Using *Mycobacterium tuberculosis* single nucleotide polymorphisms to predict fluoroquinolone treatment response

Marva Seifert, Edmund Capparelli, Donald Catanzaro, Timothy Rodwell

TB International Workshop On Clinical Pharmacology of Tuberculosis Drugs
The Hague, Netherlands October 23, 2018

A TB Patient Dies Every 18 Seconds

By the end of this talk ~50 more TB patients will have died

Introduction

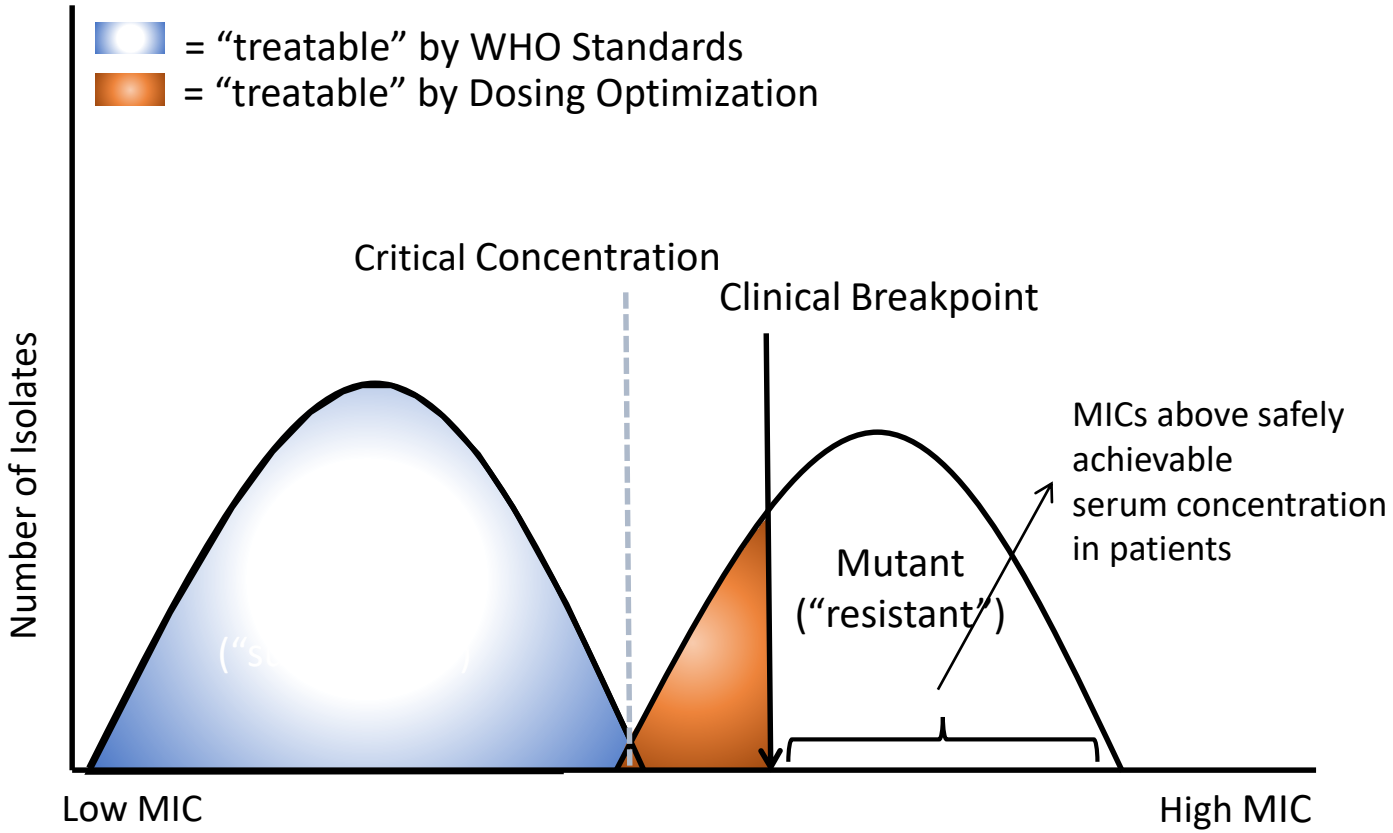
- TB treatment success rates
  - 82% for all TB
  - 55% for MDR-TB (2016 cohort)
  - 34 % for XDR-TB (2015 cohort)

- Options for improvement of treatment success rates
  - Novel therapies
  - Optimize current treatment

Global Tuberculosis Report 2018. Geneva: World Health Organization, 2018.

Optimizing Current Treatment

- Based on phenotypic/genotypic resistance detection
- Critical Concentration vs. clinical breakpoint
- Lost opportunity to optimize dosing



Global Tuberculosis Report 2018. Geneva: World Health Organization, 2018.

Goals of Study

Proof of Concept

- Mtb mutations can predict Fluoroquinolone MICs
- Predicted MICs can be combined with population-level PK/PD modeling to provide insights into individual dosing decisions

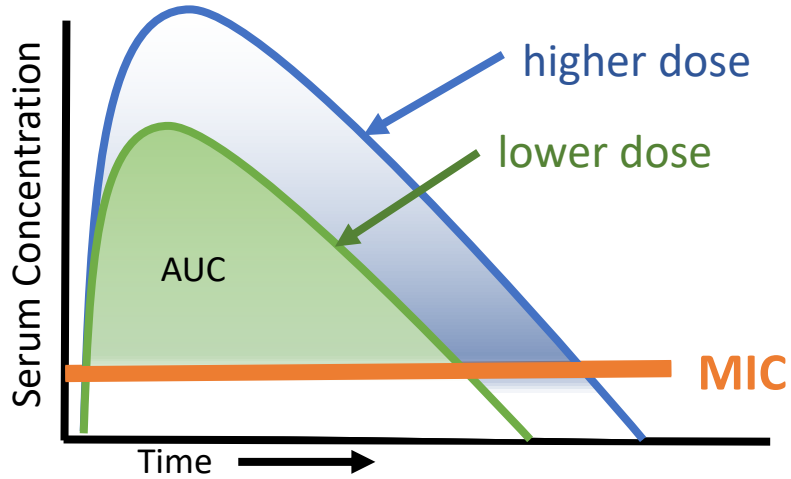
Methods: Isolate selection and categorization

