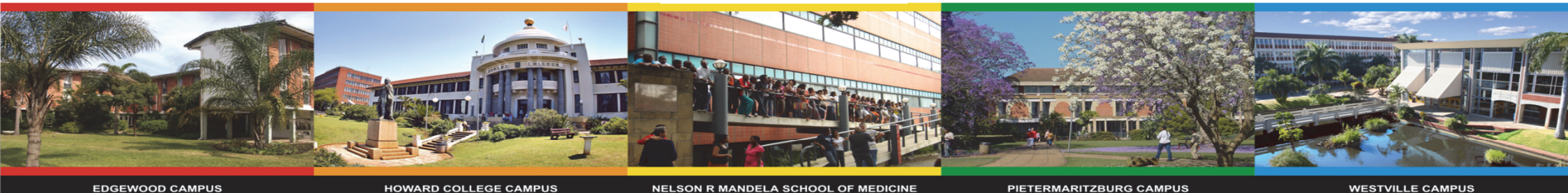




Big challenges in TB drug resistance

Richard Lessells

SAHCS Conference 2018



EDGEWOOD CAMPUS

HOWARD COLLEGE CAMPUS

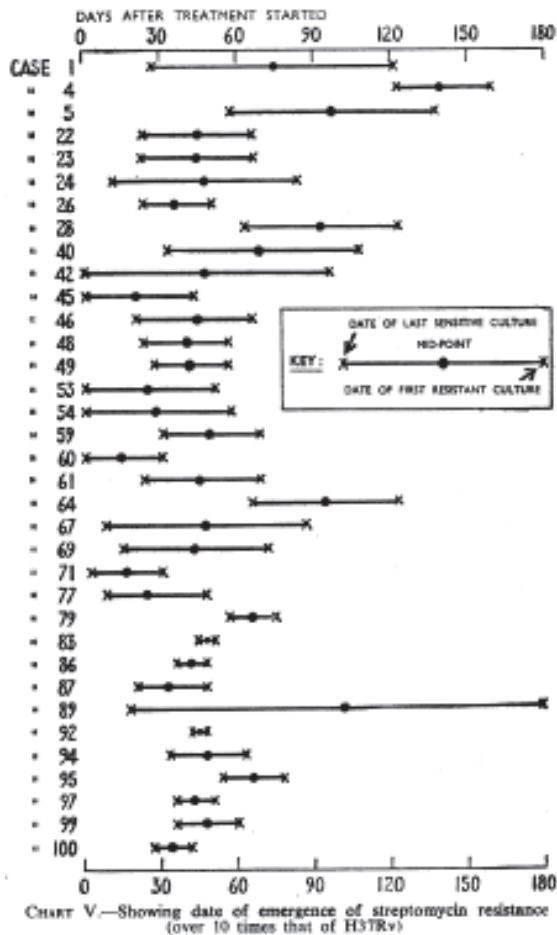
NELSON R MANDELA SCHOOL OF MEDICINE

PIETERMARITZBURG CAMPUS

WESTVILLE CAMPUS

UKZN INSPIRING GREATNESS

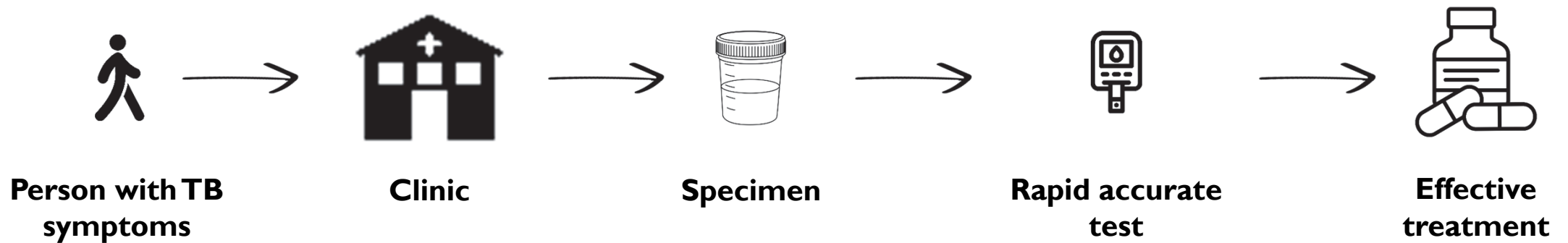
History of TB drug resistance



- UK MRC streptomycin trial 1947
- Resistance developed early with streptomycin monotherapy (median 45 days) and associated with poorer outcome
- Resistance developed less frequently if combined streptomycin with INH ± PAS
- Concept of combination anti-TB therapy born

UK MRC BMJ 1948

What do we need?



