Helios

Tuberkulosekonferenz Berlin-Brandenburg

Der besondere Fall

-

„Die versteckte TB“

Silke Polsfuß und David Krieger
Helios Klinikum Emil von Behring, Berlin

11.01.2024

Teil 1

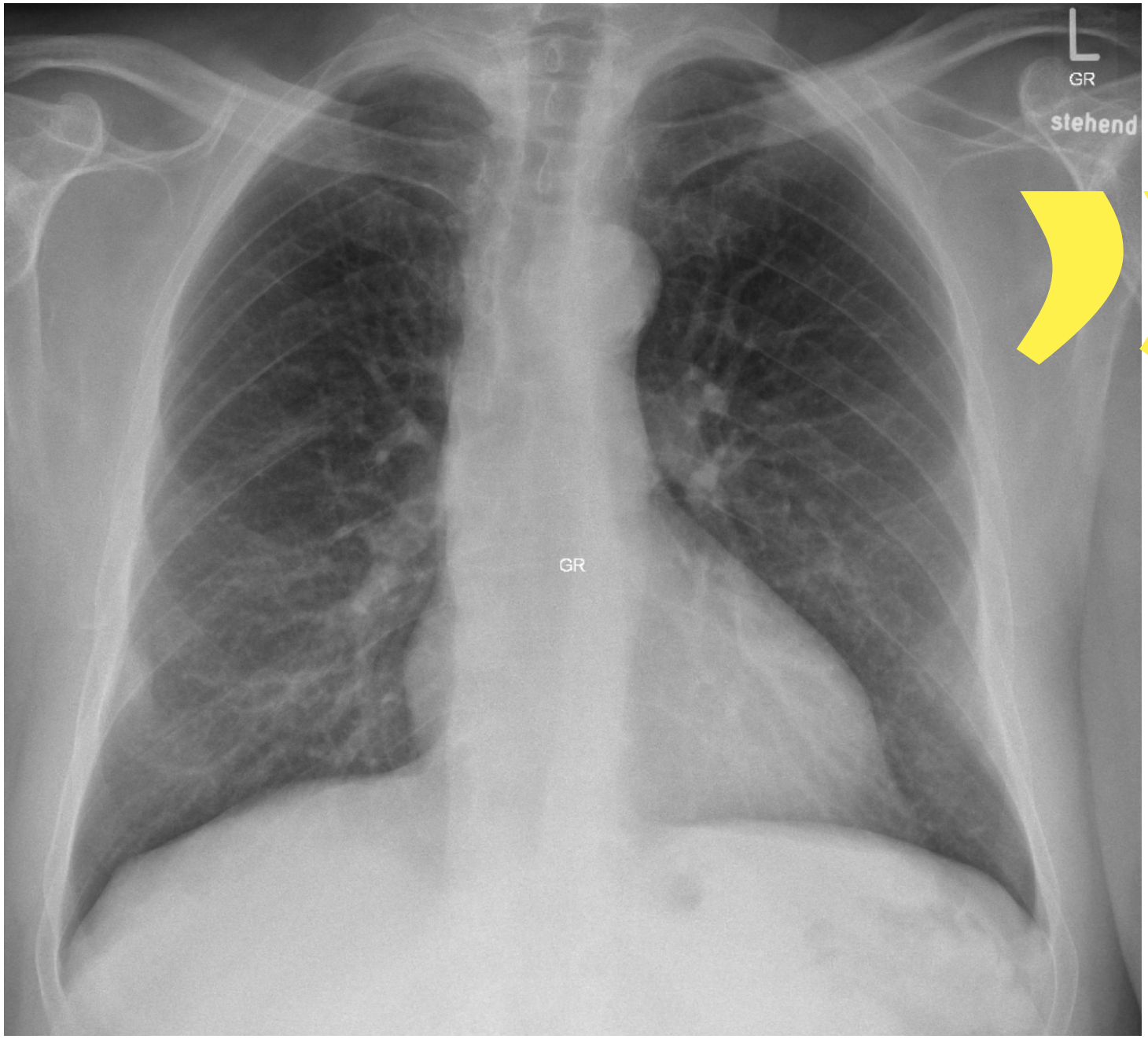
Der Patient

Der Patient

- 59 – jähriger Patient, aus Moldawien stammend
- Selbständige Vorstellung in unserer Notaufnahme, aufgrund:
  - Seit 4 Wochen subfebrile Temperaturen
  - Husten mit „weißlichem Auswurf“ (– keine Hämoptysen)
  - 15 kg Gewichtverlust in den letzten Wochen