- Clinical isolate selection
  - Archived clinical isolates from repositories in Mumbai (India), Chisinau (Moldova), Manila (Philippines) South Africa
  - Isolates were sequenced at gyrA using Pyrosequencing, Sanger, or PacBio whole genome sequencing
  - Randomly selected up to 20 isolates with the following *gyrA* SNPs: 88TCG, 90GTG, 91CCG, 94GGC, 94GCC, 94AAC, 94TAC, 94CAC, as well as *gyrA* wild types
- Isolate processing (n=138)
  - Cultured isolates and did DST with serial dilutions GFX, MFX, LFX, and OFX (~5 dilutions above critical concentration and ~3 dilutions below)
- SNP categorization into high or low MICs
  - SNPs grouped by MIC modes (wildtype, low resistance, and high resistance)
  - Differentiation was demonstrated statistically (Kruskal-Wallis test, Dunn's test)

Rodwell TC, Valafar F, Douglas J, et al. Predicting extensively drug-resistant Mycobacterium tuberculosis phenotypes with genetic mutations. Journal of clinical microbiology 2014; 52(3): 781-9.
Hillery N, Groessl EJ, Trollip A, et al. The Global Consortium for Drug-resistant Tuberculosis Diagnostics (GCDD): design of a multi-site, head-to-head study of three rapid tests to detect extensively drug-resistant tuberculosis. Trials 2014; 15: 434.

