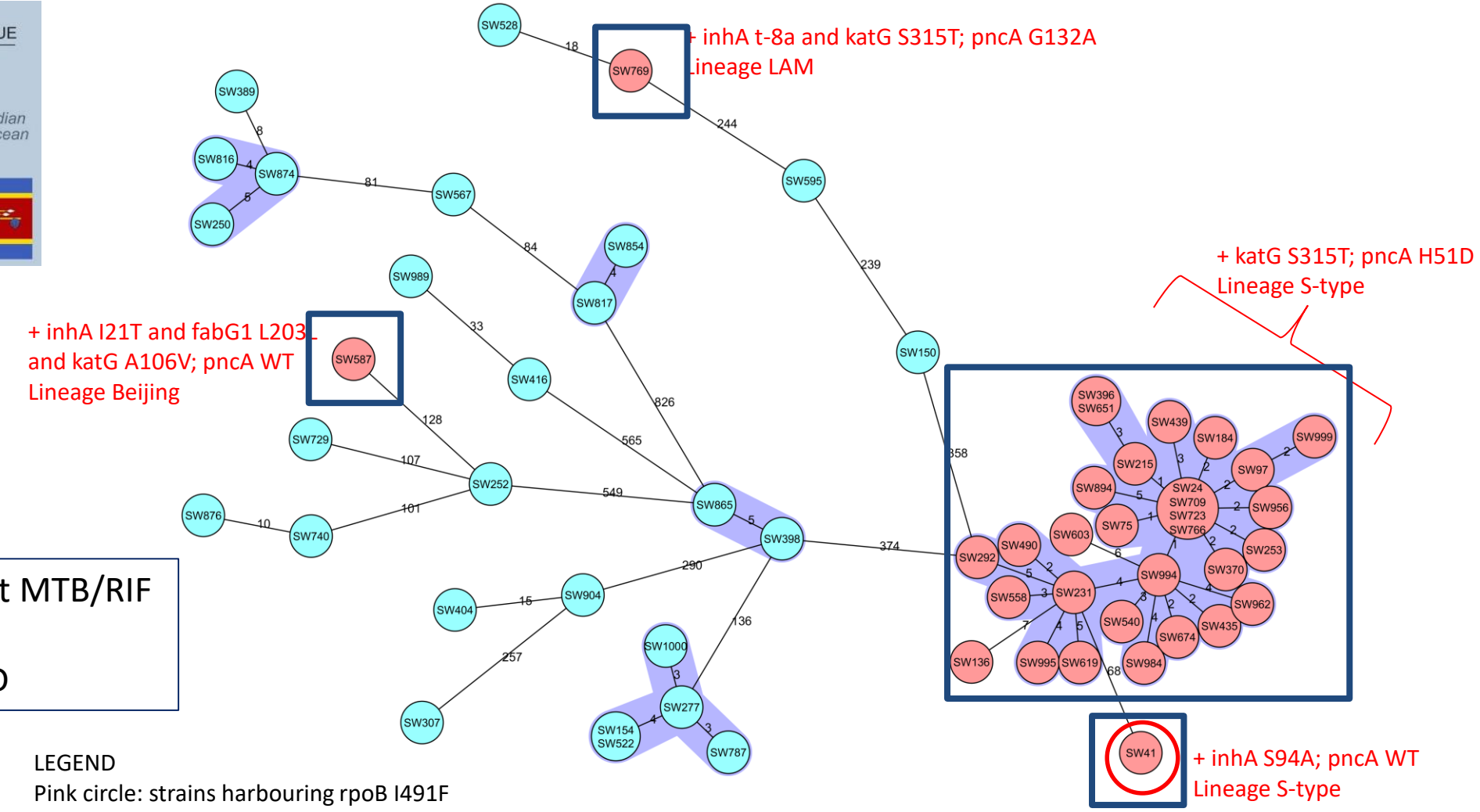
cgMLST analysis: Minimum spanning tree of DRS strains carrying *rpoB* mutations conferring resistance to RIF