Vor 3 Jahren im Heimatland wegen TB behandelt

Sohn und Vater an Tuberkulose gestorben



Röntgen – Thorax <u>ohne</u> wesentliche Auffälligkeiten

Mikroskopie
SÄUREFESTE STÄBCHEN nachgewiesen ++

Keimidentifikation
Mycobacterium tuberculosis - MDR**

Mikroskopie
SÄUREFESTE STÄBCHEN nachgewiesen +++

Keimidentifikation
Mycobacterium tuberculosis - MDR**

Mikroskopie
SÄUREFESTE STÄBCHEN nachgewiesen +

Keimidentifikation
Mycobacterium tuberculosis - MDR**

Verfahren
M.tub. Komplex DNA (IS6110 repetitives Element) *
positiv
Mykobakterien DNA (ITS1 Genregion) *
positiv
M. tub. Komplex Mol. Res. (rpoB/katG/inhA/embB/gyrA) *

Mutationsanalyse der wichtigsten Genabschnitte:

RMP: Mutation im rpoB Gen 450L => resistent

INH :inhA Promoter Wildtyp, katG Mutation (315T), => high level INH Resistenz!

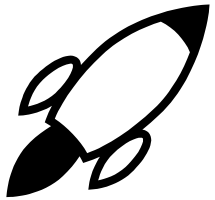
EMB: keine Mutation im embB Gen => wahrscheinlich S, erweiterte Sequenzierung ab Kultur wenn gewünscht

Moxifloxacin: keine Mutation im gyrA Gen => wahrscheinlich S

PZA: pncA Gen Sequenzierung folgt ab Kultur, falls gewünscht.