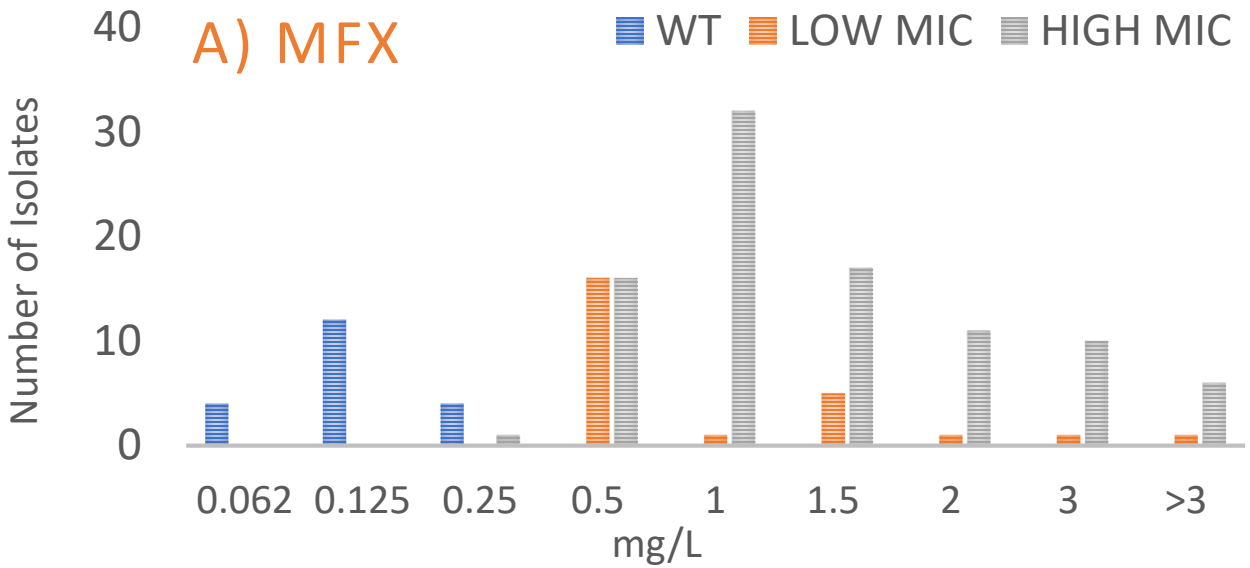
Methods: Population PK/PD modeling

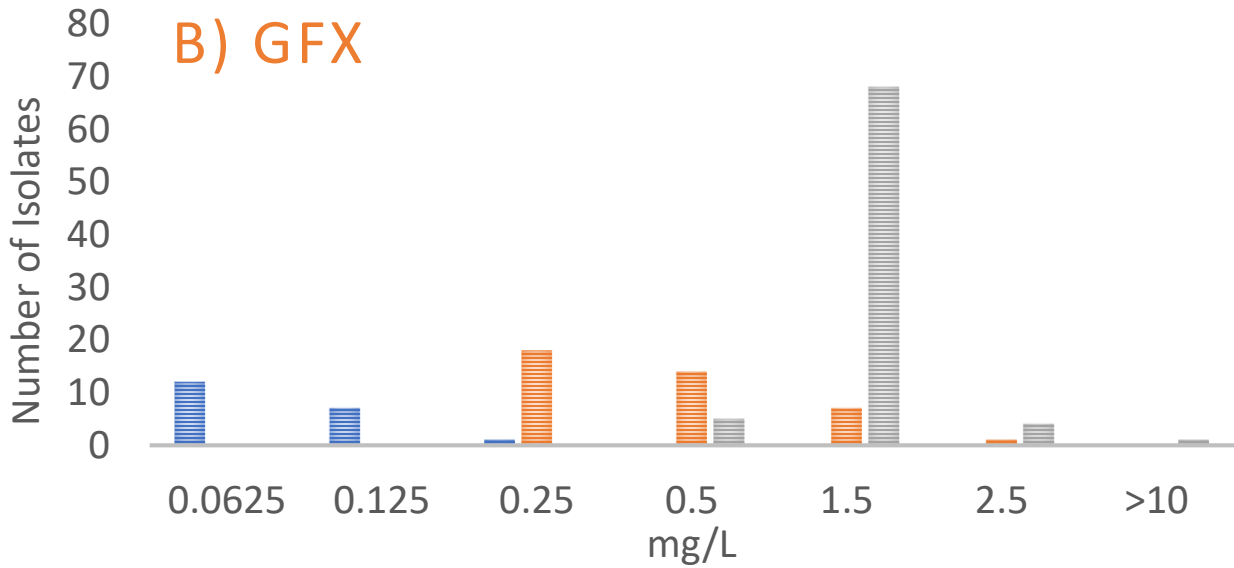
- 10,000 patients were simulated using NONMEM
  - AUC (for each FQ) calculated based on virtual subjects PK parameters and standard PK equations (AUC=bioavailability*dose/clearance)
- Probability of AUC/MIC target attainment
  - Simulated using SAS 9.4 & published population PK/PD models for each FQ, linked (randomly) to SNP estimated MIC distributions
  - FQ AUC/MIC targets based on published literature

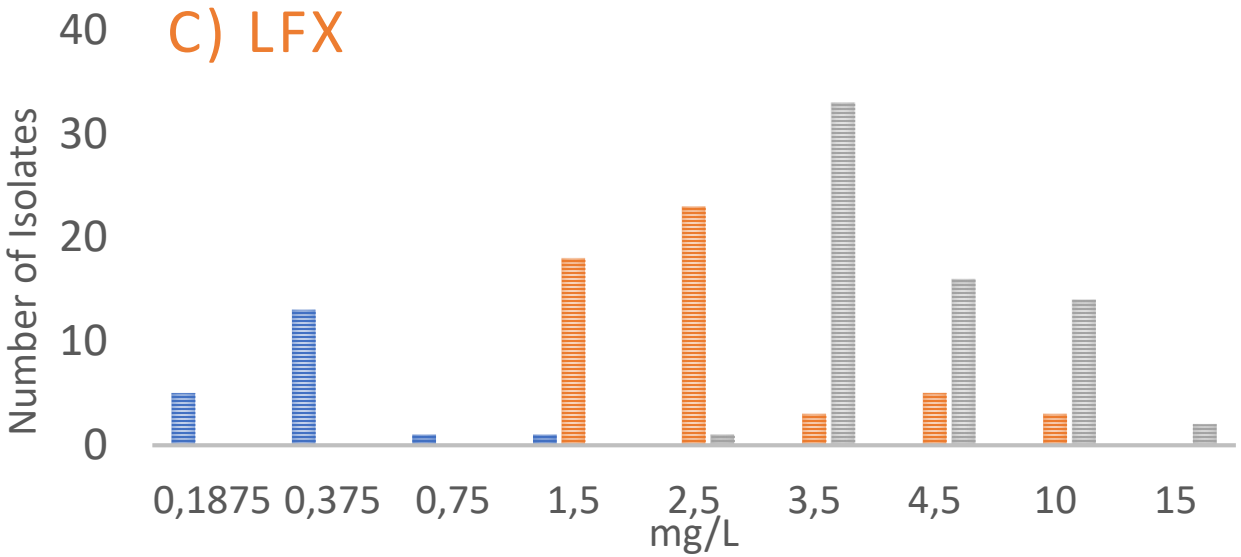


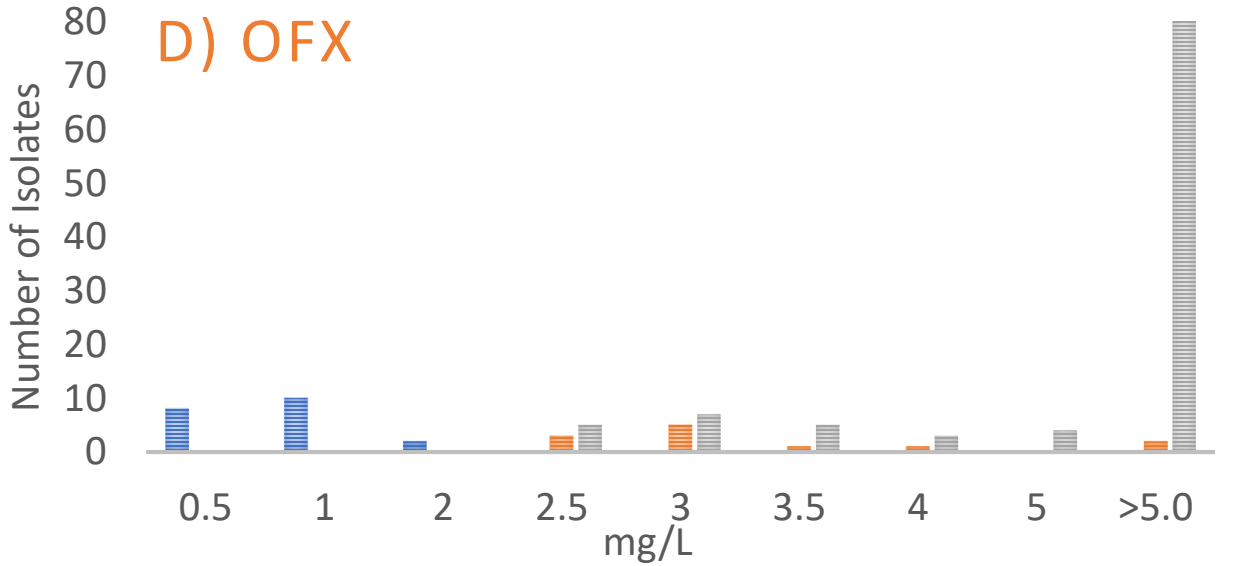
Peloquin CA, Hadad DJ, Molino LP, et al. Population pharmacokinetics of levofloxacin, gatifloxacin, and moxifloxacin in adults with pulmonary tuberculosis. Antimicrobial agents and chemotherapy 2008; 52(3): 852-7.
Zvada SP, Denti P, Sirgel FA, et al. Moxifloxacin population pharmacokinetics and model-based comparison of efficacy between moxifloxacin and ofloxacin in African patients. Antimicrobial agents and chemotherapy 2014; 58(1): 503-10.
Smythe W, Merle CS, Rustomjee R, et al. Evaluation of initial and steady-state gatifloxacin pharmacokinetics and dose in pulmonary tuberculosis patients by using monte carlo simulations.
Chigutsa E, Meredith S, Wiesner L, et al. Population pharmacokinetics and pharmacodynamics of ofloxacin in South African patients with multidrug-resistant tuberculosis. Antimicrobial agents and chemotherapy 2012; 56(7): 3857-63.