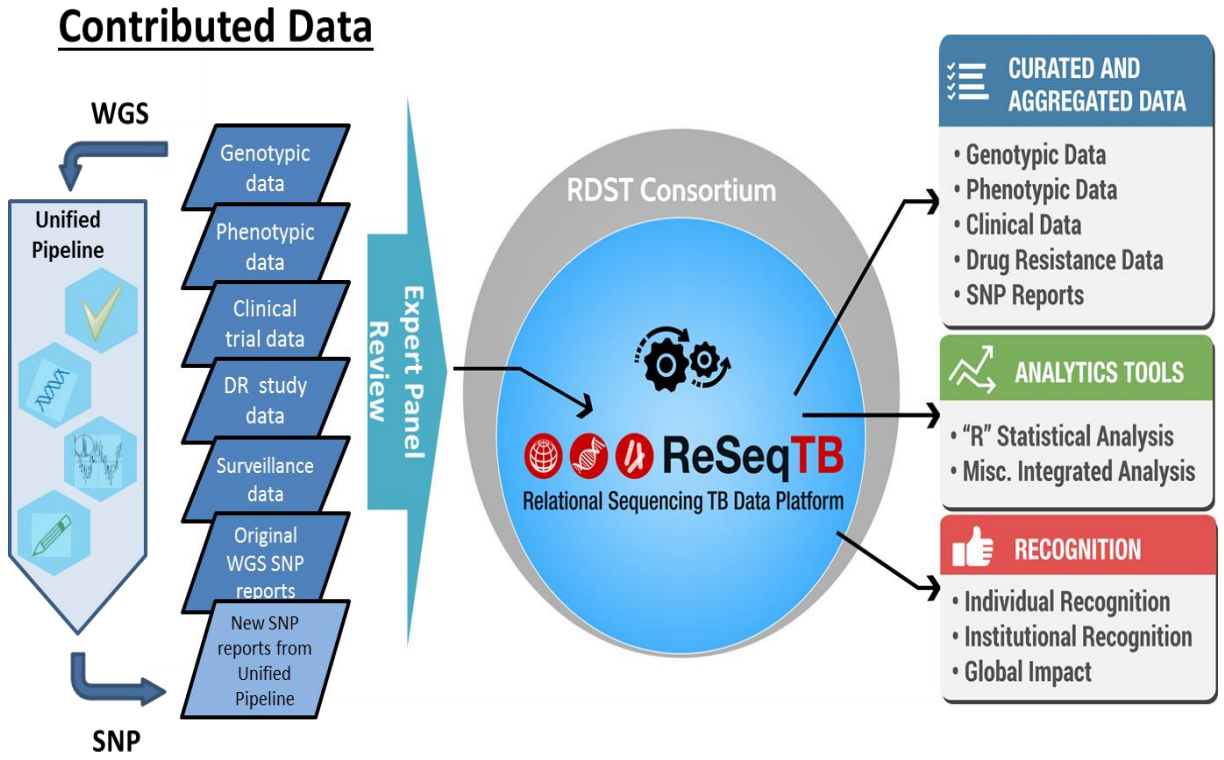


I491F not targeted by Xpert MTB/RIF
Not detected
Not treated=TRANSMITTED

LEGEND
Pink circle: strains harbouring rpoB I491F
Light blue circle: strains harbouring rpoB mutations other than I491F
Purple shadow: clustered strains (≤5 alleles)

ONGOING, UNPUBLISHED

Fast advancement in knowledge and standardization



ReSeqTB
Relational Sequencing TB Data Platform

ReSeqTB
Relational Sequencing TB Data Platform

Miotto et al ERJ 2017

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"mutations encyclopedia"

Drug (phenotypic testing)		Gene	High confidence mutations	Moderate confidence mutations	Minimal confidence mutations	No association with resistance
First-line	RIF	*rpoB*	D516A, D516F, D516G, D516G+L533P, D516ins, D516N, D516V, D626E, Del N518, F505V+D516Y, F514dupl, H526C, H526D, H526F, H526G, H526L, H526R, H526Y, M515I+D516Y, Q513-F514ins, Q513H+L533P, Q513K, Q513L, Q513P, S522Q, S531F, S531L, S531Q, S531W	D516Y, H526P, L533P, S522L	H526N, I572F, L511P	
	INH	*inhA-mabA*	g-102a^{G-NC}	c-15t		L68F, g-47c, t-80g, T4I
		katG	S315I, S315N, S315T, Pooled frameshifts and premature Stop codons			A110V, L499M, R463L
		mshA		A187V^{G-NC}		N111S
Second-line (group A)	MOX	*gyrA*	A90V, D94A, D94G, D94N, D94Y, G88C, S91P			E21Q, G247S, G668D, S95T, V712L
	OFX/LEV	*gyrA*	A90V, D94A, D94G, D94H, D94N, D94Y, G88A, G88C, S91P	D89N		E21Q, G247S, G668D, S95T, T80A, V712L
		gyrB	A504V, E459K			
Second-line (group B)	AMK	*rrs*	a1401g, g1484t			
	KAN	*eis*	c-14t, g-10a		c-12t, g-37t	a1338c
		rrs	a1401g, a514c^{NC}, c1402t, g1484t			
		rrs+eis	*rrs* c517t^{NC} + *eis* g-37t			
	CAP	*rrs*	a1401g, c1402t, g1484t			c517t
		tlyA	N236K, Pooled frameshifts and premature Stop codons			D149H
	STR	*rpsL*	K43G, K43R, K43T, K88Q, K88R, T40I			
		rrs	a1401g^{NC}, a514c, a514t, c462t, c513t, c517t			
		gidB		E92D^{G-NC}		L16R, V110G, Pooled frameshifts and premature Stop codons
Second-line (group C)	ETH/PTH	*inhA*	c-15t+I194T, c-15t+S49A	c-15t		
		ethA				Q347Stop
Second-line (group D)	PZA	*pncA*	a-11g, A134V, A3E, A46V, C138Y, C14R, C72R, D12A, D12N, D49G, D49N, D63G, D8E, D8G, D8N, F94L, F94S, G108R, G132A, G132D, G132S, G162D, G17D, G24D, G97C, G97D, G97S, H137P,	A171E, K96E, K96T, M175I, P54L, Q10R, W68G	D12G, F58L, H71R, I133T, V139A	I31T, I6L, indel - c-125del, K48T, L35R, T114M, T47A

Building the framework for standardized clinical laboratory reporting of next generation sequencing data for resistance-associated mutations in *Mycobacterium tuberculosis* complex

Jeffrey A. Tornheim,[1‡] Angela M. Starks,[2‡] Timothy C. Rodwell,[3,4] Jennifer L. Gardy,[5,6] Timothy M. Walker,[7] Daniela Maria Cirillo,[8] Lakshmi Jayashankar,[9] Paolo Miotto,[8] Matteo Zignol,[10] Marco Schito[11]

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2a. One-Page Report

Barcode XXXXXXXXXXXX

MYCOBACTERIUM TUBERCULOSIS SEQUENCING REPORT

Sample Details

Patient Name	JOHN DOE	Patient ID	12345678910
Birth Date	2000-JAN-01	Location	SOMEPLACE
Sample Type	SPUTUM	Sample Collection Date	2016-DEC-25
Sample Source	PULMONARY	Sequenced From	CULTURED ISOLATE (LJ)
Sample ID	A12345678	Sample Received Date/Time	2017-JAN-02, 12:22
Laboratory Technician	TECHNICIAN NAME	Report Date/Time	2017-JAN-05, 11:45
Requested By	REQUESTER NAME	Requester Contact	REQUESTER@EMAIL.COM

Assay Details

Sequencer	ILLUMINA HISEQ 2500	Method	WHOLE GENOME SEQUENCING
Pipeline	RESEQTBV.3.2C (https://platform.reseqtb.org)	Reference	H37RV (NC_000962.3)

Final Result

The sample was positive for ***Mycobacterium tuberculosis***.
It is **resistant to isoniazid, rifampin, capreomycin, kanamycin, ofloxacin, and moxifloxacin.**

Lineage

Mycobacterium tuberculosis, lineage 2.2.1 (**East-Asian Beijing**).