Ideally we want this to happen within a single clinical encounter

SA TB drug resistance survey 2012-2014

KwaZulu-Natal, new cases



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SA TB drug resistance survey

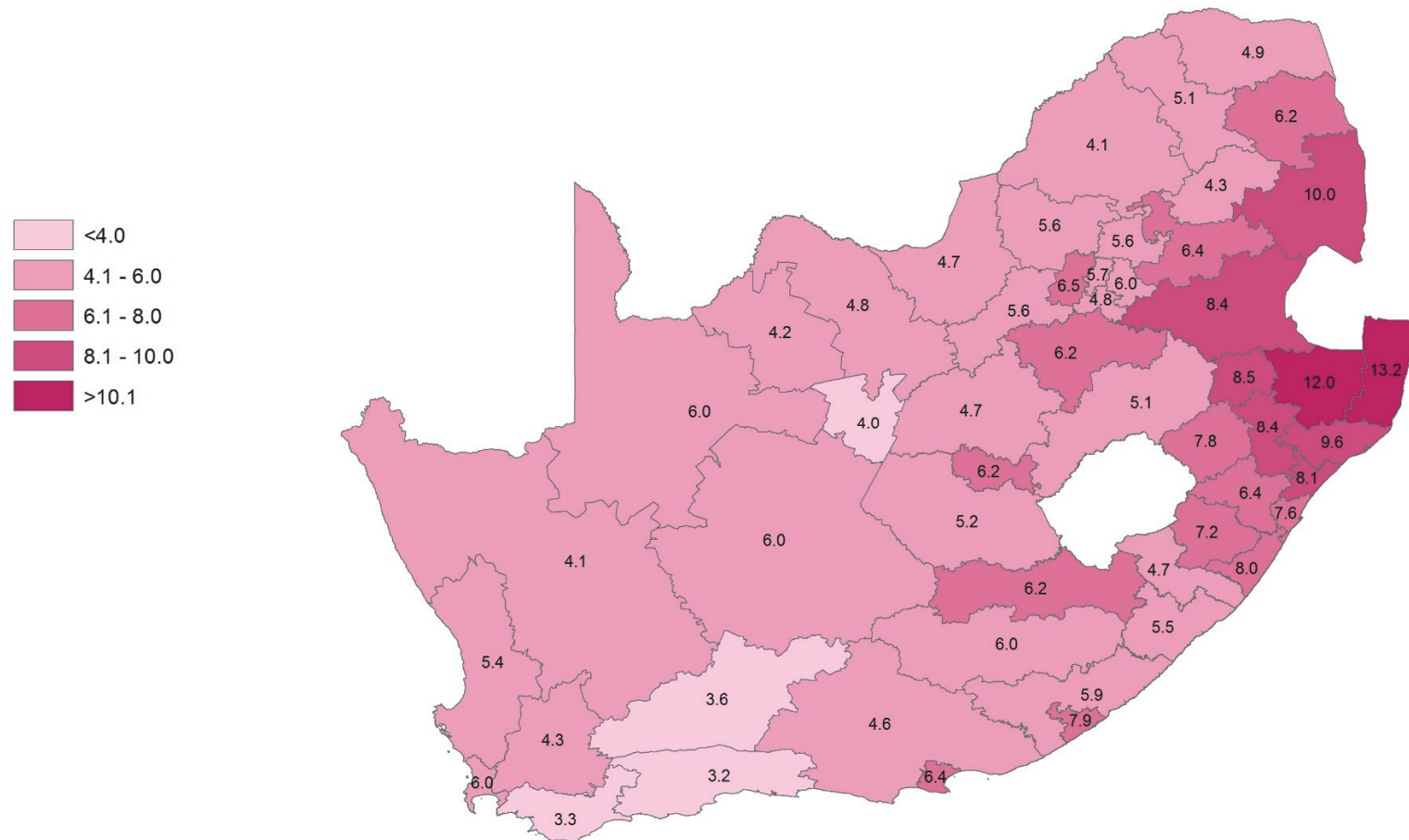
KwaZulu-Natal, previously treated cases



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Heterogeneity of drug-resistant TB epidemic

Proportion of positive Xpert tests with rifampicin resistance, 2014



District Health Barometer

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What do we mean by TB drug resistance?



