



COMMON ACTION AGAINST HIV/TB/HCV
ACROSS THE REGIONS OF EUROPE

Genotypic prediction of tuberculosis drug resistance and
implementation of effective MDR-TB management:

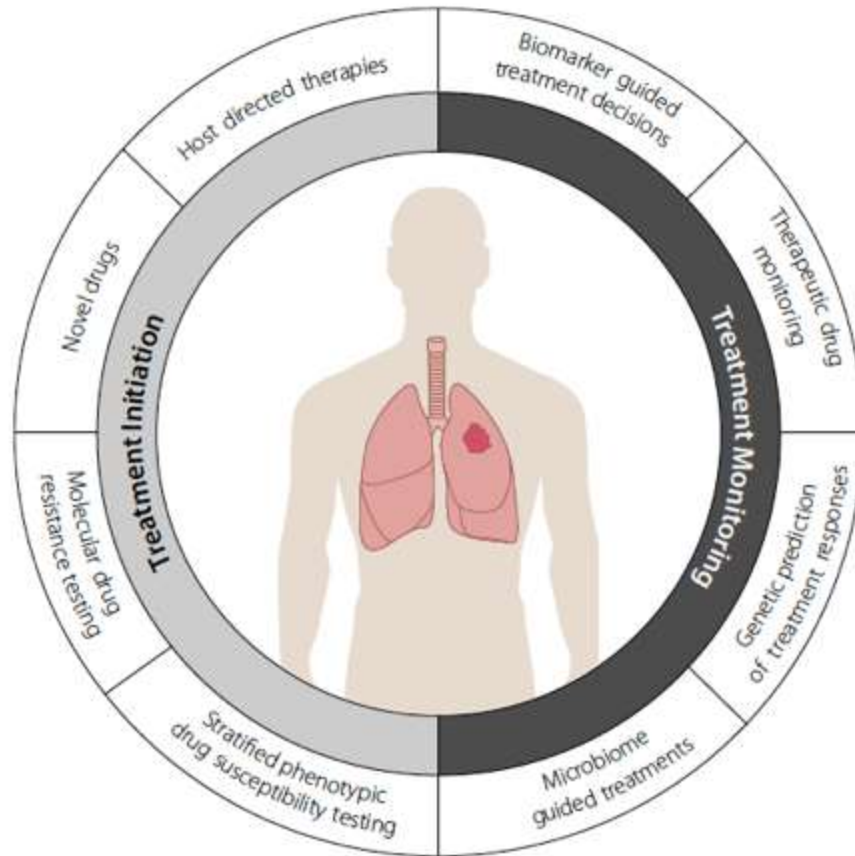
Results from the CARE project and future perspectives