Drug Susceptibility

Resistance is reported when a high likelihood resistance-conferring mutation is detected in loci of interest.[1] **No mutation detected does not exclude the possibility of resistance.**

- ☐ No mutations detected
- ☐ Multi-drug resistance predicted
- ☑ **Extensive drug resistance predicted**

	Interpretation	Drug	Gene Target (Mutation, Allele %)	Comments
First Line	Resistant	Isoniazid	*katG* (Ser315Thr, 100%)	
		Rifampin	*rpoB* (Ser450Leu, 100%)	Rifabutin resistance likely
	Susceptible	Ethambutol		No mutation detected
		Pyrazinamide		***Expert consultation advised***
Second Line	Resistant	Capreomycin	*rrs* (C1402T, nucleotide 100%)	
		Kanamycin	*rrs* (C1402T, nucleotide 100%)	
		Moxifloxacin	*gyrA* (Ala90Val, 14%)	At least low-level resistance predicted
		Ofloxacin	*gyrA* (Ala90Val, 14%)	
	Susceptible	Amikacin		No mutation detected
		Ethionamide		No mutation detected
		Streptomycin		No mutation detected

Disclaimer

[1]Loci of interest derived from ReSeqTB Data Platform and from Miotto P, et al. Eur Respir J. 2017 PMID: 29284687
Low frequency hetero-resistance below the limit of detection by sequencing may affect typing results. The interpretation provided is based on the current understanding of genotype-phenotype relationships. All results reference the *M. tuberculosis* mutation numbering system which differs from the *E. coli* numbering system.

Authorized By

Name	AUTHORIZER NAME	Position	LAB SUPERVISOR
Signature		Date	2017-JAN-05
Reporting Laboratory	LAB NAME	LAB ADDRESS	LAB PHONE NUMBER

2b. Long Report Resistance Predictior

Resistance Predictions for First Line TB Drugs

Interpretation	Drug	Gene Target (Codon Change, Amino Acid Change, Allele %)	Confidence in Resistance Association	Comments
Resistant	Isoniazid	*katG* (G944C, Ser315Thr, 100%)	High	
		inhA		No mutation detected
		mshA		No mutation detected
	Rifampin	*rpoB* (C1349T, Ser450Leu, 100%)	High	Rifabutin resistance likely
Susceptible	Ethambutol	*embB*		No mutation detected
	Pyrazinamide	*pncA* (T416C, Val139Ala, 98%)	Minimal	Mutation known to disrupt enzymatic activity and functional genetics in vitro. Insufficient data to determine clinical impact of this mutation.

2c. Long Report NGS Statistics

Depth and Coverage Details

Locus of Interest[1]	# Reads Mapped (Depth of Coverage)	Proportion Covered (Coverage Width %)	*Mutation Frequency (% Alternate Allele)*
atpE	79	100	-
ddn	97	99.9	-
embB	88	98.8	-
fbiA	87	100	-
fbiB	91	100	-
fbiC	75	100	-
fgd1	88	100	-
gyrA	73	100	Ala90Val (13.6%*)
gyrB	76	100	-
inhA	91	100	-
katG	90	99.9	Ser315Thr (100%)
mmpR	62	100	G193Insertion (98.4%)
pncA	62	100	Val139Ala (98.4%)
rplC	78	99.9	Cys154Arg (97.4%)
rpoB	83	100	Ser450Leu (100%)
rrl	82	100	-
rrs	59	99.9	C1402T (96.6%)
tlyA	58	98.5	-

*Hetero-resistance is defined in this report as a proportion of reads for a given allele between 10% and 90%.

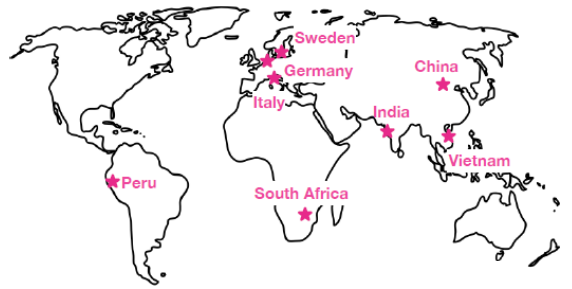
[1]Loci of interest derived from ReSeqTB Data Platform and from Miotto P, et al. Eur Respir J. 2017 PMID: 29284687

ReSeqTB
Relational Sequencing TB Data Platform

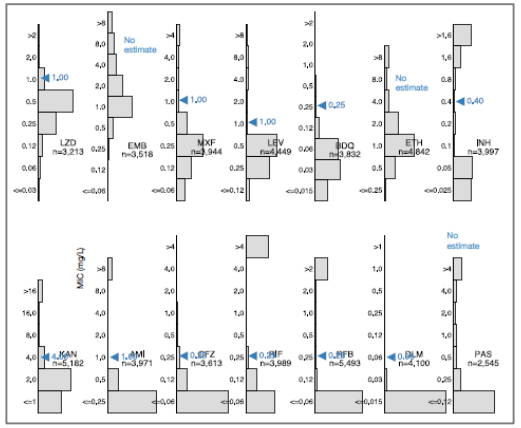
Comprehensive Resistance Prediction for Tuberculosis: an International Consortium (CRyPTIC) to speed up diagnosis of tuberculosis