Clinical resistance: failure to respond to a particular drug

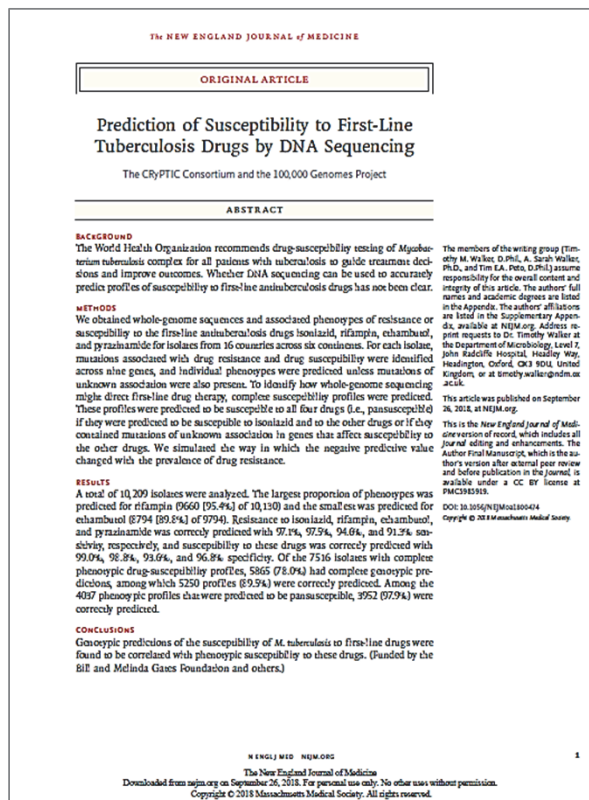


Phenotypic resistance: lack of inhibition of *M. tuberculosis* growth by a critical concentration of a specific drug



Genotypic resistance: presence of genetic mutation(s) known to be associated with drug resistance

Understanding genotypic-phenotypic correlation



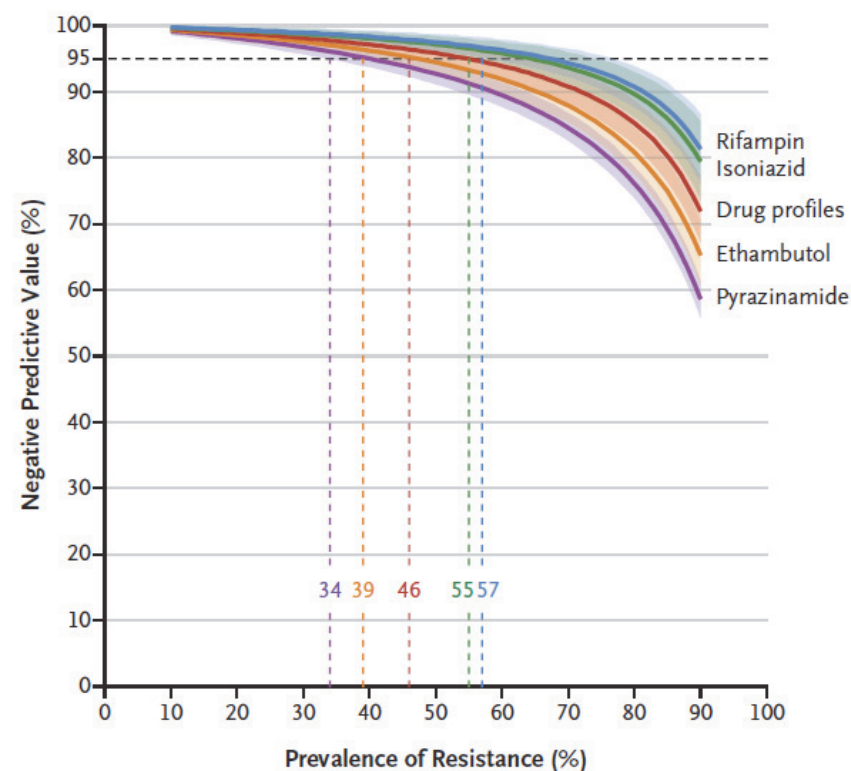
- International collaboration (CRyPTIC)
- 10 209 isolates analysed (37% drug resistance)
- ~12% of isolates from South Africa or eSwatini
- Compared whole genome sequence data to phenotypic DST (MGIT, solid culture, or MODS)