Results: SNPs categorized as high or low level resistance

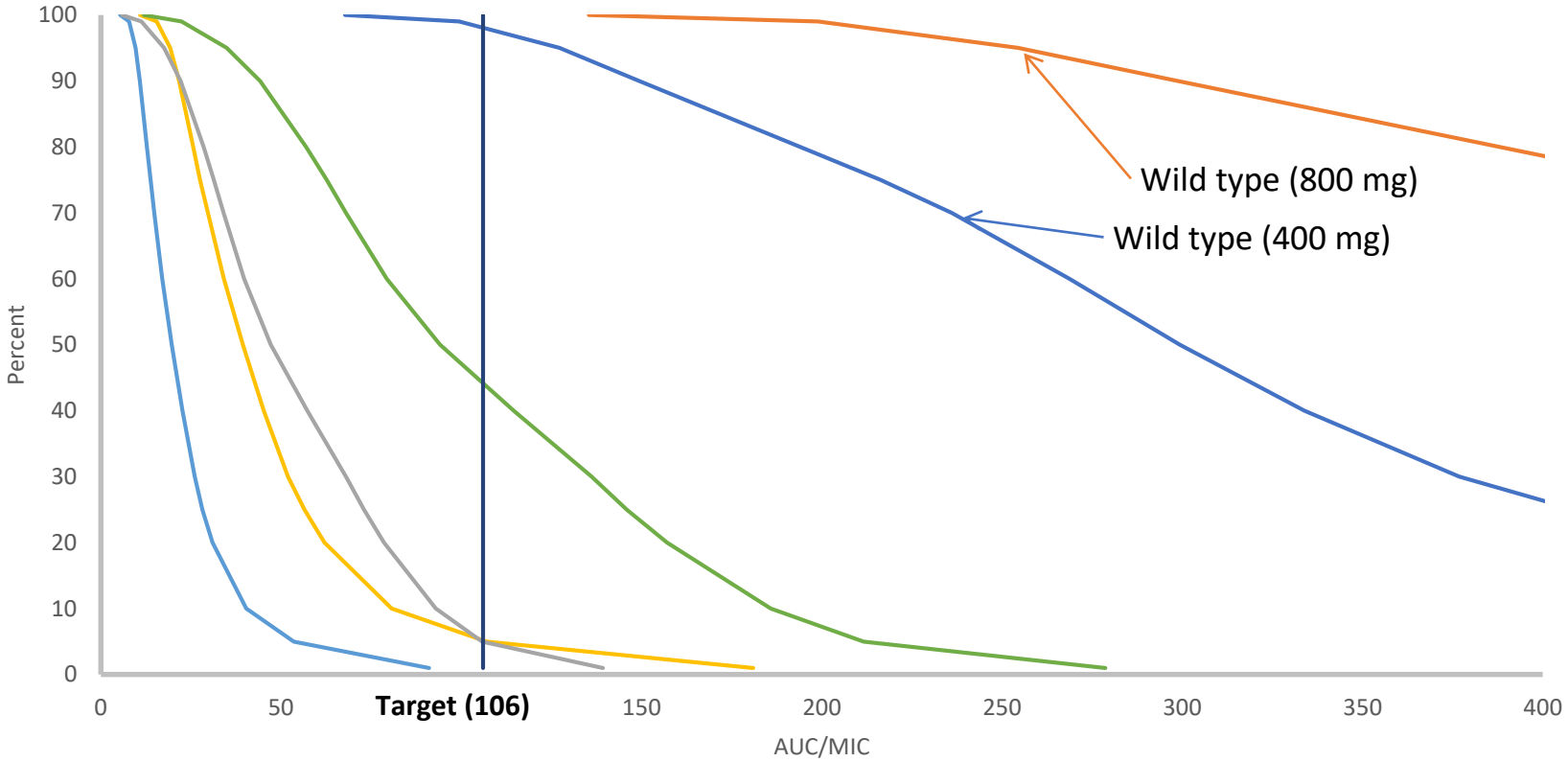






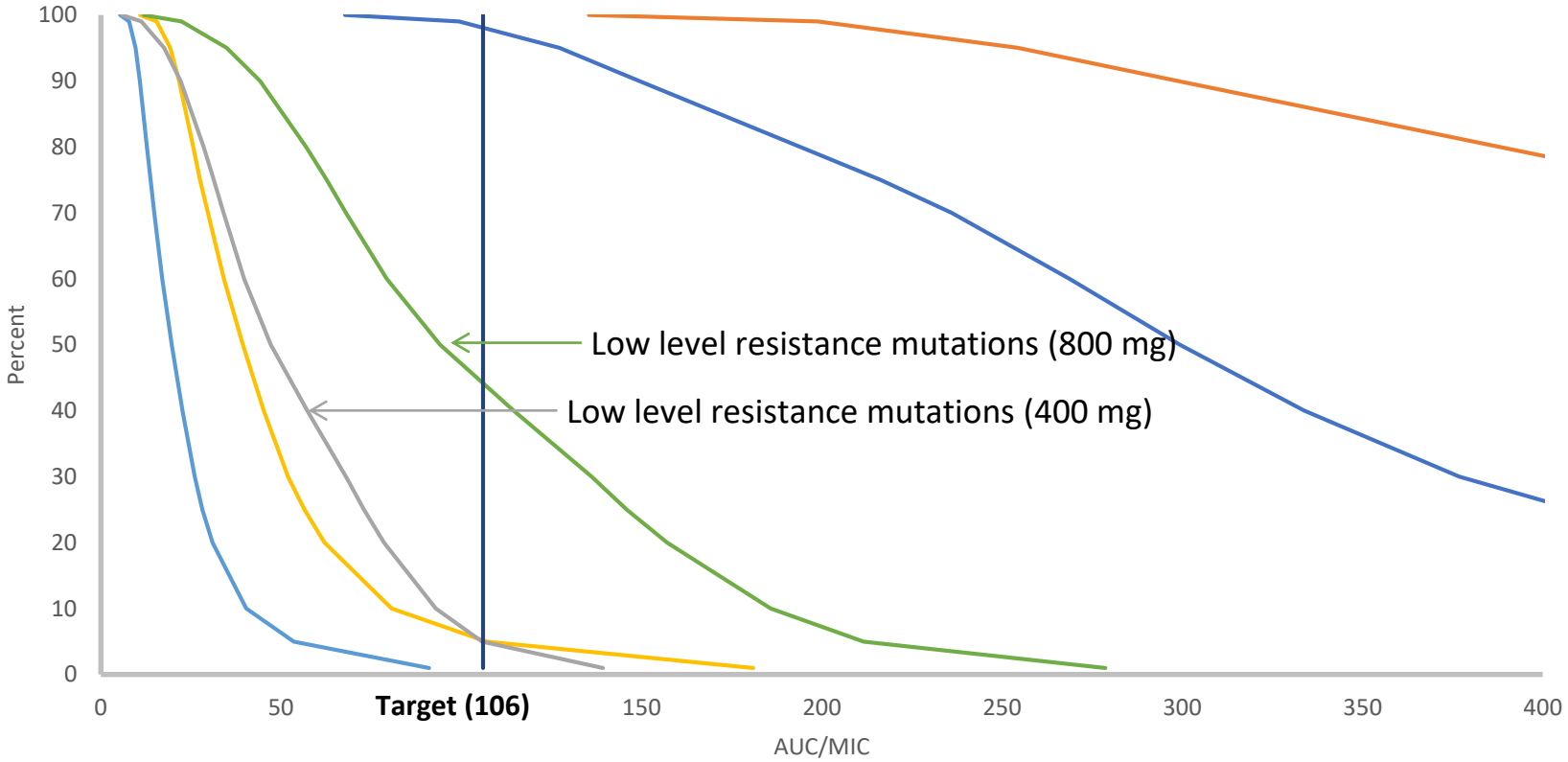


Cumulative distribution plots of proportion of population likely to reach defined therapeutic targets for MFX



Gumbo T, Louie A, Deziel MR, Parsons LM, Salfinger M, Drusano GL. Selection of a moxifloxacin dose that suppresses drug resistance in Mycobacterium tuberculosis, by use of an in vitro pharmacodynamic infection model and mathematical modeling. The Journal of infectious diseases 2004; 190(9): 1642-51.
Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis.; 2014.

Cumulative distribution plots of proportion of population likely to reach defined therapeutic targets for MFX



MFX (target 106)