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Research Center Borstel



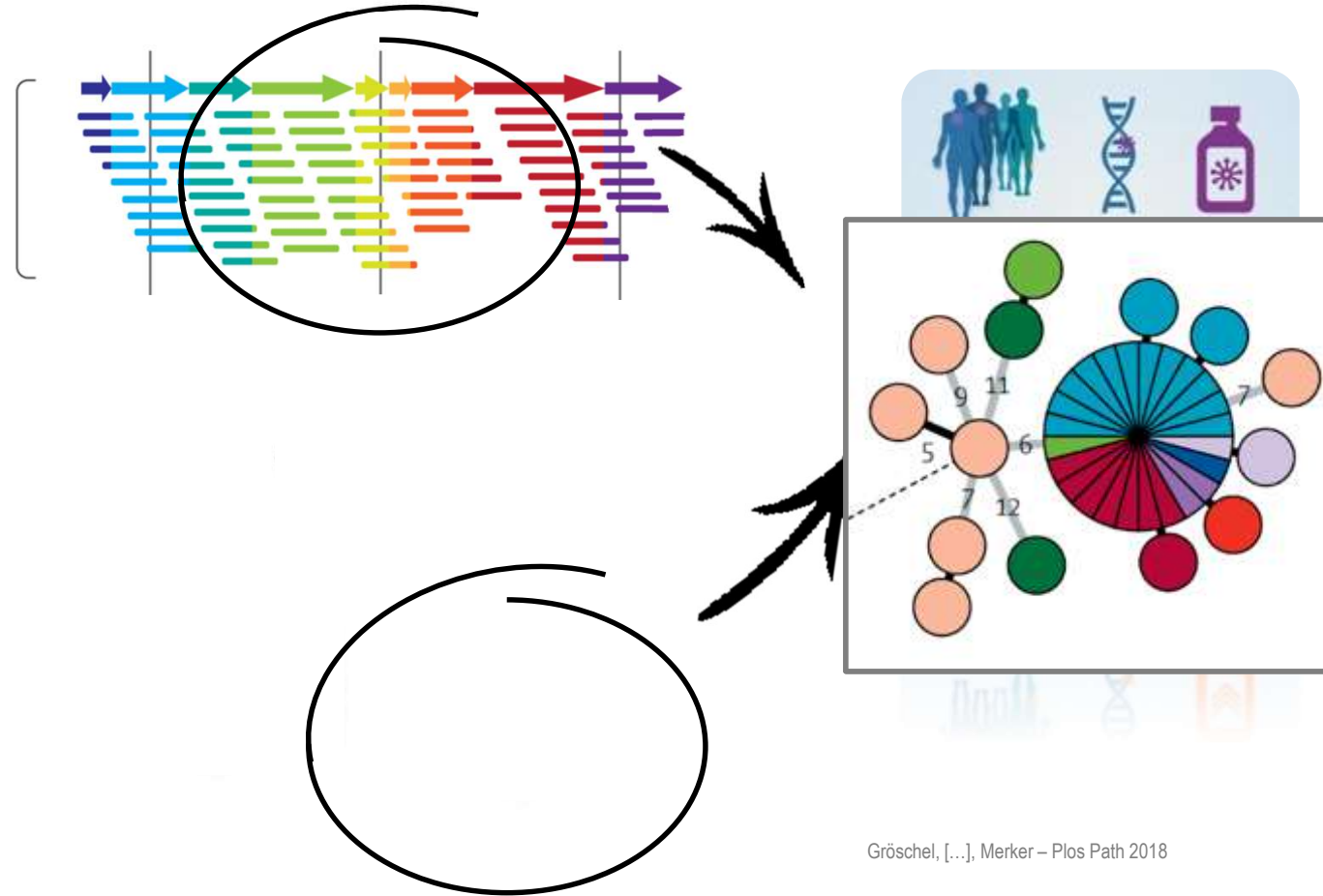


Precision Medicine



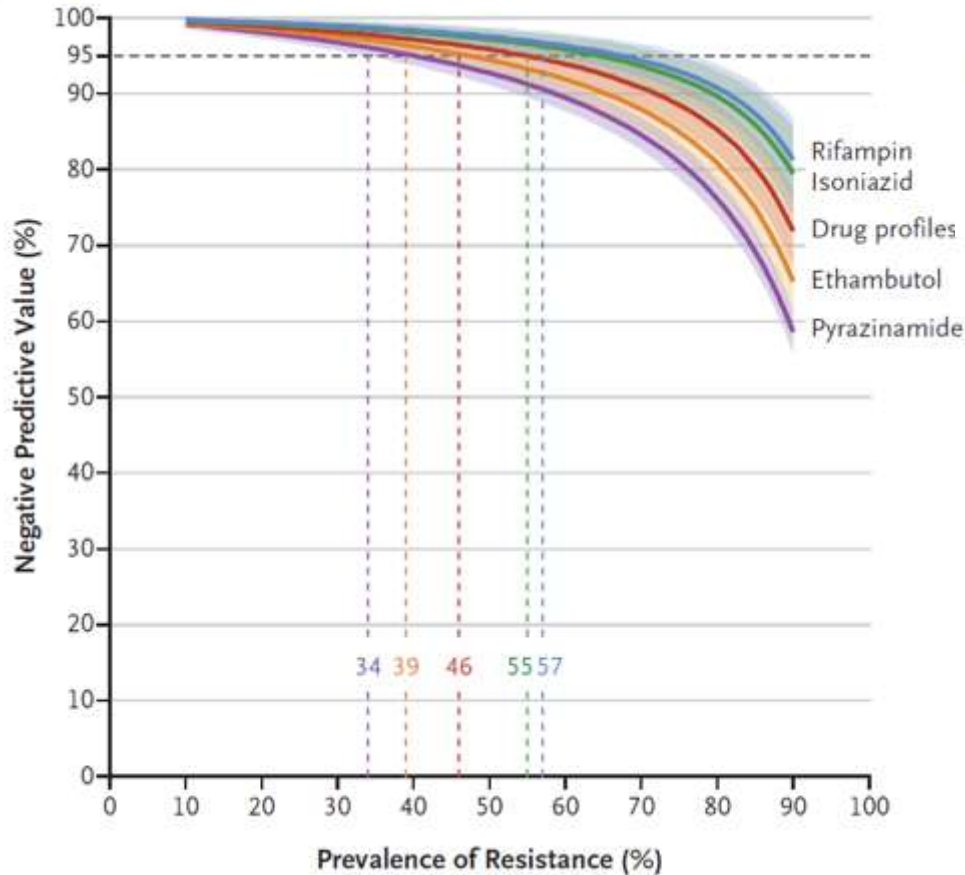
Geno2pheno pipeline

(A) Reference mapping





Prediction of first-line drug susceptibility



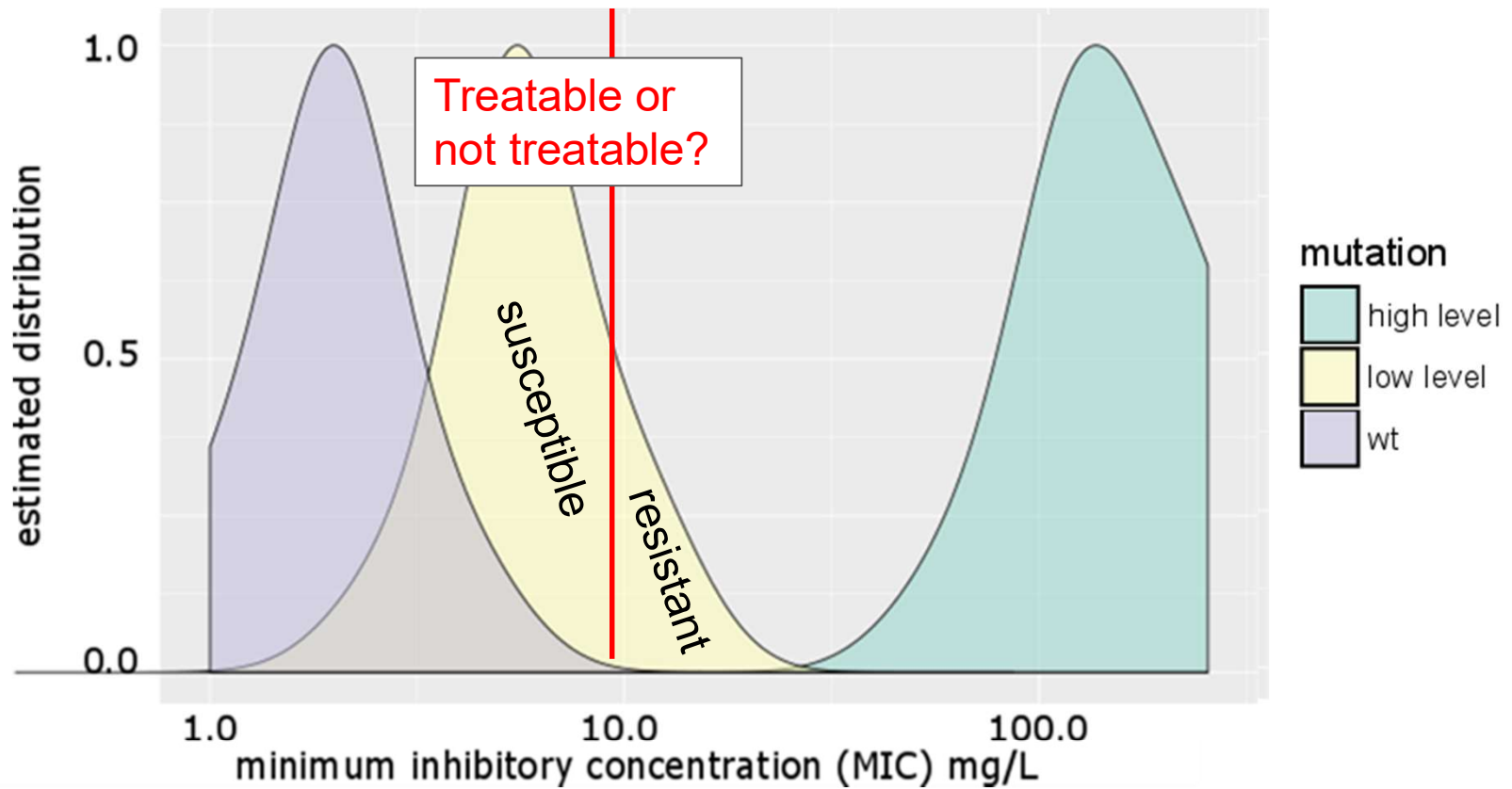
WHO target product profile:
90% sensitivity
95% specificity

source: Cryptic consortium – NEJM 2018

Analysis and Drug	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
<i>percent</i>				
WGS, all isolates				
Isoniazid	97.1 (96.5–97.7)	99.0 (98.7–99.2)	97.9 (97.4–98.4)	98.6 (98.3–98.9)
Rifampin	97.5 (96.9–98.1)	98.8 (98.5–99.0)	97.0 (96.3–97.6)	99.0 (98.7–99.2)
Ethambutol	94.6 (93.3–95.7)	93.6 (93.0–94.1)	75.1 (73.0–77.0)	98.8 (98.5–99.1)
Pyrazinamide	91.3 (89.3–93.0)	96.8 (96.3–97.2)	80.9 (78.4–83.2)	98.7 (98.4–99.0)



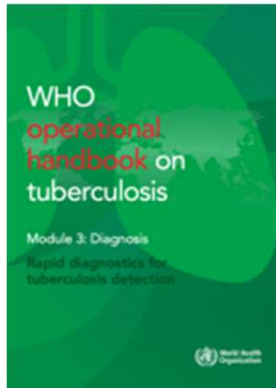
What is resistance?