CRyPTIC

CRyPTIC laboratories in this study



UKMYC6 plate design



ECOFF definition of individual drugs

Drug	Abbreviation	Tentative ECOFF
Isoniazid	INH	0.4 mg/L
Rifampicin	RIF	0.25 mg/L
Ethambutol	EMB	4 mg/L
Amikacin	AMI	1 mg/L
Kanamycin	KAN	4 mg/L
Moxifloxacin	MXF	1 mg/L
Levofloxacin	LEV	1 mg/L
Ethionamide	ETH	4 mg/L
Rifabutin	RFB	0.25 mg/L
Linezolid	LZD	1 mg/L
Clofazimine	CFZ	0.25 mg/L
Bedaquiline	BDQ	0.25 mg/L
Delamanid	DLM	0.06 mg/L
para-aminosalicylic acid	PAS	–

Rancoita P et al AAC 2018
Fowler et 2019 in preparation

Some *rpoB* mutants are associated to false-sensitive DST for rifampicin

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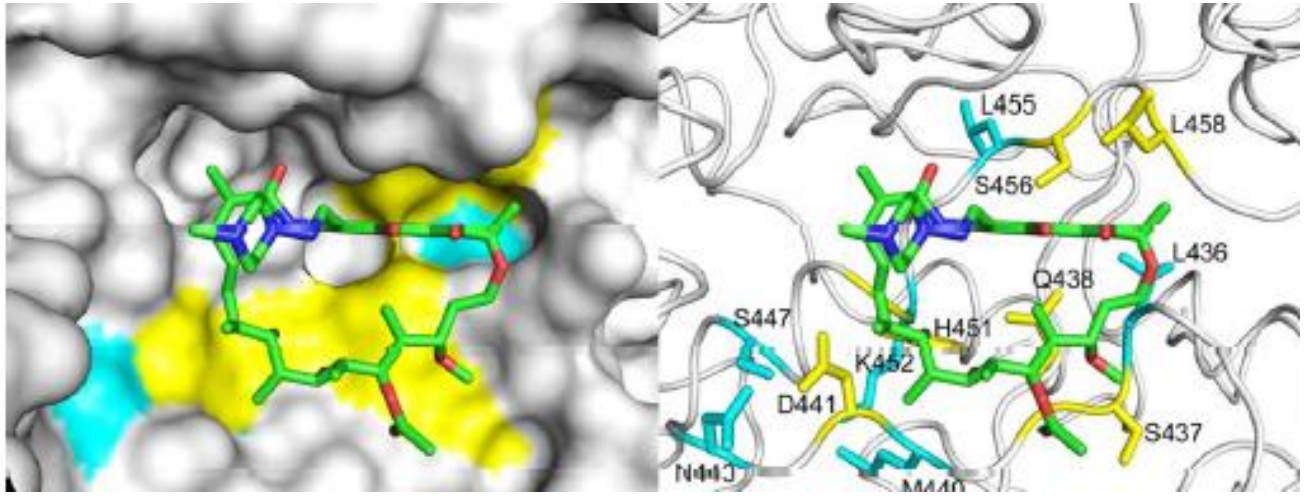
"Disputed mutations" cause DISCREPANT genotypic/phenotypic results



in silico analysis of the effect of disputed mutations on the structural interaction between the RpoB protein and rifampin

The binding affinity towards rifampin is affected

➢ Strains should be considered RESISTANT to rifampin

Miotto P, et al. J Clin Microbiol. 2018 Apr 25;56(5).

INH resistance is a heterogeneous phenotype

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➢ Possibility to use different isoniazid doses depending on the type of mutation detected

- If ***inh*A mutations** only are detected INH could be used; high doses are likely to be effective.
- If ***kat*G mutations** only are detected, use of high doses is an option.
  - ➢ Most *kat*G mutations (other than 315 codon) confer moderate resistance that might be treated with higher doses of INH; even the most common S315T variant leads to a variable range of resistance.
  - ➢ In the absence of additional mutations affecting the *inh*A gene (and *eth*A gene, so far uniquely detectable by sequencing approaches), ethionamide can be considered an option for the intensive phase of the shorter regimen.
- If ***inh*A + *kat*G mutations** are concurrently detected, INH drug use should be avoided, since these patterns are linked to high resistance levels.
- **Additional** mutations in ***katG*** and ***inhA*** not included in LPA increase MIC

Ghodousi A. *et al*. AAC 2019

WGS to predict sensitivity

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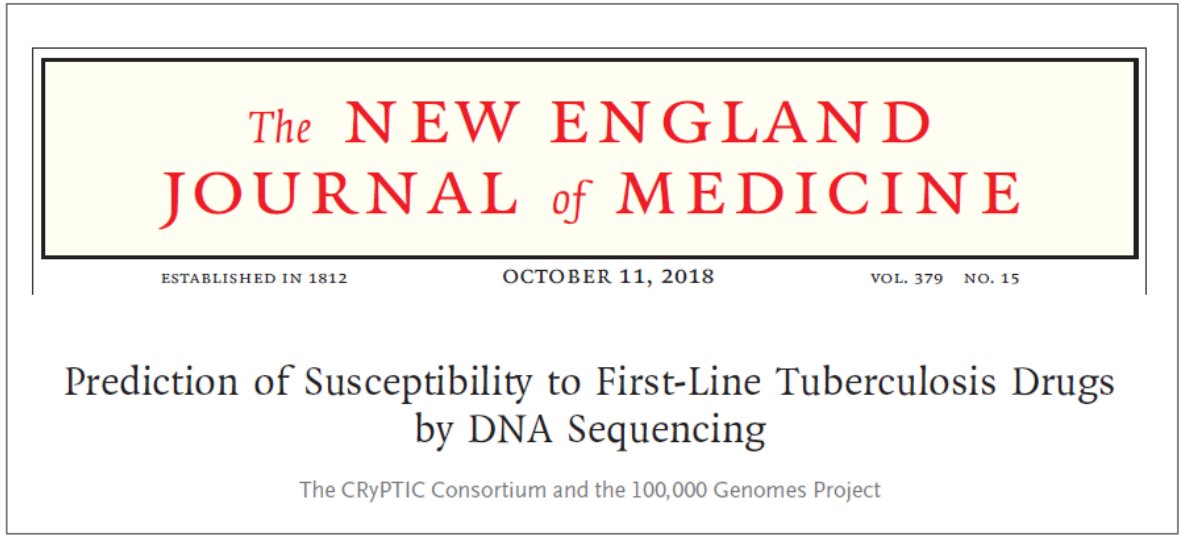