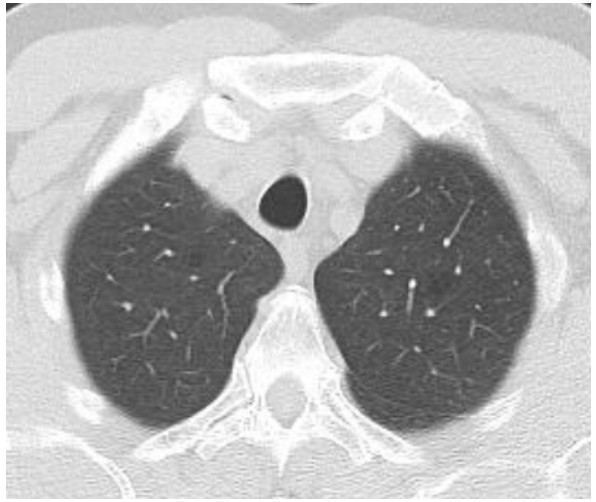
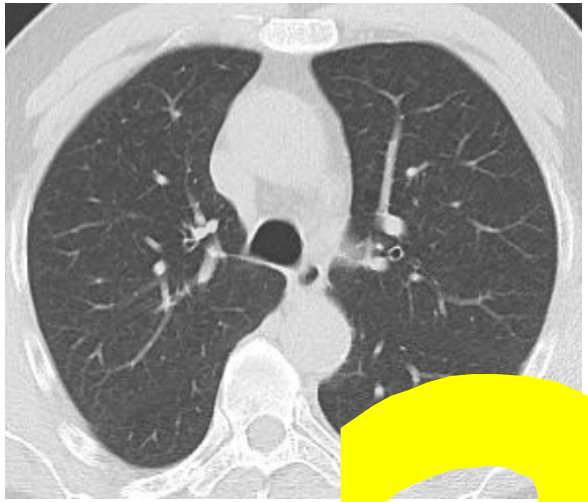
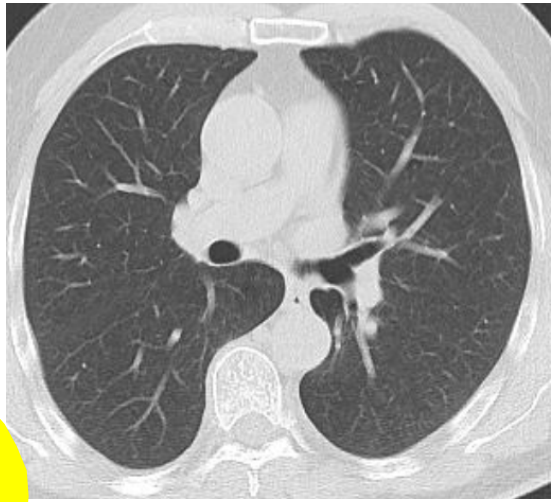
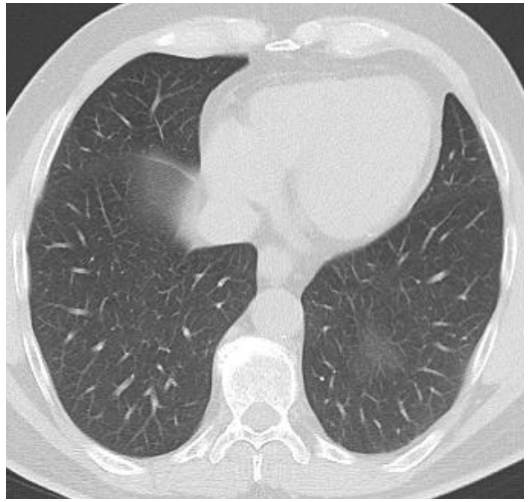
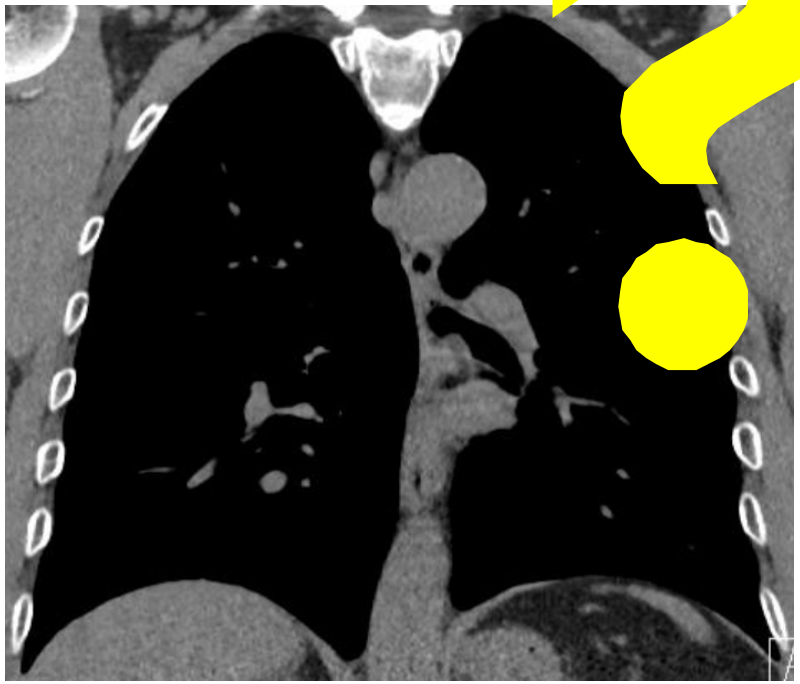
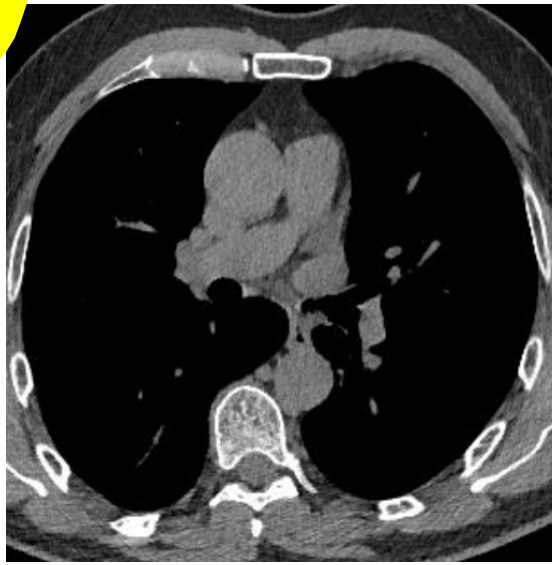
ACHTUNG: Molekular MDR