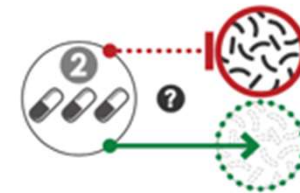
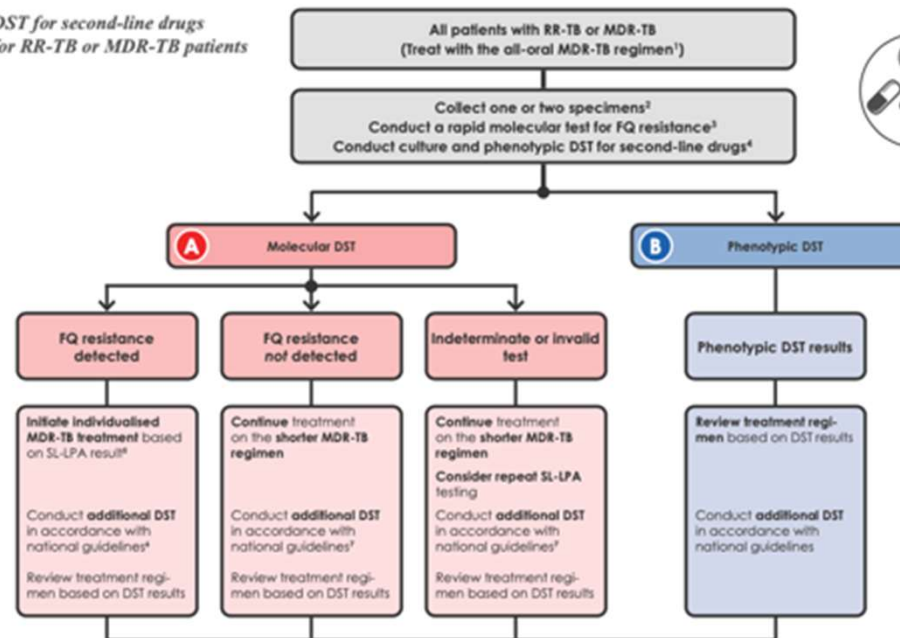


How to evaluate geno2pheno?

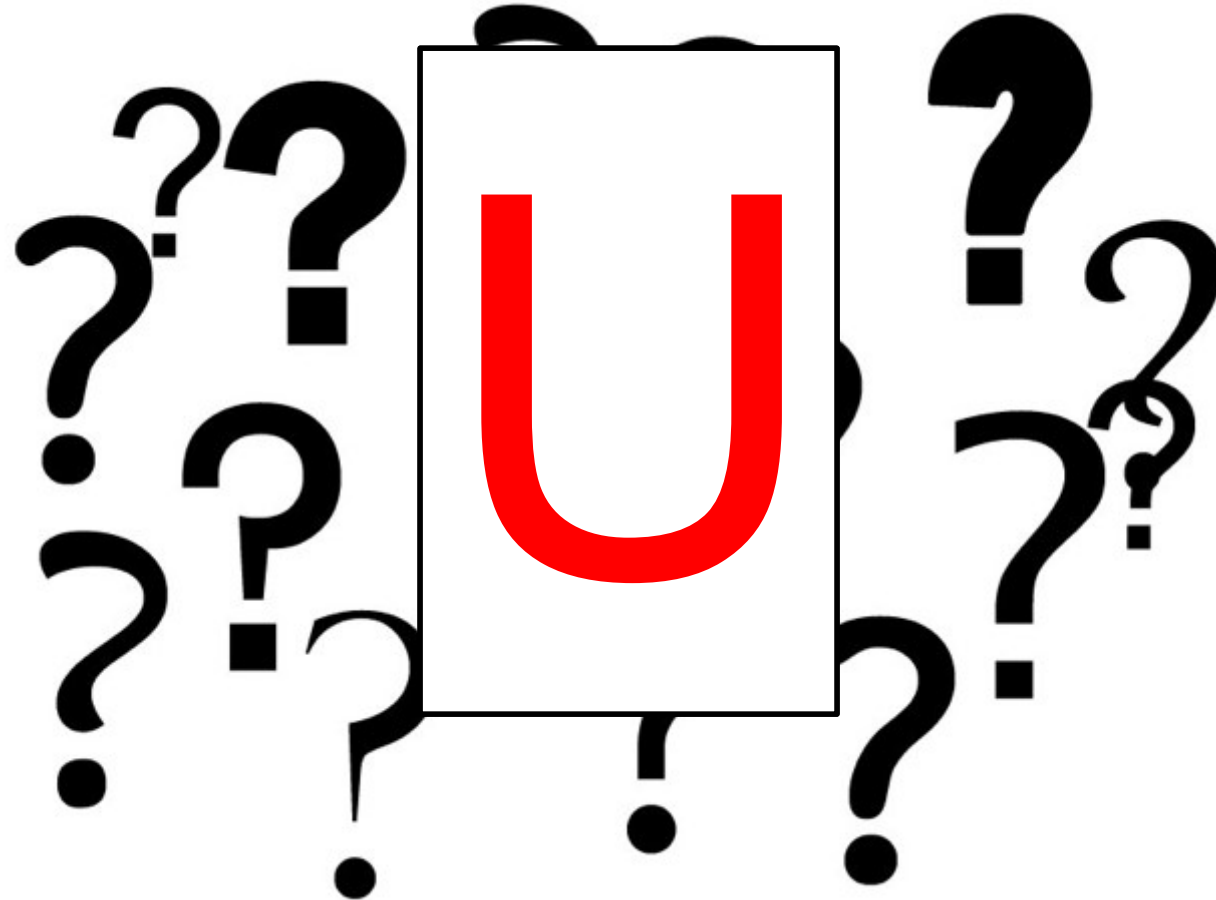
- Phenotypic DST is not the Gold-Standard!
- TB reference labs consider molecular and phenotypic data
- We need a consensus/expert interpretation as Gold-Standard!