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 11, 2018 VOL. 379 NO. 15

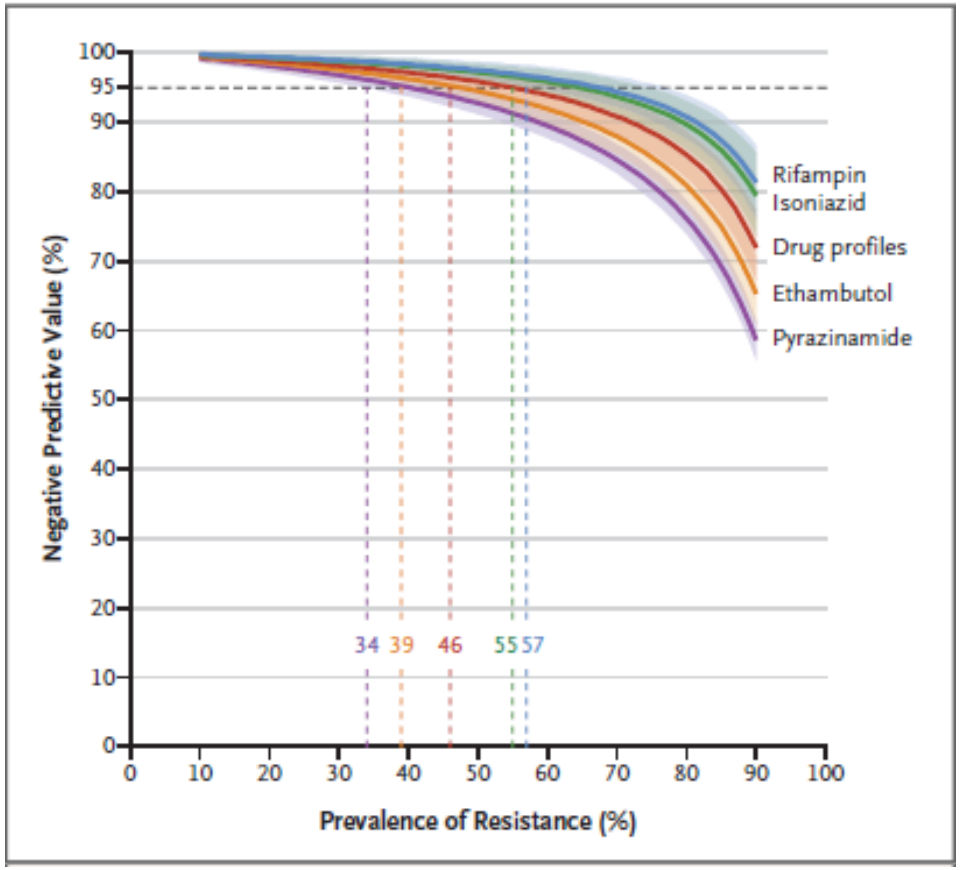
Prediction of Susceptibility to First-Line Tuberculosis Drugs by DNA Sequencing

The CRyPTIC Consortium and the 100,000 Genomes Project

Analysis of 10.209 MTB isolates
16 Countries, 6 continents
All major lineages represented

- Resistance to H, R, E, Z was correctly predicted with 97.1%, 97.5%, 94.6%, and 91.3% sensitivity,
- Susceptibility to these drugs was correctly predicted with 99.0%, 98.8%, 93.6%, and 96.8% specificity.
- 7516 isolates with complete phenotypic drug-susceptibility profiles, 5865 (78.0%) had complete genotypic predictions, among which 5250 profiles (89.5%) were correctly predicted.
- On the 4037 phenotypic profiles predicted to be pan-susceptible, 3952 (97.9%) were correctly predicted.

Simulated Negative Predictive Values for Individual Drugs and Complete Drug Profiles



Negative predictive values are shown for individual drugs and complete drug profiles, according to the simulated prevalence of resistance to each drug, or within each drug profile (any resistance).

- WGS can predict profiles of susceptibility to first-line anti-TB drugs with a degree of accuracy sufficient for clinical use