Beginn der antituberkulösen Therapie



- **„BPaLM“**
  - Bedaquilin (B)
  - Pretomanid (Pa)
  - Linezolid (L)
  - Moxifloxacin (M)

CT Thorax

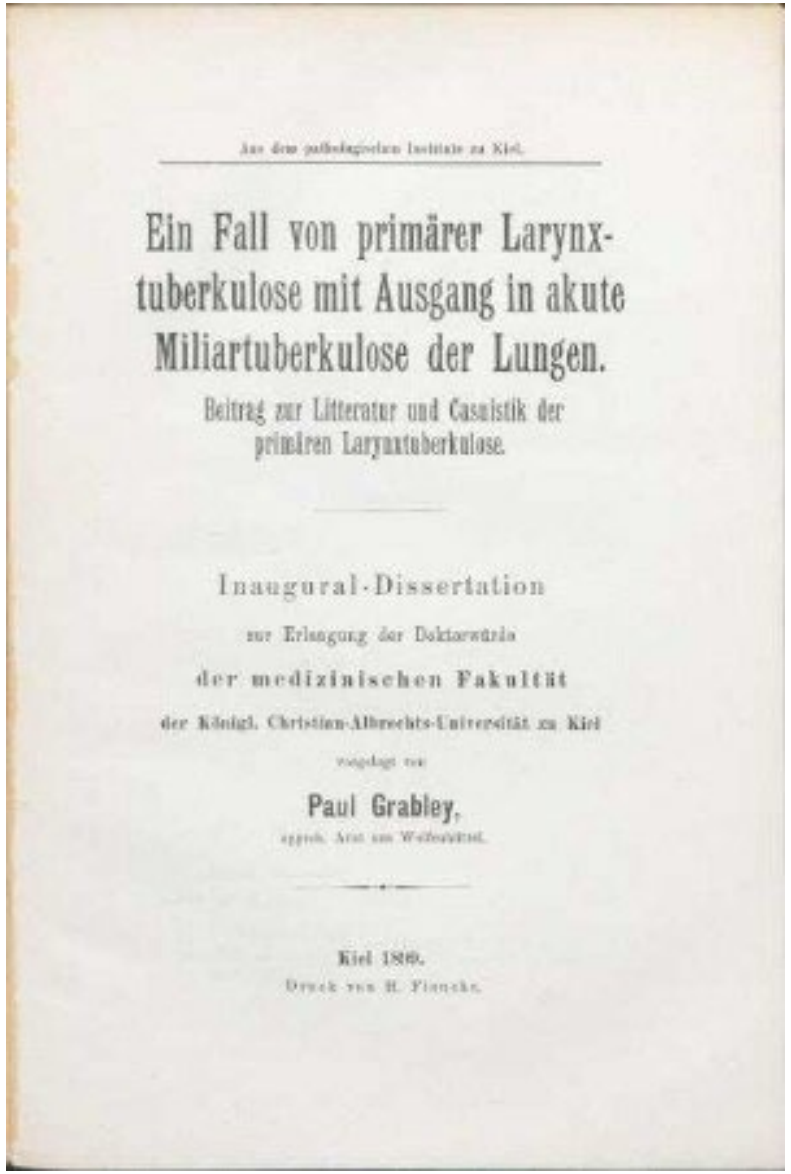







HNO-ärztliche Vorstellung

Frage nach Vorliegen einer Larynx-Tuberkulose?

Befund:

„Ausschluss einer akuten tuberkulösen Pharyngolaryngitis“



Aus dem pathologischen Institute zu Kiel.

Ein Fall von primärer Larynx-tuberkulose mit Ausgang in akute Miliartuberkulose der Lungen.

Beitrag zur Litteratur und Casuistik der primären Laryxtuberkulose.