CRyPTIC NEJM 2018

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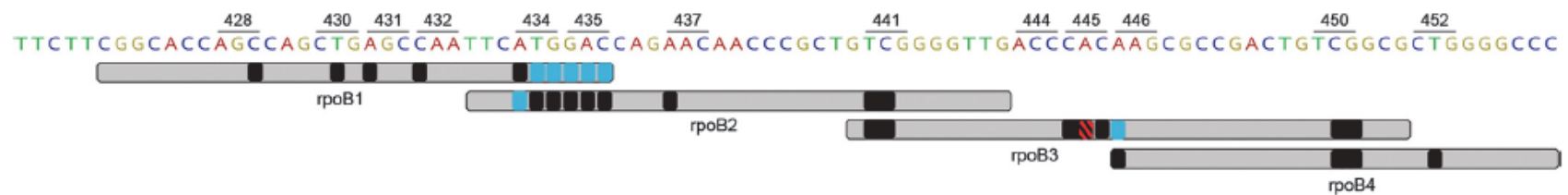
Understanding genotypic-phenotypic correlation

Drug	Prediction of resistance (sensitivity)	Prediction of susceptibility (specificity)
Isoniazid	97.1%	99.0%
Rifampicin	97.5%	98.8%
Ethambutol	94.6%	93.6%
Pyrazinamide	91.3%	96.8%



CRyPTIC NEJM 2018

Do we have the tools we need to detect drug resistance?



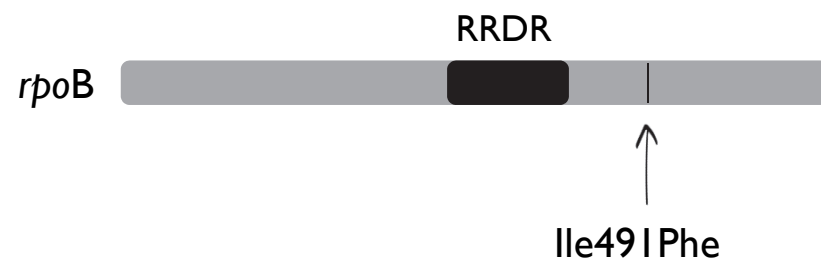
- Xpert Ultra detects mutations in rifampicin resistance-determining region (RRDR) of *rpoB* gene
- Line probe assay (MTBDR*plus*) also targets same region of *rpoB* gene

Do we have the tools we need to detect drug resistance?

Outbreak of multidrug-resistant tuberculosis in South Africa
undetected by WHO-endorsed commercial tests:
an observational study



Ndlovuho A.Makhado, Edith Matabane, Mauro Faccin, Claire Pinçon, Agathe Jouet, Fatrouz Boutachkout, Léonie Gominne, Cyril Gaudin, Gugu Maphahlela, Patrick Bekert, Stefan Niemann, Jean-Charles Delvenne, Michel Delmée, Lufuno Razwiedani, Maphashane Nichabeleng, Philip Supply*, Bouke C de Jong*, Emmanuel André*



- Mutation outside RRDR first identified in eSwatini DRS 2009
- Screened 249 rifampicin-susceptible, isoniazid-resistant isolates from four provinces South Africa (GP, NW, LP, MP)
- 37/249 (15%) had Ile49I Phe mutation
- Phylogenetic analysis suggested spread from eSwatini into South Africa