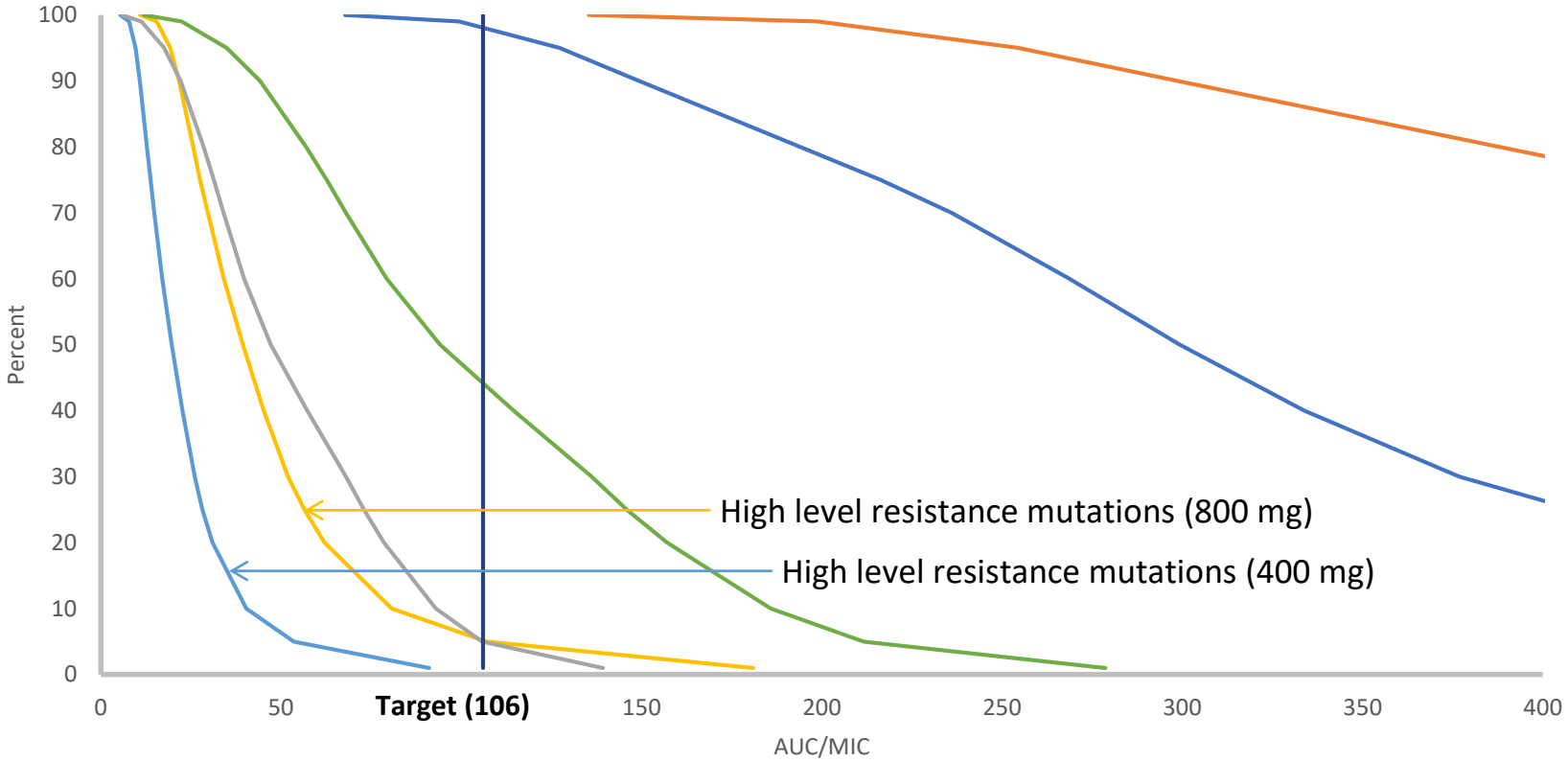
5% of low MIC pop @ 400 mg/day

44% of low MIC pop @ 800 mg/day

Gumbo T, Louie A, Deziel MR, Parsons LM, Salfinger M, Drusano GL. Selection of a moxifloxacin dose that suppresses drug resistance in Mycobacterium tuberculosis, by use of an in vitro pharmacodynamic infection model and mathematical modeling. The Journal of infectious diseases 2004; 190(9): 1642-51.

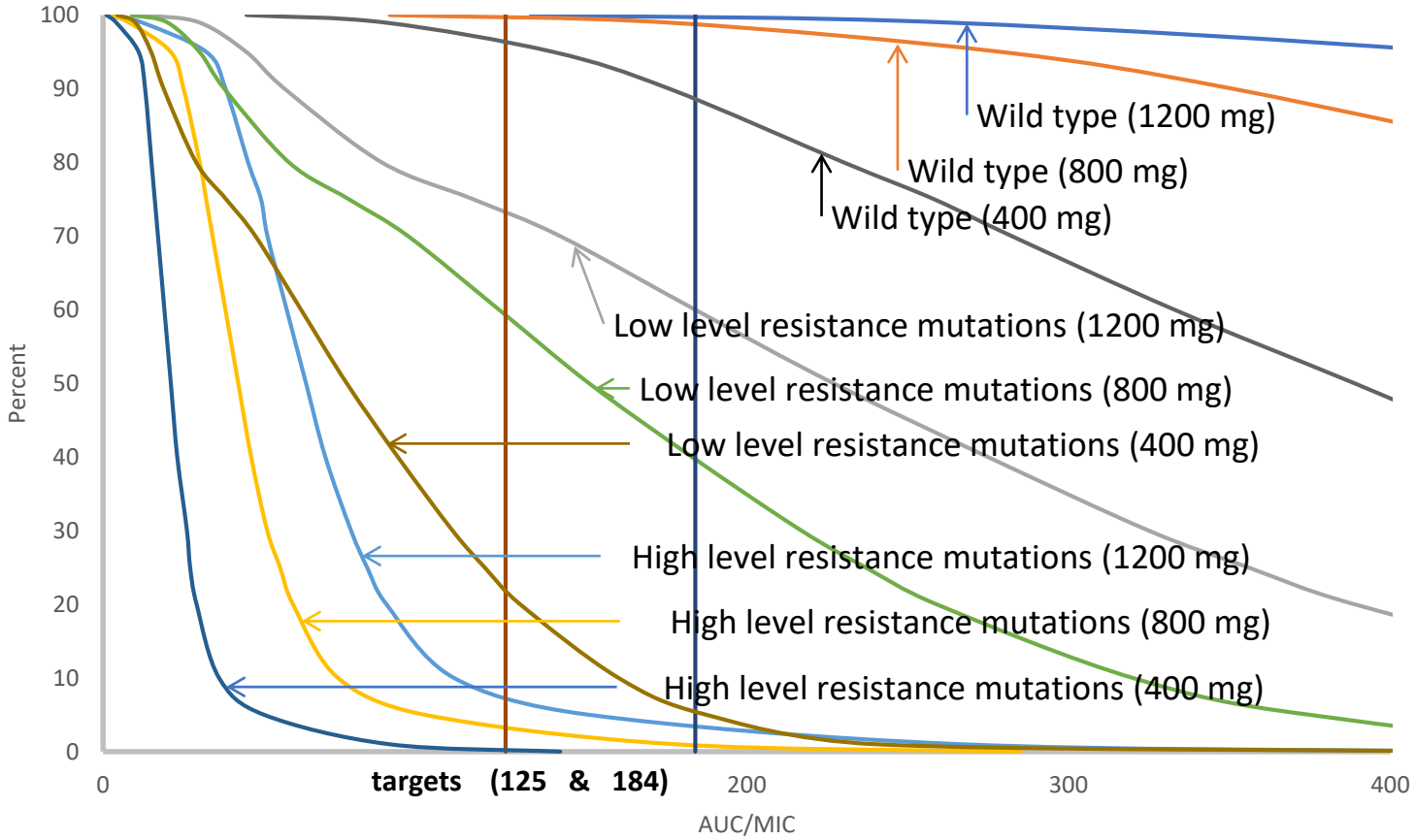
Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis.; 2014.