3 *DST for second-line drugs for RR-TB or MDR-TB patients*

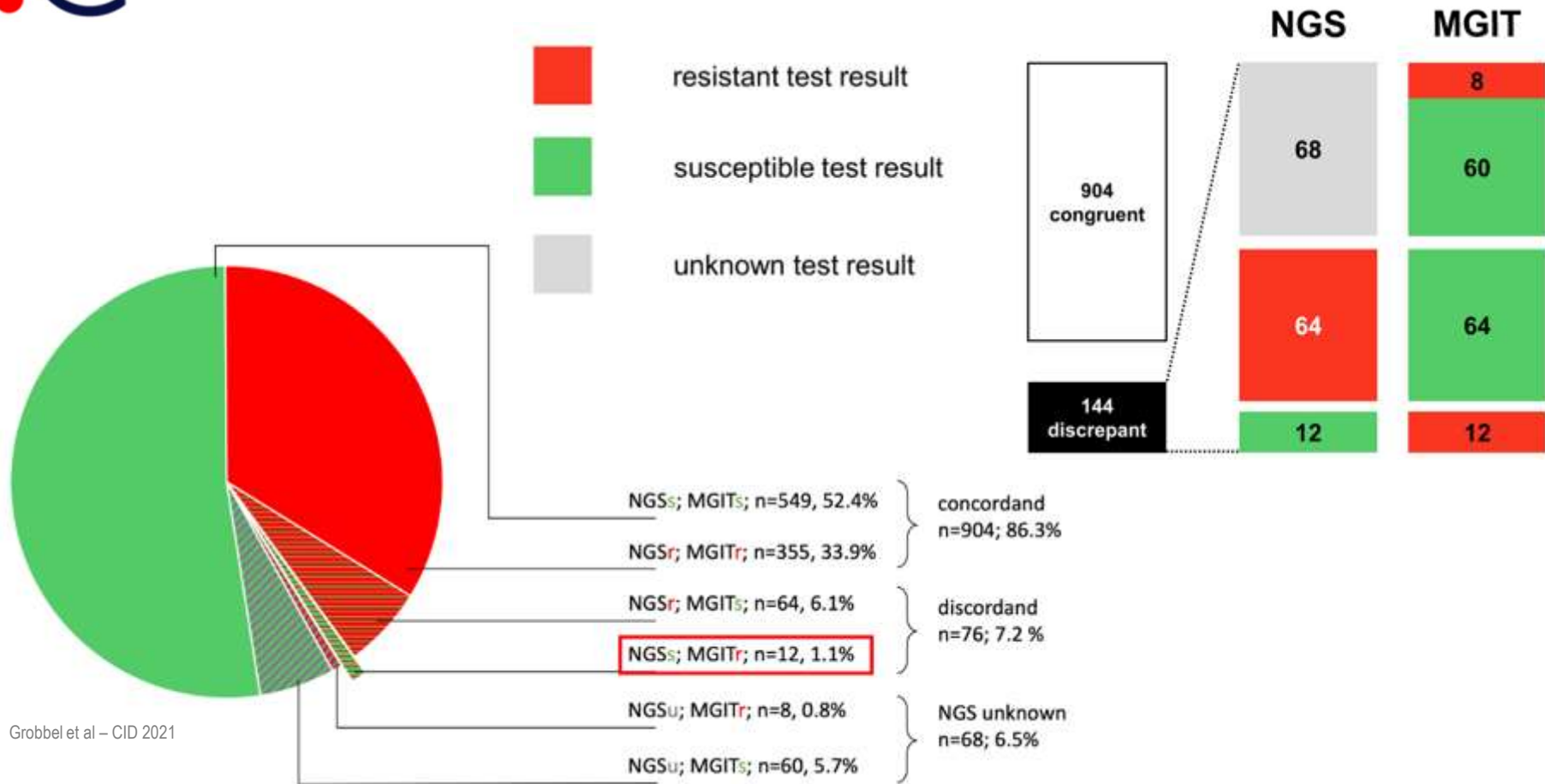


Unknown mutations

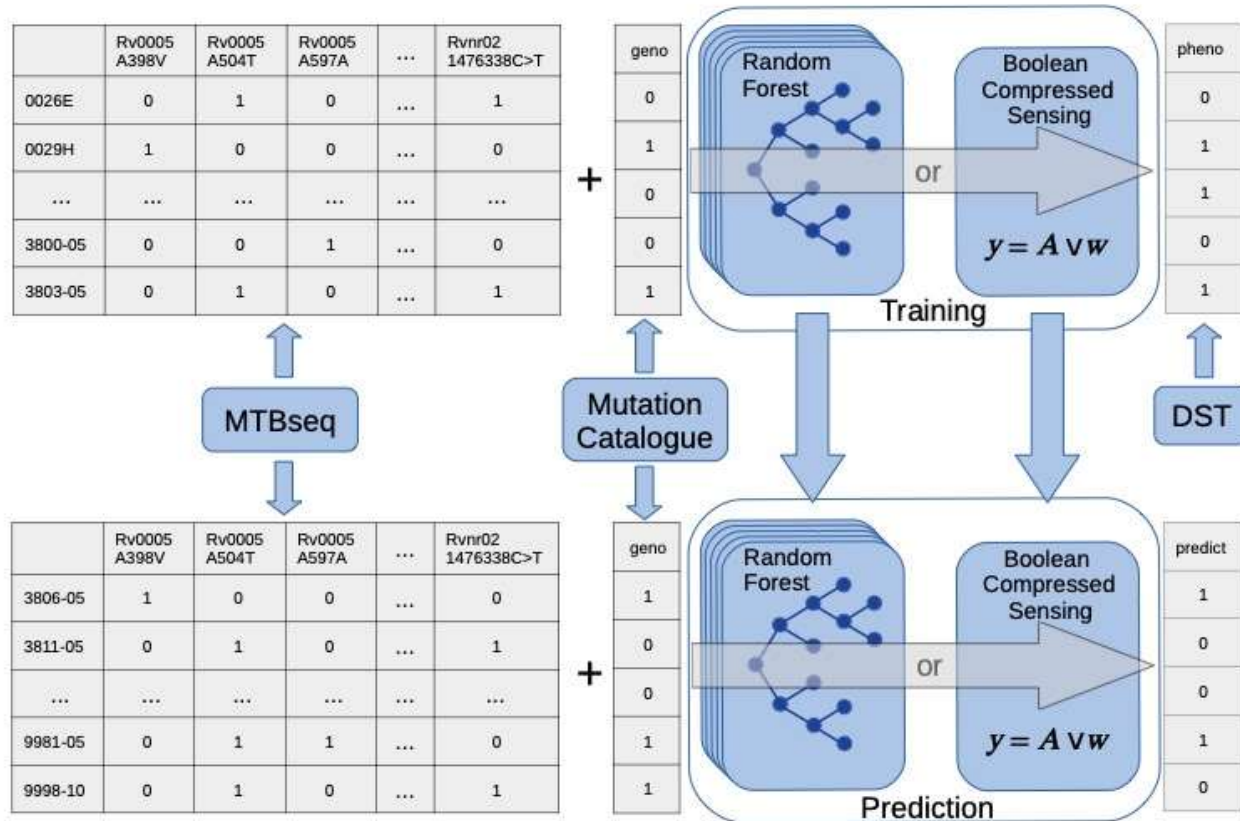




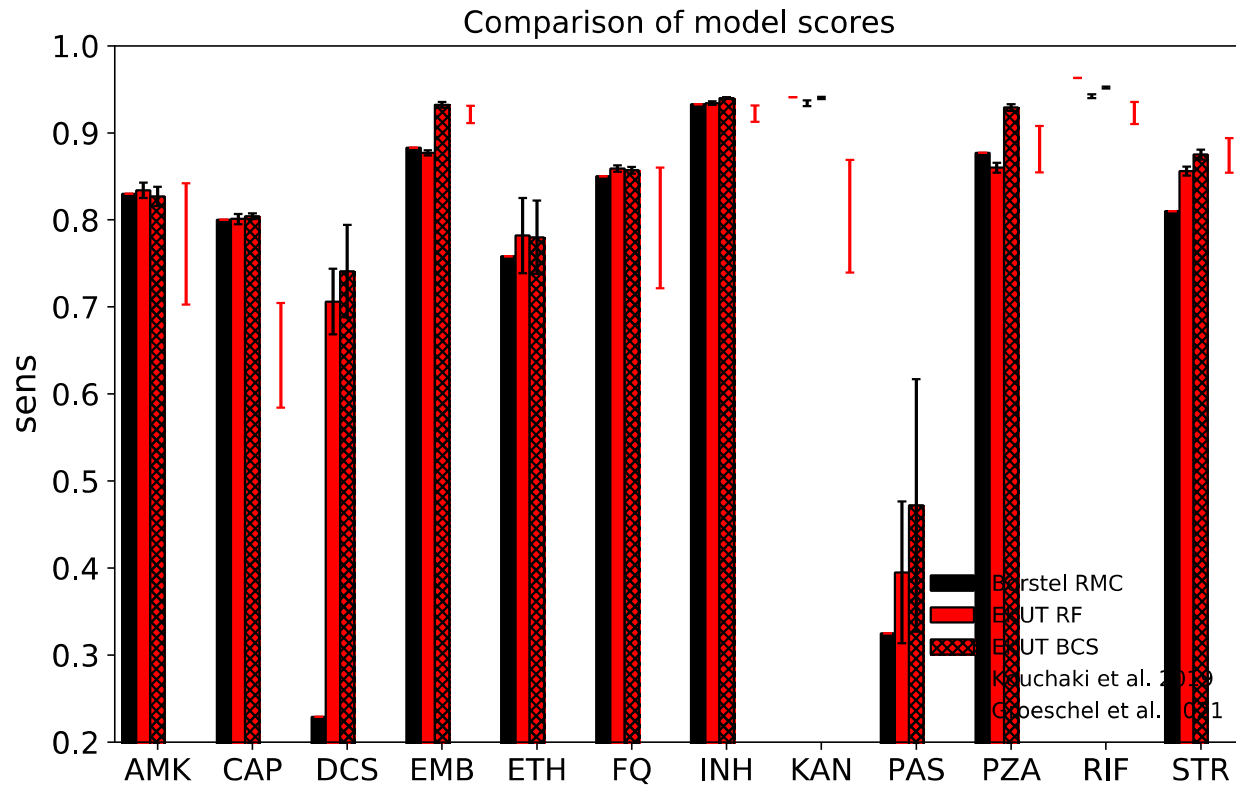
Unknown = Susceptible?