Makhado Lancet ID 2018

SA TB drug resistance survey 2012-2014

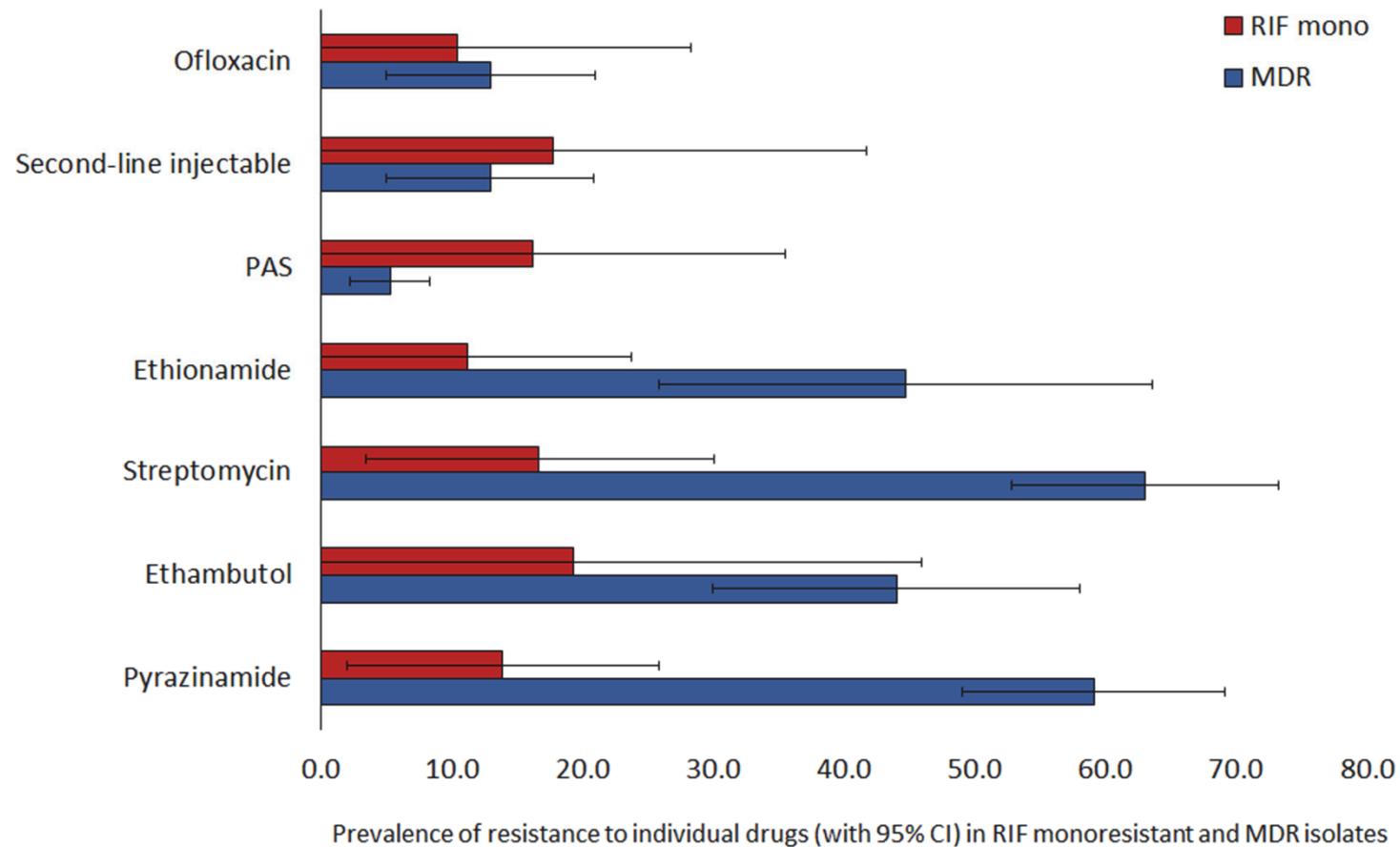
KwaZulu-Natal, new cases



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SA TB drug resistance survey 2012-2014

Resistance to other drugs amongst rifampicin-resistant isolates



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New DR-TB treatment regimen

Does our molecular diagnostic algorithm predict susceptibility/resistance to these drugs?