Bedaquiline resistance emerges under treatment

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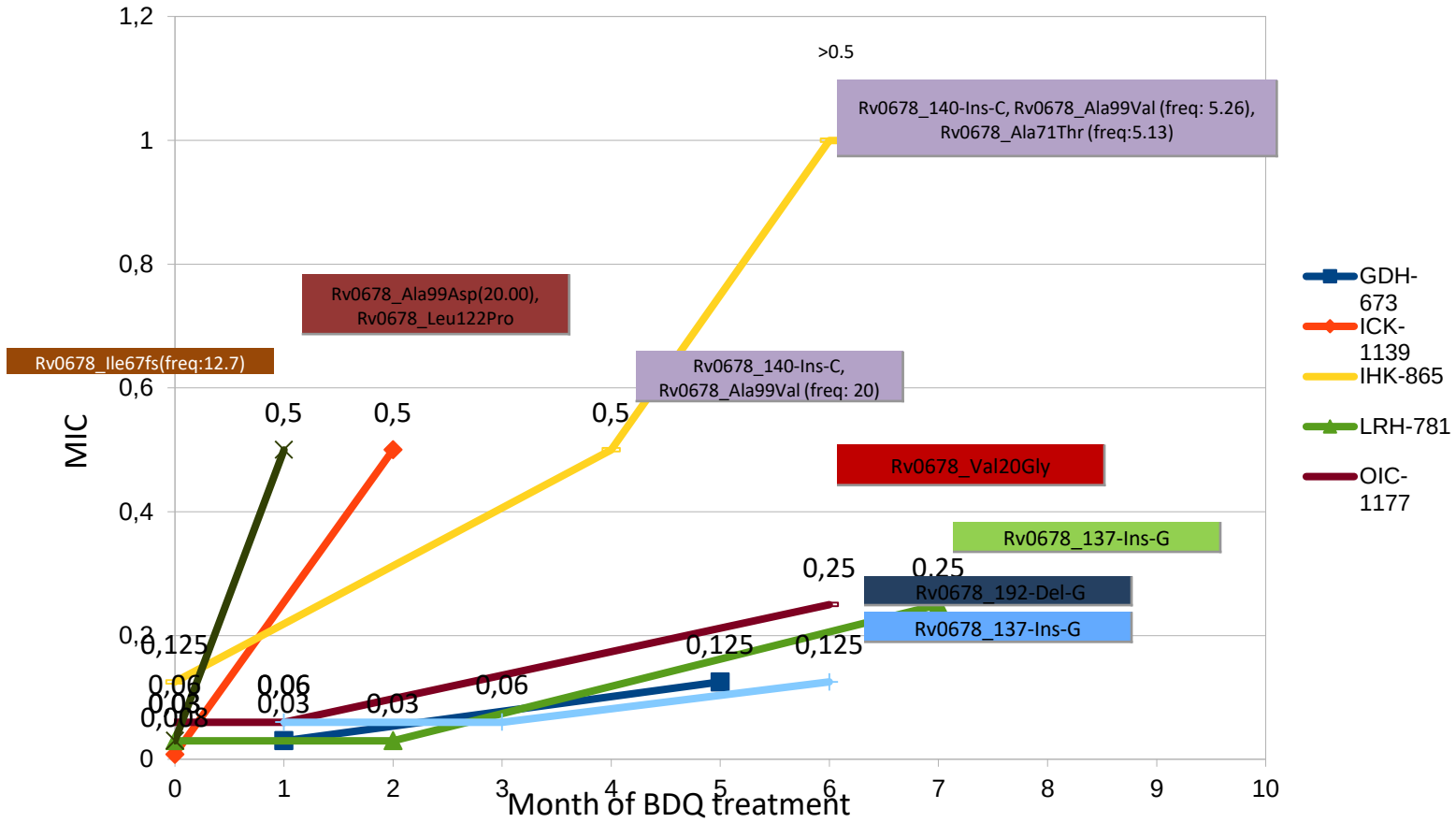

Drugs MICs distribution and correlation with mutations from Cryptic-Italy collection

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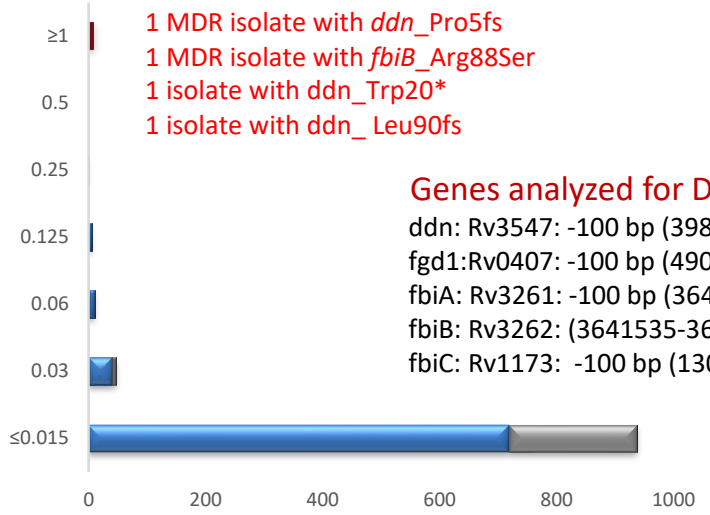
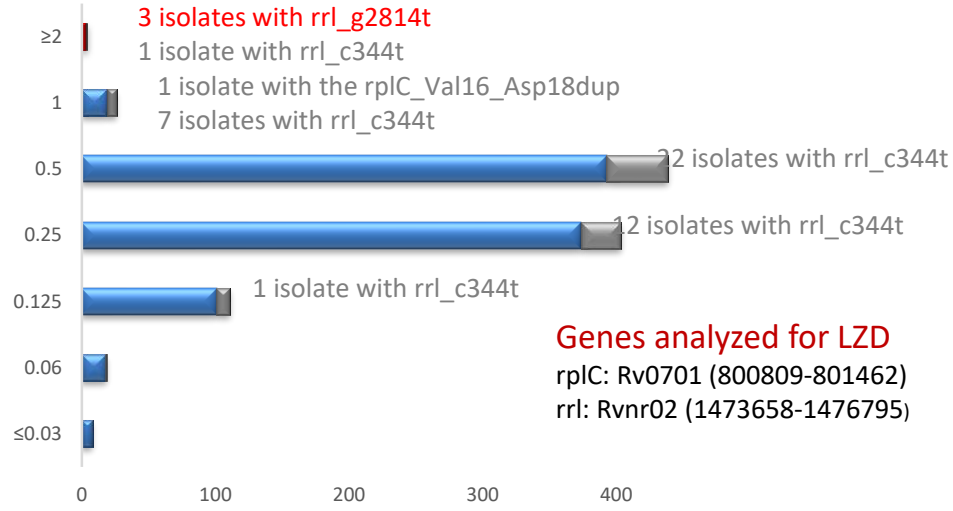
Delamanid