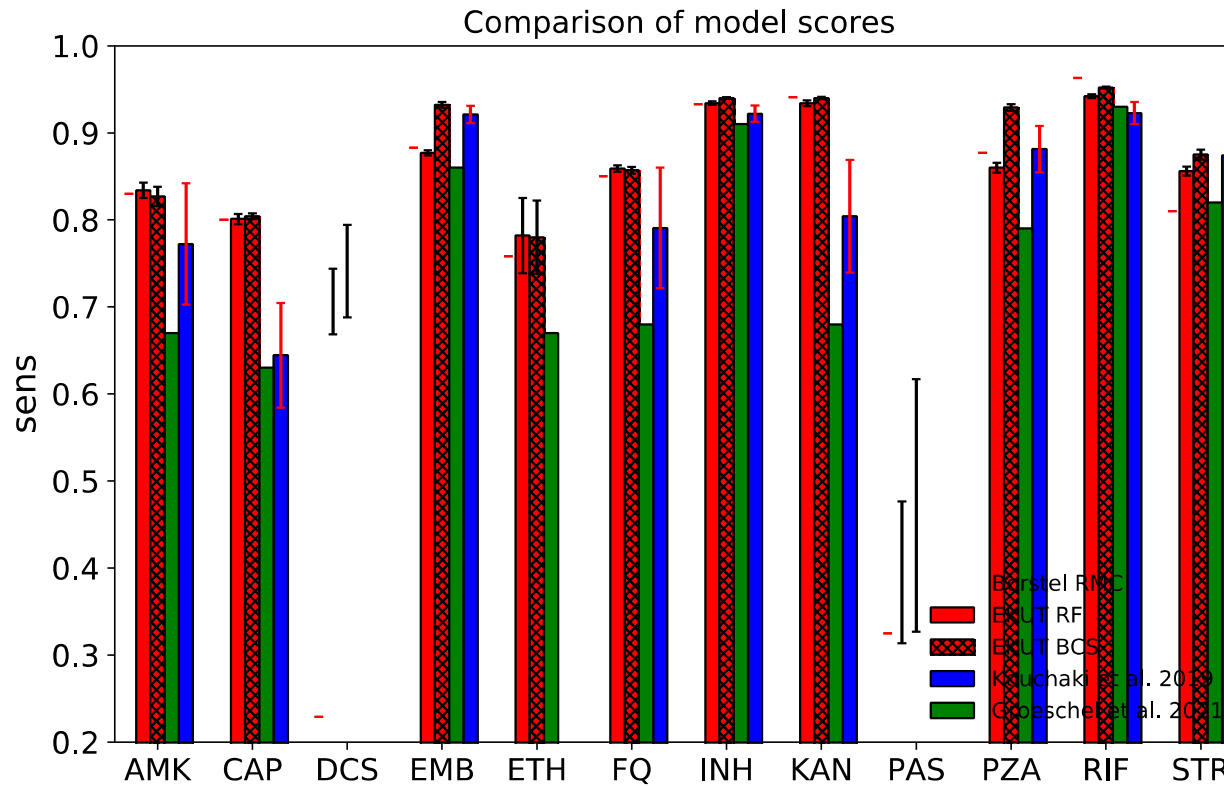
Grobbel et al - CID 2021



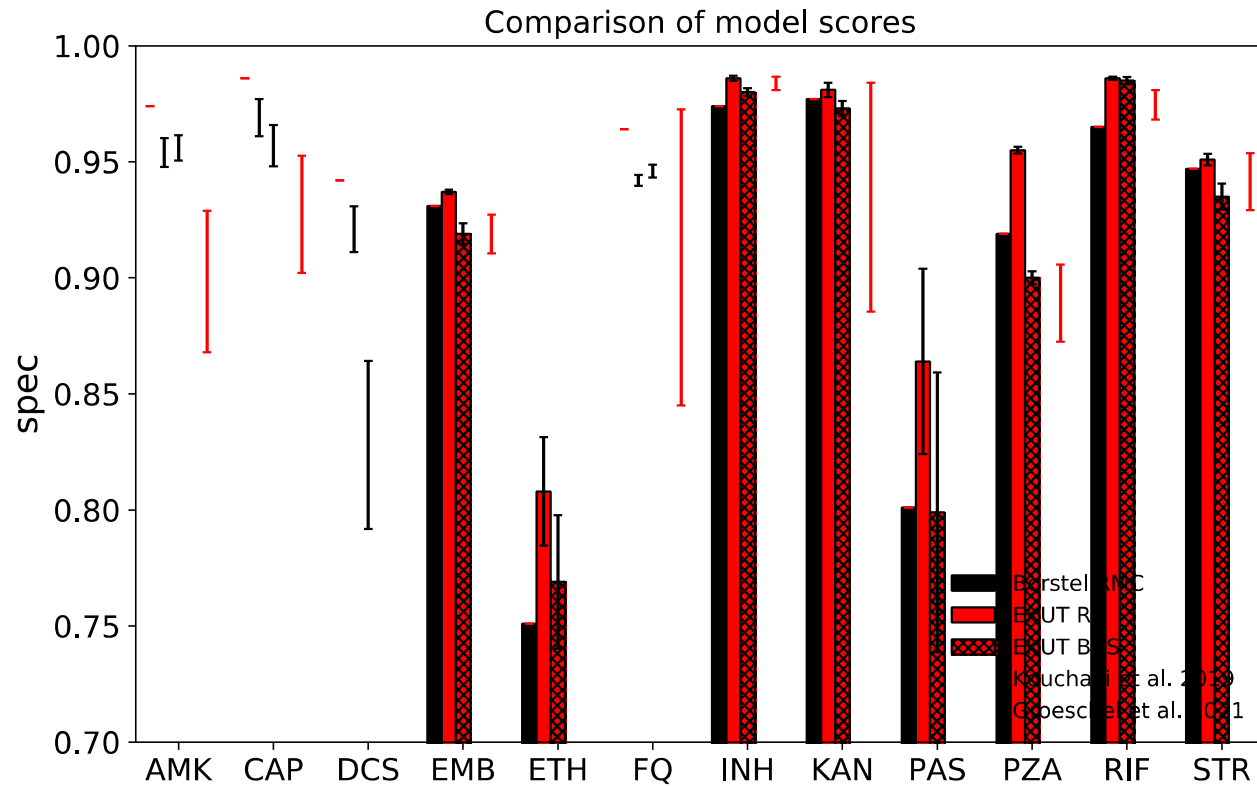
Results



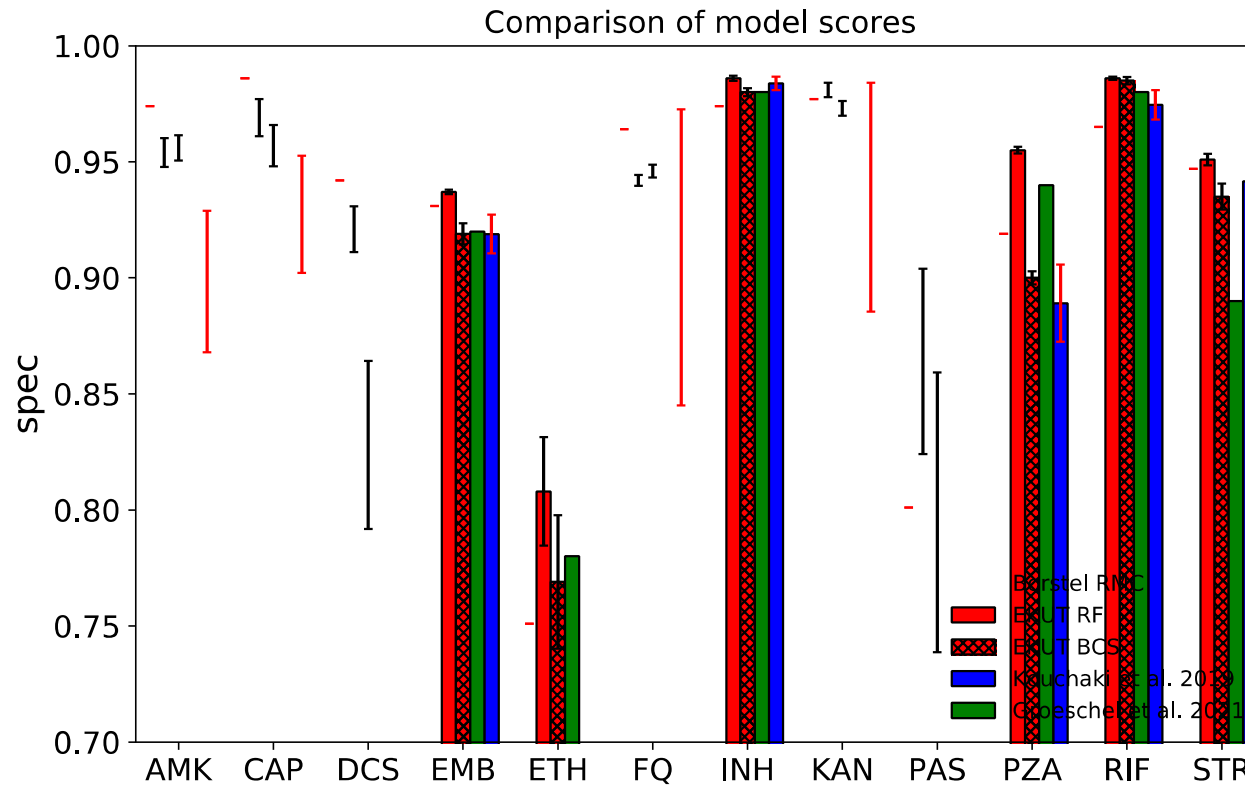
Results



Results



Results

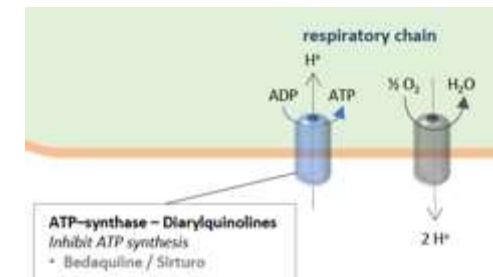
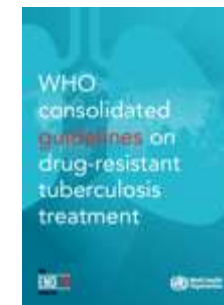