BDQ – LZD – INHhd – LFX – CFZ – Z - E

x

x

✓

✓

x

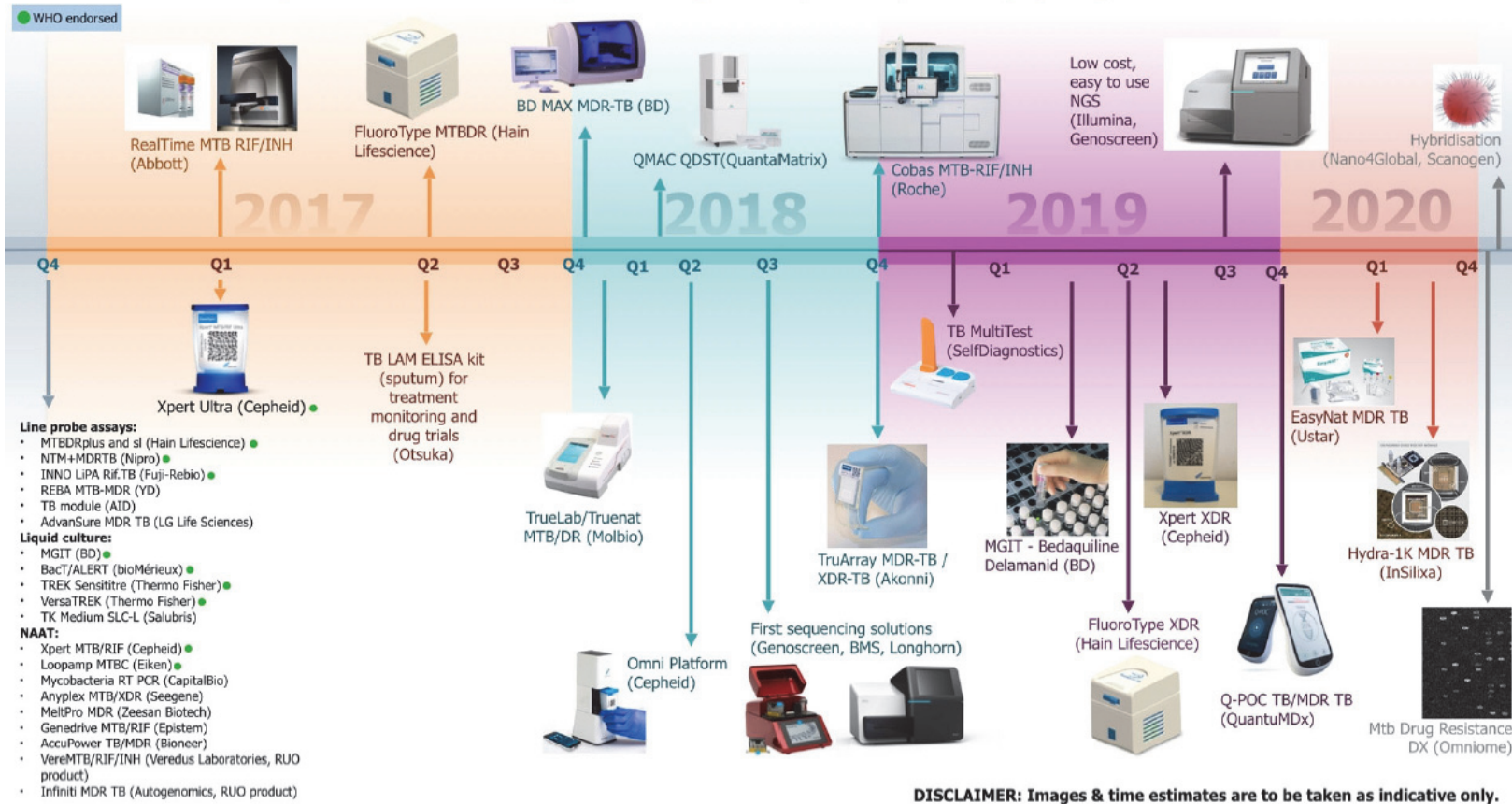
x

x

- Highlights need to better align diagnostic development with advances in treatment strategies

TB diagnostics pipeline

Diversification of sputum-based testing and drug susceptibility testing (DST)