Cumulative distribution plots of proportion of population likely to reach defined therapeutic targets for MFX



Gumbo T, Louie A, Deziel MR, Parsons LM, Salfinger M, Drusano GL. Selection of a moxifloxacin dose that suppresses drug resistance in Mycobacterium tuberculosis, by use of an in vitro pharmacodynamic infection model and mathematical modeling. The Journal of infectious diseases 2004; 190(9): 1642-51.
Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis.; 2014.

Cumulative distribution plots of proportion of population likely to reach defined therapeutic targets for GFX

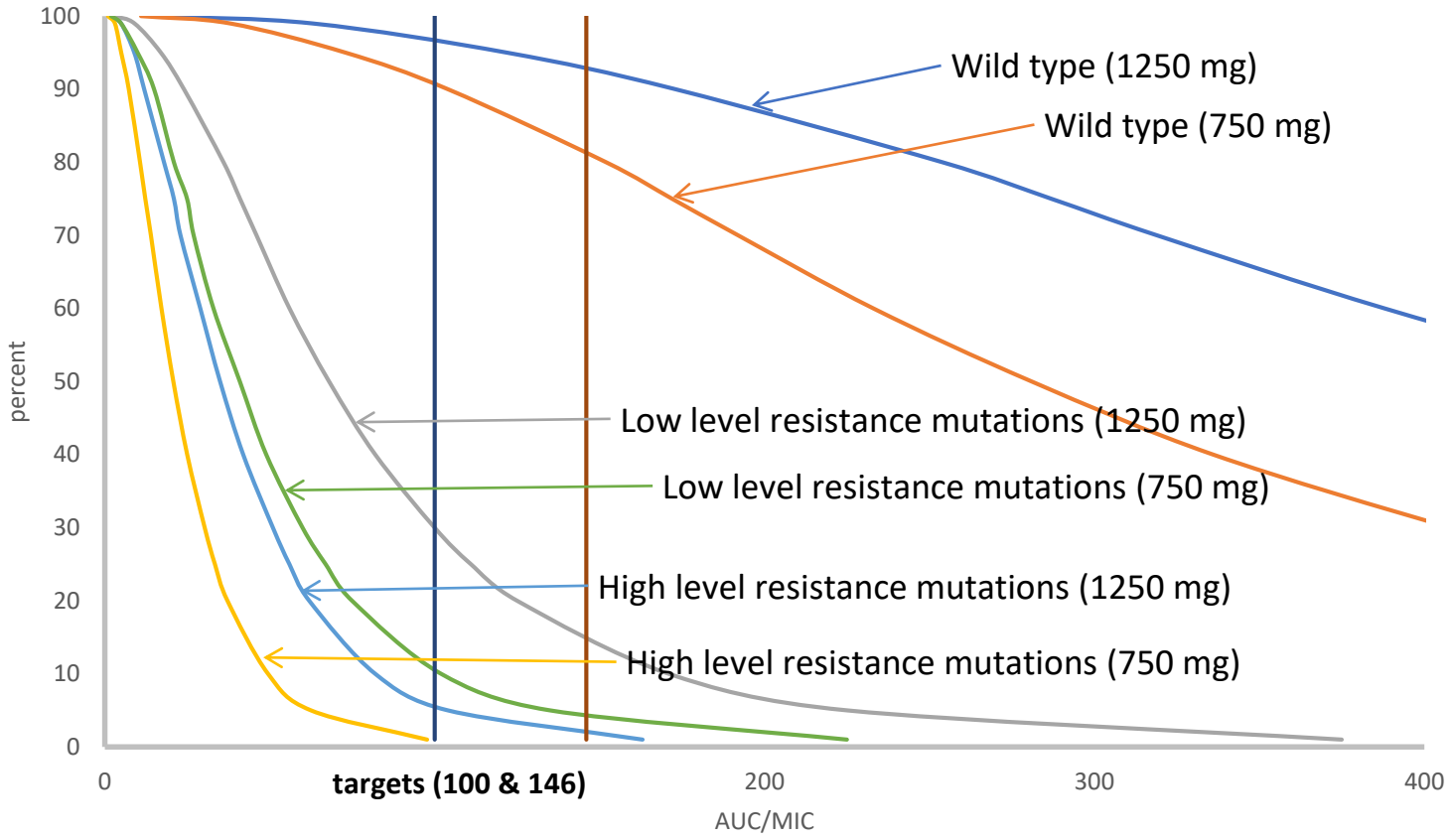


GFX (target 125)

22% of low MIC population at 400 mg/day
59% of low MIC population at 800 mg/day
73% of low MIC population at 1200 mg/day

Gumbo T, Louie A, Deziel MR, Parsons LM, Salfinger M, Drusano GL. Selection of a moxifloxacin dose that suppresses drug resistance in Mycobacterium tuberculosis, by use of an in vitro pharmacodynamic infection model and mathematical modeling. The Journal of infectious diseases 2004; 190(9): 1642-51.
Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis.; 2014.