1 MDR isolate with *ddn*_Pro5fs
1 MDR isolate with *fbiB*_Arg88Ser
1 isolate with ddn_Trp20*
1 isolate with ddn_ Leu90fs

Genes analyzed for DLM
ddn: Rv3547: -100 bp (3986744- 3987299)
fgd1:Rv0407: -100 bp (490683-491793)
fbiA: Rv3261: -100 bp (3640443- 3641538)
fbiB: Rv3262: (3641535-3642881)
fbiC: Rv1173: -100 bp (1302831-1305501)

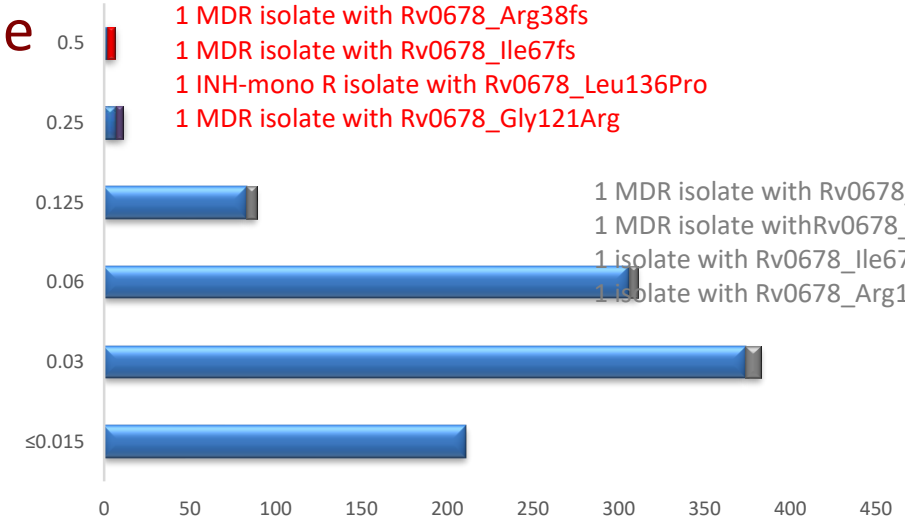
Linezolid



3 isolates with rrl_g2814t
1 isolate with rrl_c344t
1 isolate with the rplC_Val16_Asp18dup
7 isolates with rrl_c344t
22 isolates with rrl_c344t
12 isolates with rrl_c344t
1 isolate with rrl_c344t

Genes analyzed for LZD
rplC: Rv0701 (800809-801462)
rrl: Rvnr02 (1473658-1476795)

Bedaquiline



1 MDR isolate with Rv0678_Arg38fs
1 MDR isolate with Rv0678_Ile67fs
1 INH-mono R isolate with Rv0678_Leu136Pro
1 MDR isolate with Rv0678_Gly121Arg
1 MDR isolate with Rv0678_Leu117Arg
1 MDR isolate withRv0678_c.-14G>A
1 isolate with Rv0678_Ile67fs
1 isolate with Rv0678_Arg134Gly

Genes analyzed for BDQ
Rv0678: -100 bp (778890-779487)
atpE: Rv1305 (1461045-1461290)
pepQ: Rv2535c: +100 bp (2859300-2860518)

Targeted Next Generation Sequencing on ONT device

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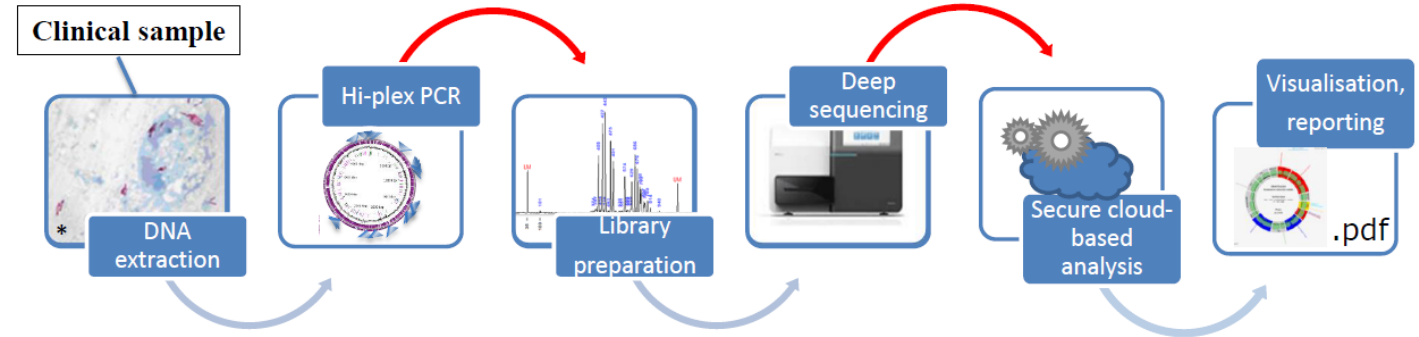
Deeplex-MycTB (Genoscreen): hi-plex amplification of main TB drug resistance targets (1st and 2nd line plus LZD and BDQ/CFZ) plus mycobacterial species identification (*hsp65*) and MTBC genotyping targets (spoligotyping + phylo SNPs)

GenoScreen



SCIENTIFIC REPORTS

OPEN

Culture and Next-generation sequencing-based drug susceptibility testing unveil high levels of drug-resistant-TB in Djibouti: results from the first national survey

Received: 14 July 2017
Accepted: 29 November 2017
Published online: 15 December 2017