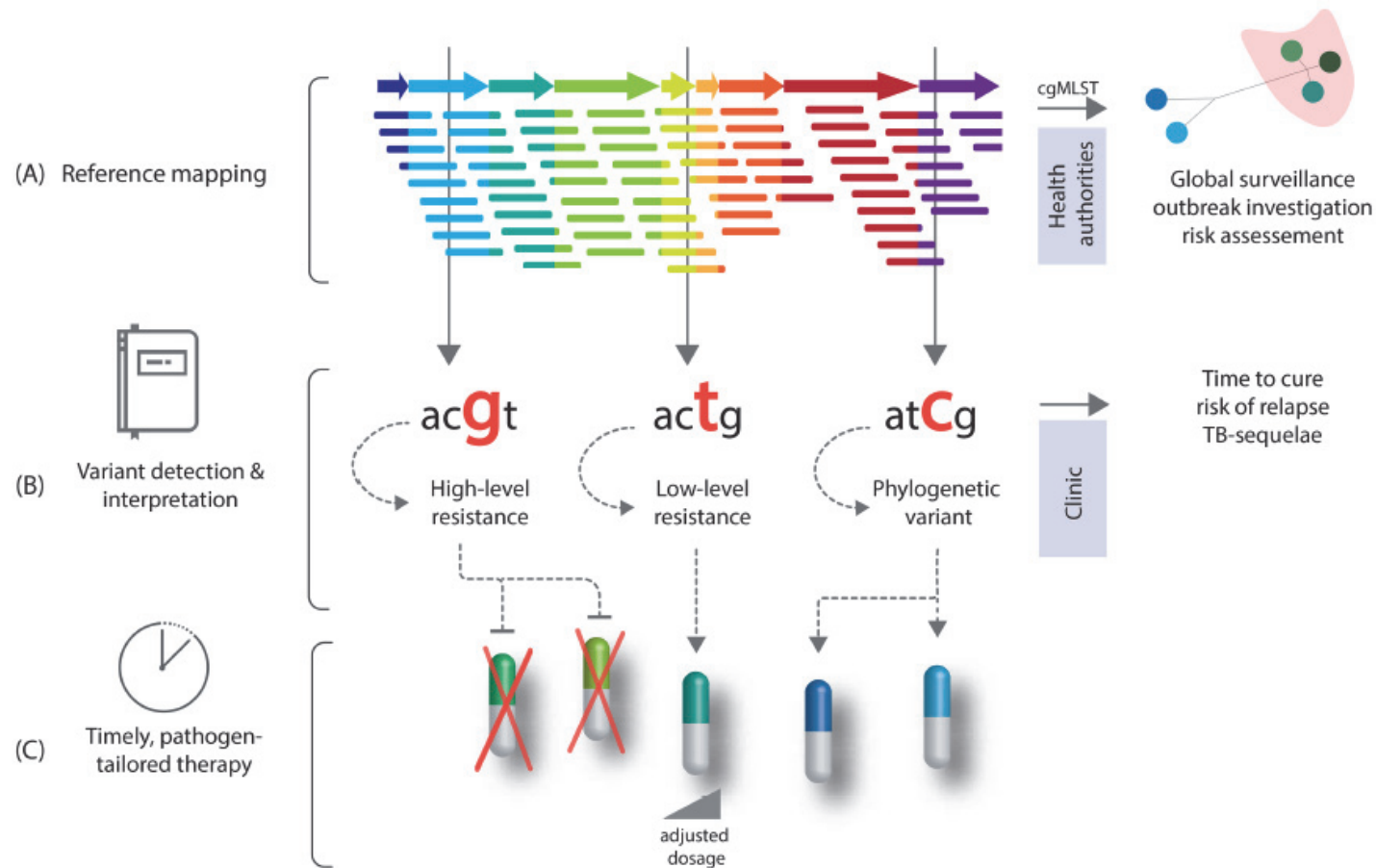


Is whole genome sequencing the answer?



- Fast moving field – rapid developments in sequencing technology
- Major technical challenge for TB remains difficulty of sequencing directly from sputum
- Broader challenge is incomplete understanding of genotype-phenotype-outcome correlation

Is whole genome sequencing the answer?



Groschel PLoS Pathogens 2018

Is whole genome sequencing the answer?

The Individualized M(X) Drug-resistant TB Treatment Strategy Study (InDEX)



The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. [Know the risks and potential benefits](#) of clinical studies and talk to your health care provider before participating. Read our [disclaimer](#) for details.

ClinicalTrials.gov Identifier: NCT03237182

Recruitment Status **●**: Recruiting

First Posted **●**: August 2, 2017

Last Update Posted **●**: September 6, 2018

See [Contacts and Locations](#)

Sponsor:

Centre for the AIDS Programme of Research in South Africa

Information provided by (Responsible Party):

Dr Nesri **Padayatchi**, Centre for the AIDS Programme of Research in South Africa

InDEX trial (CAPRISA) – RCT comparing routine diagnostics plus whole genome sequencing to routine diagnostics alone for rifampicin-resistant TB in KwaZulu-Natal

Summary

- We currently lack effective tools to detect all forms of drug-resistant TB relevant to our context
- Diagnostic development needs to be better aligned with the advances in DR-TB treatment
- Whole genome sequencing may have a role but several challenges exist to bringing this into routine health care