Cumulative distribution plots of proportion of population likely to reach defined therapeutic targets for LFX



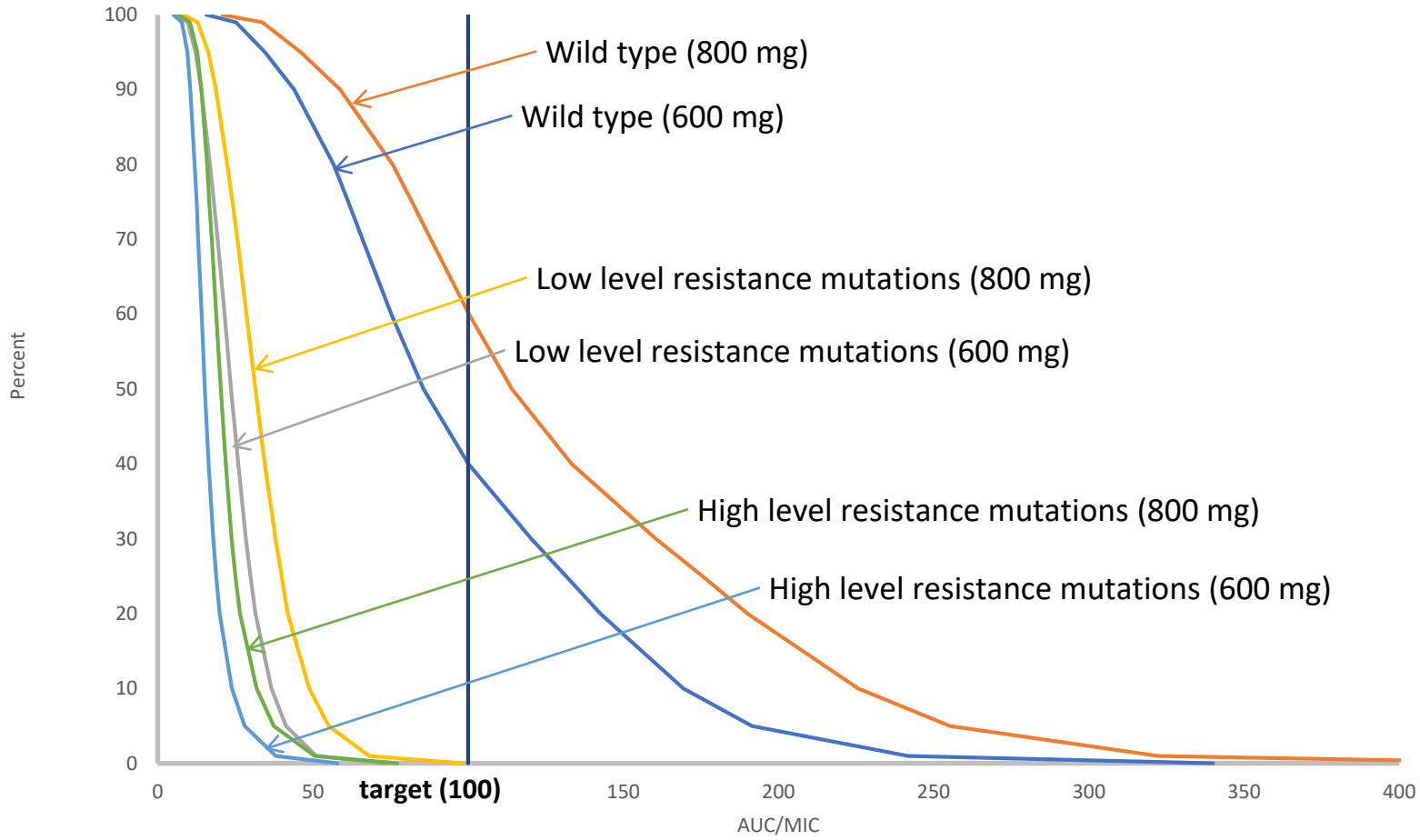
LFX (target 146)

4% of low MIC pop @ 750 mg/day

14% of low MIC pop @ 1250 mg/day

Lanoix JP, Chaisson RE, Nuermberger EL. Shortening Tuberculosis Treatment With Fluoroquinolones: Lost in Translation? Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2016; 62(4): 484-90.
Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis.; 2014.

Cumulative distribution plots of proportion of population likely to reach defined therapeutic targets for OFX



OFX (target 100)

0% of low MIC pop @ 600 mg/day

0% of low MIC pop @ 800 mg/day

Lanoix JP, Chaisson RE, Nuermberger EL. Shortening Tuberculosis Treatment With Fluoroquinolones: Lost in Translation? Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2016; 62(4): 484-90.
Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis.; 2014.

Conclusions from this Proof-of-Concept Study

- SNPs in *gyrA* gene of *Mtb* can be used to predict MIC distributions against individual fluoroquinolones
- SNP estimated MICs together with population PK/PD models could be used as decision support tools for rapid individualized TB treatment based on rapid molecular diagnostics
- Methods are generalizable to other antimicrobial agents which have reliable genetic markers of resistance in *Mycobacterium tuberculosis*

Acknowledgements

We are grateful to Mark Pettigrove for his laboratory support for this study

Disclosure Statement

Dr. Rodwell reports grants from National Institutes of Health (NIH) and salary support from the not-for-profit organization Foundation for Innovative New Diagnostics (FIND). Dr. Capparelli reports personal fees from Celltrion, personal fees from Melinta, personal fees from Patara, personal fees from Atox Bio, personal fees from Ironshore, outside the submitted work. Drs. Seifert and Catanzaro have nothing to disclose.

Funding

This work was supported by NIH R01AI111435 and T32HL134632