Inaugural-Dissertation

zur Erlangung der Doktorwürde

der medizinischen Fakultät

der Königl. Christian-Albrechts-Universität zu Kiel

vorgelegt von

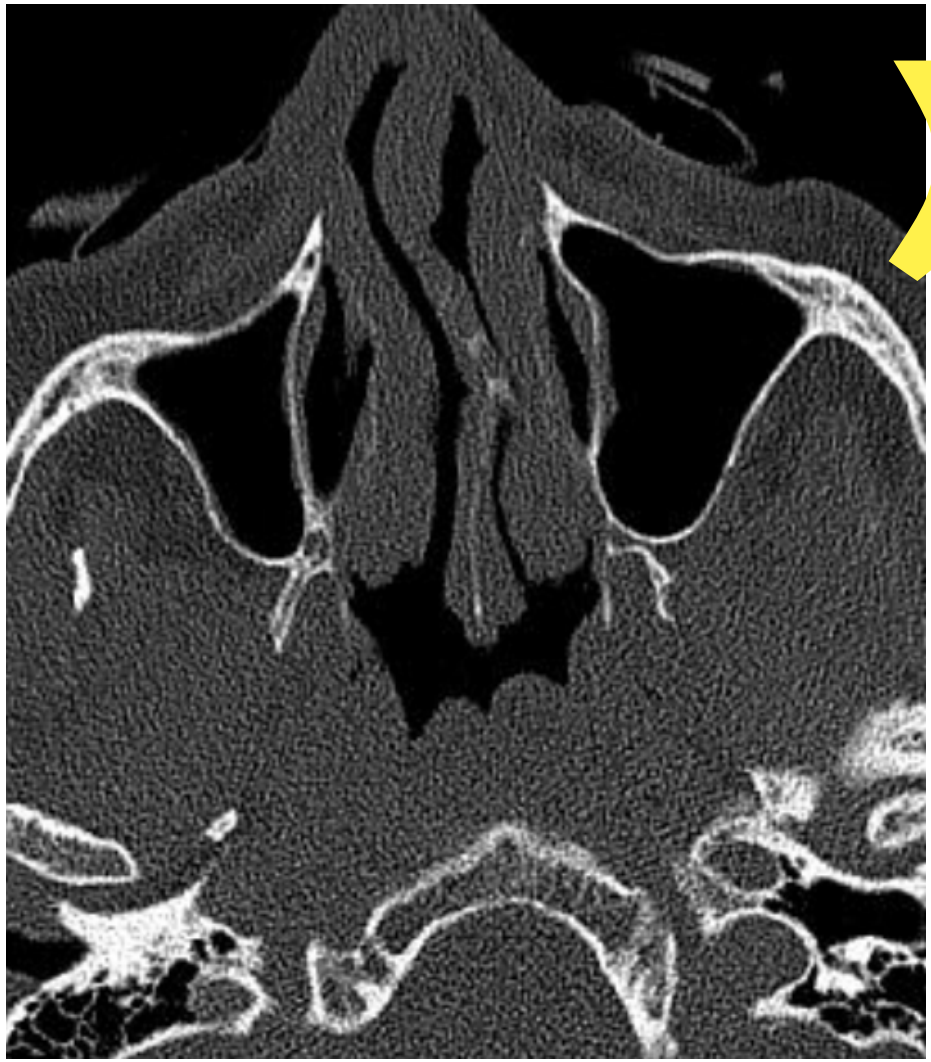
Paul Grabley,

approb. Arzt aus Wollenhagen.

Kiel 1889.

Druck von H. Fiencke.

CT NNH

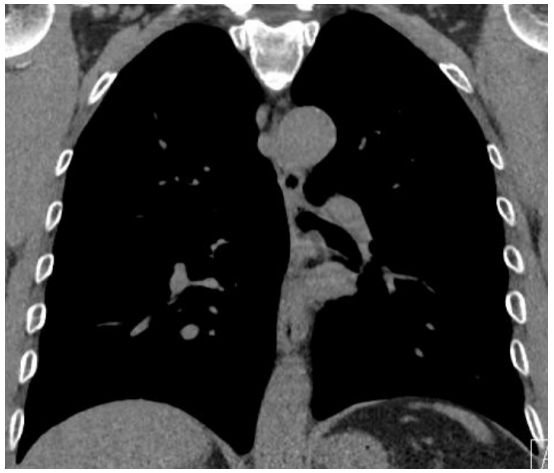


Kein Anhalt für eine akute oder chronische Sinusitis.