Emergence of BDQ resistance



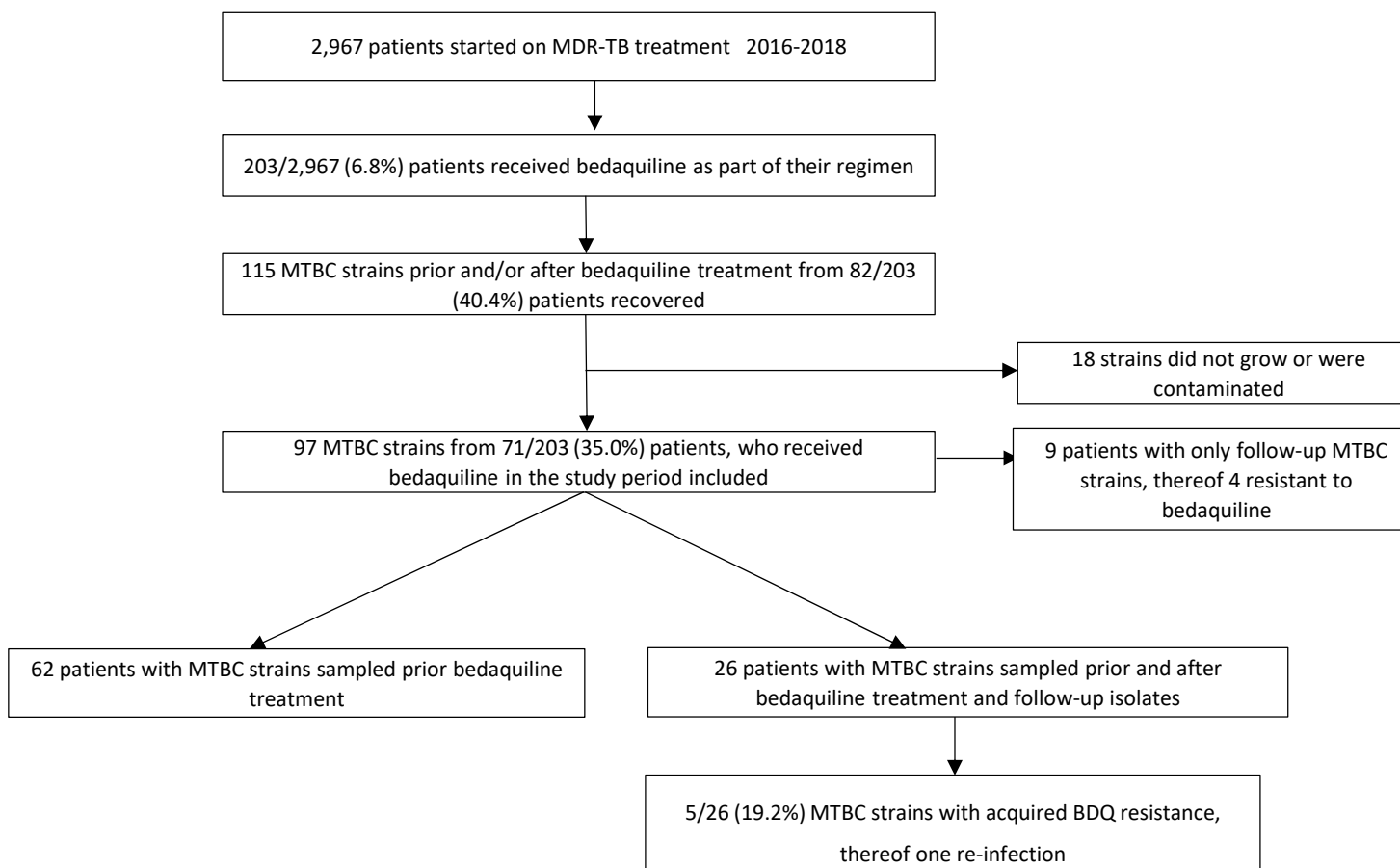
Groups & steps	Medicine
Group A: Include all three medicines	levofloxacin OR Lfx
	moxifloxacin OR Mfx
	bedaquiline ^{2,3} Bdq
Group B: Add one or both medicines	linezolid ⁴ Lzd
	clofazimine Cfz
	cycloserine OR Cs terizidone Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	ethambutol E
	delamanid ^{5,6} Dlm
	pyrazinamide ⁶ Z
	imipenem–cilastatin OR Ipm–Cln meropenem ⁷ Mpm
	amikacin (OR streptomycin) ⁸ Am (S)
	ethionamide OR Eto prothionamide ⁹ Pto
p-aminosalicylic acid ⁹ PAS	



No commercial molecular DST testing available



Emergence of BDQ resistance





Emergence of BDQ resistance

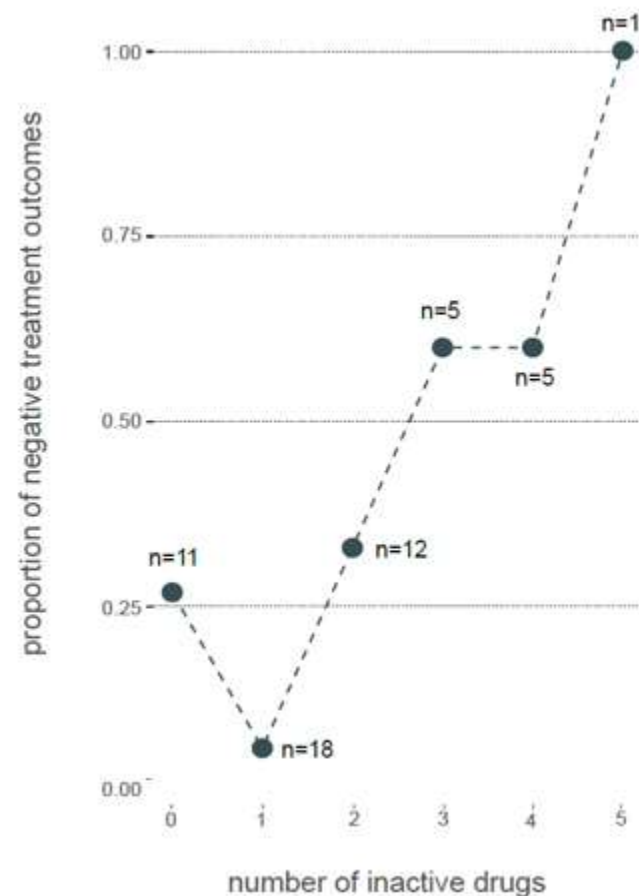
Bedaquiline resistance emerged in >15% of *Mycobacterium tuberculosis* complex strains obtained from follow-up isolates of MDR-TB patients in Moldova (Rv0678, atpE)

Insufficient backbone regimens and cavitory disease associated with treatment failure and death.

BDQ (CFZ/LZD)-DST established in Moldova (in collaboration with FZB TB reference centre)

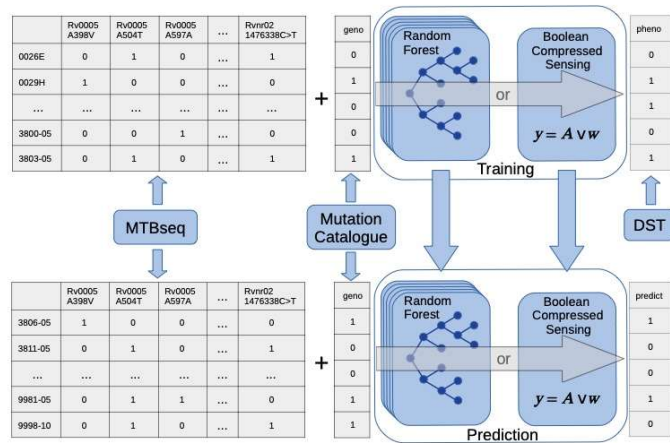
Also BDQ needs a functional drug regimen!