Elisa Tagliani[1], Mohamed Osman Hassan[2], Yacine Waberi[2], Maria Rosaria De Filippo[1], Dennis Falzon[3], Anna Dean[3], Matteo Zignol[3], Philip Supply[3], Mohamed Ali Abdoulkader[2], Hawa Hassangue[4] & Daniela Maria Cirillo[1]

Portable, real-time device

MinION (Oxford Nanopore Technologies) is a portable and real-time device for DNA and RNA sequencing

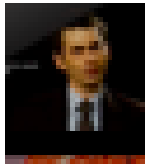
Oxford NANOPORE Technologies

American Society for Microbiology | Journal of Clinical Microbiology

Same-Day Diagnostic and Surveillance Data for Tuberculosis via Whole-Genome Sequencing of Direct Respiratory Samples

Antonina A. Votintseva,[a] Phelim Bradley,[b] Louise Pankhurst,[a] Carlos del Ojo Elias,[b] Matthew Loose,[c] Kayzad Nilgiriwala,[d] Anirvan Chatterjee,[d] E. Grace Smith,[a,e] Nicolas Sanderson,[a] Timothy M. Walker,[a] Marcus R. Morgan,[a] David H. Wyllie,[a,f,h] A. Sarah Walker,[a,i] Tim E. A. Peto,[a,i] Derrick W. Crook,[a,f,h] Zamin Iqbal,[b]

Training and technology transfer



Emerging Bacterial Pathogens Unit

OSPEDALE SAN RAFFAELE

Background

We provide training to strengthen tuberculosis national laboratory networks and to support operational research

Since 2013

On-site Capacity building

Trained >300 TB HCW in 20 different countries

Milan Capacity Building

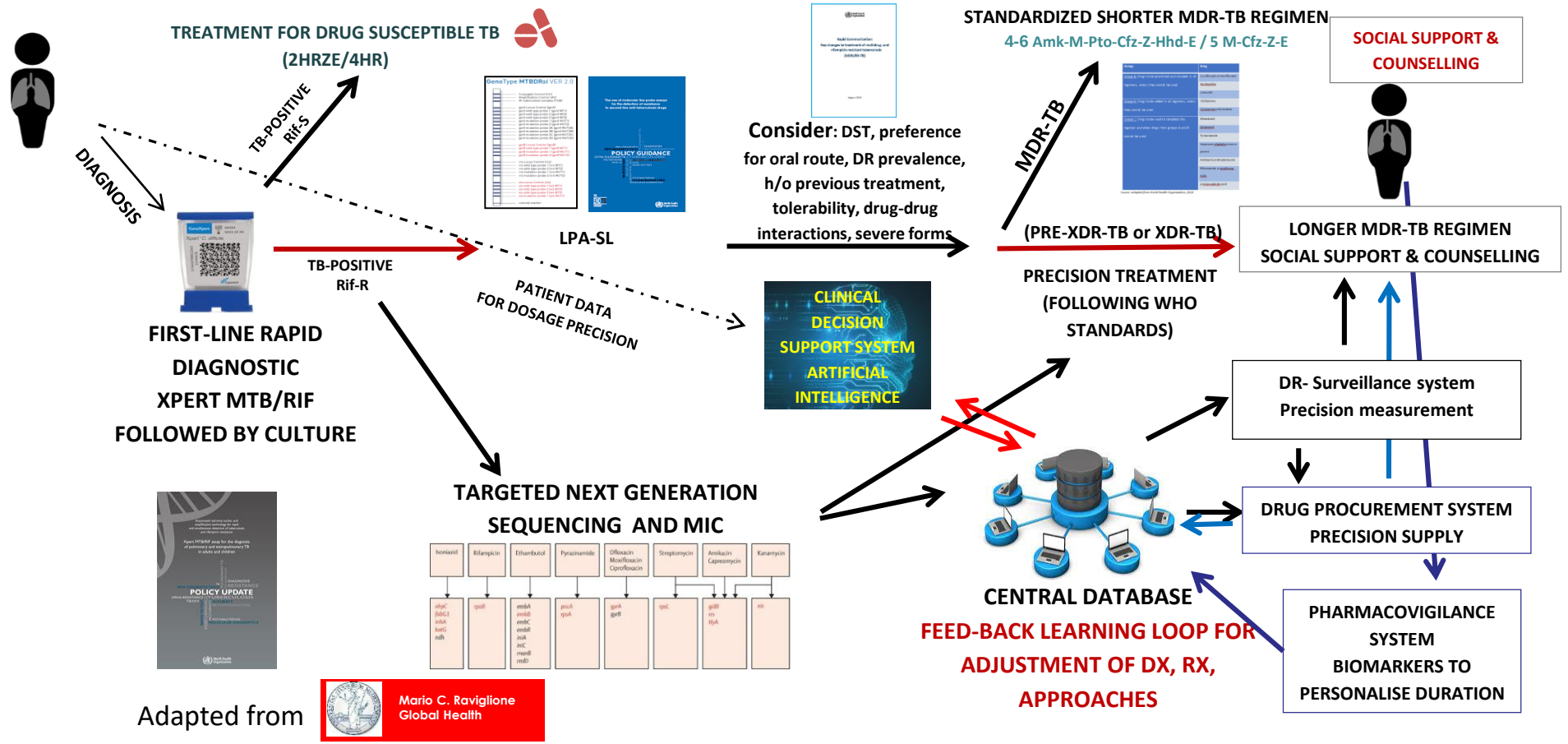
> 200 TB specialists over 26 countries in America, Africa, Asia and Europe

mid/long-term goals

- to support the implementation of genomic platforms to provide diagnostic of DR TB in hubs in Africa and Asia
- To provide tech transfer
- to explore the possibility to be involved in AMR in LIC

Precision global health in the management of TB
Merging precise individual care and large-scale programmatic functions

Emerging Bacterial Pathogens Unit
OSPEDALE SAN RAFFAELE



Thank you!