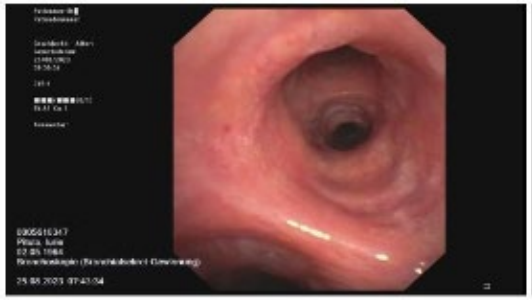
Wöchentliche Sputumkontrollen:

Datum	Mikroskopie	Kultur	TTP
28.07.	+	07.08. positiv	10 Tage
29.07.	++	14.08. positiv	15 Tage
29.07.	+	11.08. positiv	12 Tage
29.07.	+++	09.08. positiv	10 Tage
05.08.	+/-	22.08. positiv	17 Tage
14.08.	-	22.09. positiv	37 Tage
22.08.	-	Negativ (8 W bebrütet)	-
29.8.	-	Negativ (8 W bebrütet)	-
Etc …	-	-	-

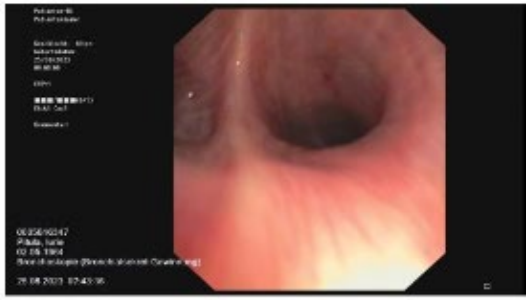
ATT-Beginn: BPaLM



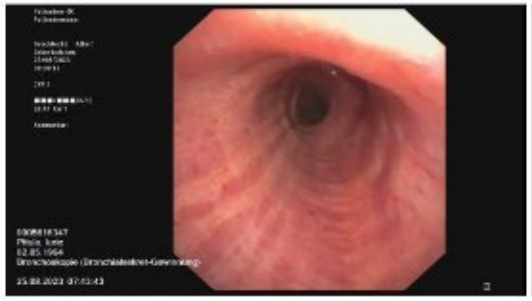
Bronchoskopie



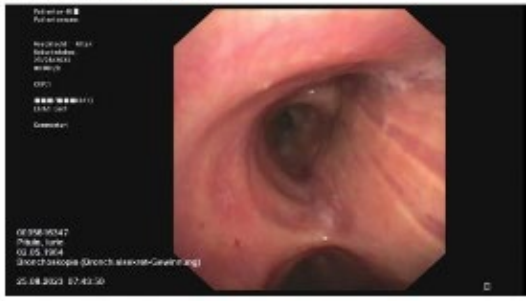
linker Oberlappen



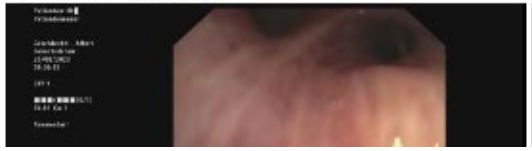
linker Unterlappen



linker Hauptbronchus

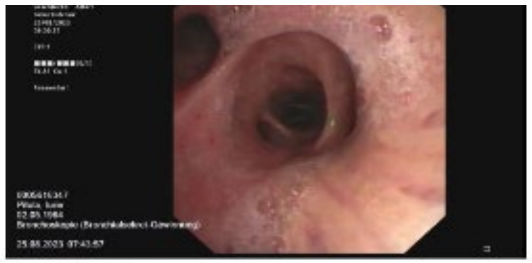


rechter Hauptbronchus



Befund

Stimmlippen unauffällig, Trachea mittelständig, Hauptkarina schlank. Rechts wie links sind alle Ostien bis auf Subsegmentebene offen, einsehbar und belüftet ohne Tumorzeichen. Der Befund im linken Hauptbronchus ist wohl Sekret gewesen.