Chesov et al – ERJ in major revision





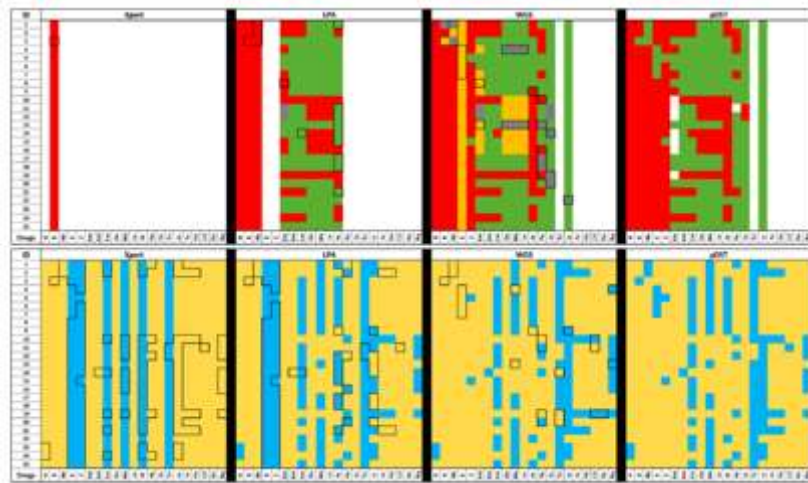
Next Steps



Groups & steps	Medicine	
Group A: Include all three medicines	levofloxacin OR	Lfx
	moxifloxacin	Mfx
	bedaquiline ^{2,3}	Bdq
	linezolid ⁴	Lzd
Group B: Add one or both medicines	clofazimine	Cfz
	cycloserine OR	Cs
	terizidone	Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	ethambutol	E
	delamanid ^{5,6}	Dlm
	pyrazinamide ⁶	Z
	imipenem-cilastatin OR	Ipim-Cln
	meropenem ⁷	Mpm
	amikacin (OR streptomycin) ⁸	Am (S)
	ethionamide OR	Eto
	prothionamide ⁹	Pto
	p-aminosalicylic acid ⁹	PAS



Next Steps



Heyckendorf et al., AAC 2018



<https://coreceptor.geno2pheno.org>

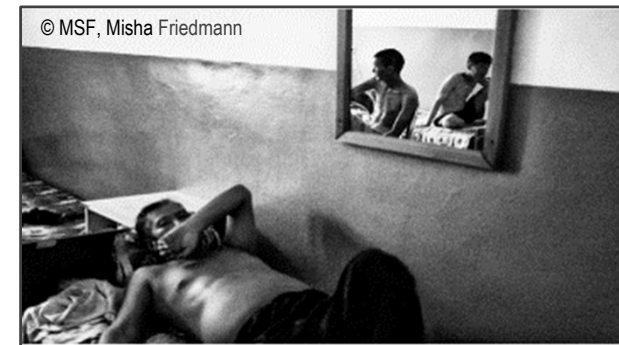


Personalized medicine

Knowledge Transfer vs. Technique Transfer

Centralized (specialized) diagnostic vs local (rapid) diagnostic

Resistance councils vs standardized treatment regimens





WP3 Summary

Patient cohorts/WGS data:

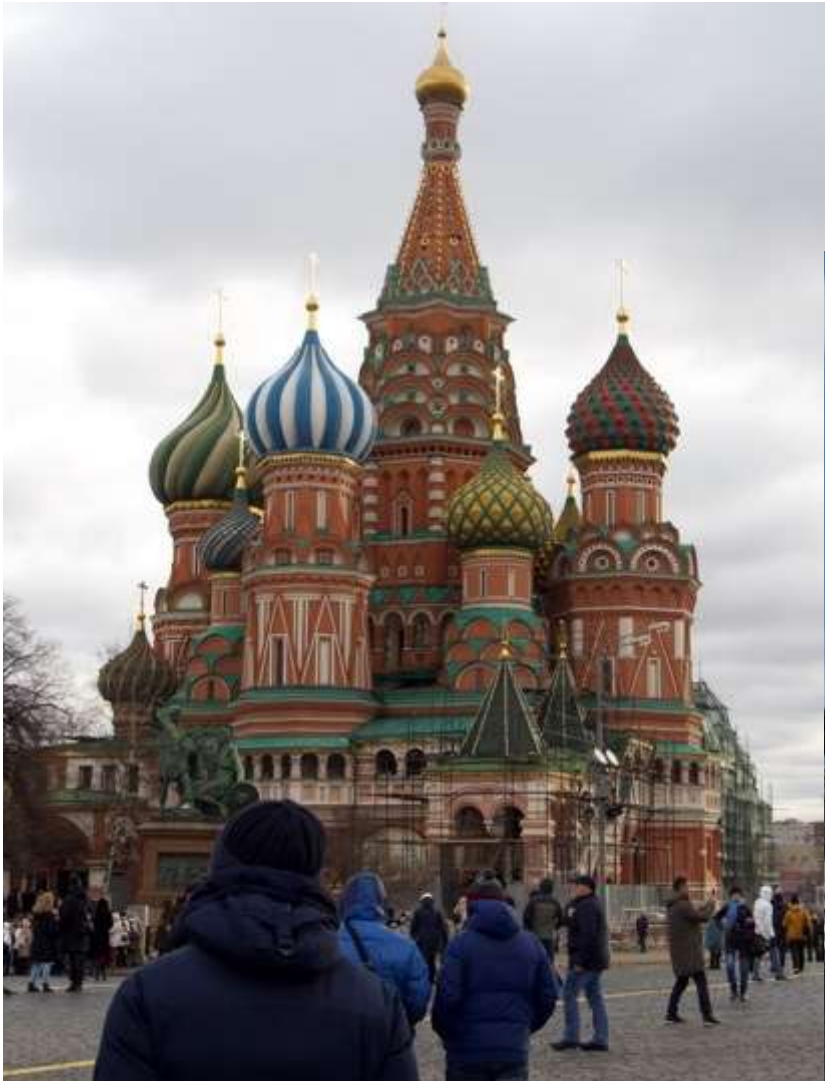
Moldova: 71/203 patients who received bedaquiline (2016-2018), and from whom *M. tuberculosis* isolates could be recovered, Chesov et al (in revision)

Moldova: 299 MDR-TB patients (2013-2018), ~50 *M. tuberculosis* isolates/year, data analysis ongoing (population genomics, resistance evolution)

St. Petersburg: 121 M/XDR-TB patients with *M. tuberculosis* WGS data, “catalogue-based” resistance prediction currently aligned with phenotypes (17/121, 14.0% with predicted BDQ resistance)

Geno2Pheno:

public WGS datasets included for machine learning training datasets
Set-up of a first working model of a geno2pheno[TB] tool in progress



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ACROSS THE REGIONS OF EUROPE



Thank You!!!