Bronchus intermedius

EUROPEAN RESPIRATORY journal
FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Culture-positive pulmonary tuberculosis with a normal chest x-ray in the absence of HIV co-infection

James Brown, Graham Bothamley
European Respiratory Journal 2012 40: P2613; **DOI:**

Table 1

Code	Reason for investigation	CT	Sputum smear	Days to culture	HIV test	Contacts	Outcome
4.090	cough; weight loss	nd	3 -	13	negative	5	Mother MLN
6.047	Haemoptysis	Normal	3 -	7	nd	4	All DNA
6.073	Cough, haemoptysis, weight loss	nd.	++, 2 -	no culture	nd	1	mother: miliary TB
6.064	Refugee; QFT 2.6 IU/L	nd	3 -	24	negative	2	Case worker QFT +
12.009	Contact; PPD 23mm, QFT 0.38 IU/L cough 2m after 1st seen	normal	1 -	25	negative	refused	

nd= not done; MLN= mediastinal lymphadenopathy; QFN= Quantiferon Gold in tube

Conclusions: Although 3 sputum samples were usually sent, often only one proved culture-positive. CT scans may not reveal active disease. Two with a positive smear had contacts who had forms of TB suggesting recent infection.

Fazit:

„Versteckte Tuberkulose“

- Zur Fallfindung im Verdachtsfall sollte in der Diagnostik strikt eine **Kombination von Bildgebung und Probenentnahme für die Mikrobiologie** herangezogen werden.

- Es sollte sich nicht auf nur ein Verfahren zum Nachweis oder Ausschluss einer aktiven Tuberkulose verlassen werden.

Teil 2

Der Stamm

Resistogramm

	[1]
Isoniazid INH *(0,20)	R (>5.0 mg/l)
Ethambutol EMB *(5)	S
Rifampicin RMP * (0,5)	R (>1.0 mg/l)
Pyrazinamid *(100)	R
Cycloserin/Terizidon * (30)	S
Moxifloxacin *(0,5)	S
Moxifloxacin *((2.0))	S
Rifabutin *(0,5)	R (>2.0 mg/l)
Amikacin *(2)	S
p- Aminosalicylsäure *(2)	S
Linezolid *(1)	S

NRZ Borstel:
Bedaquilin: atpE: Wildtyp (sensibel)
Nachbefund NRZ Borstel:
Bedaquilin: Rv0678-Gen: bp 141 ins C Mutation vorhanden => Mutation nicht bekannt, macht aber einen frameshift, deswegen ist von einer Resistenz auszugehen

Bedaquilin (1,0mg/l):MHK 4.0mg/L => RESISTENT
Clofazimin: MHK 2.0mg/l => RESISTENT
Delamanid (0,06mg/l):sensibel
Pretomanid (0,5mg/l): sensibel

!! 5.10.

- **<u>Ende Bedaquilin = Ende BPaLM</u>**
- Umstellung der ATT:
  - Delamanid, Linezolid, Moxifloxacin, Terizidon

Epidemiologie: Bedaquilin-Resistenz

MDR *M. tuberculosis* outbreak clone in Eswatini missed by Xpert has elevated bedaquiline resistance dated to the pre-treatment era

Patrick Beckert[1,2†], Elisabeth Sanchez-Padilla[3†], Matthias Merker[1†], Viola Dreyer[1], Thomas A. Kohl[1], Christian Utpatel[1], Claudio U. Köser[4], Ivan Barilar[1], Nazir Ismail[5,6,7], Shaheed Vally Omar[5], Marisa Klopper[8,9], Robin M. Warren[8,9], Harald Hoffmann[10], Gugu Maphalala[11], Elisa Ardizzoni[12], Bouke C. de Jong[12], Bernhard Kerschberger[13], Birgit Schramm[3], Sönke Andres[14], Katharina Kranzer[14,15], Florian P. Maurer[14,16], Maryline Bonnet[3,17] and Stefan Niemann[1,2,14,18*]

Abstract

Background: Multidrug-resistant (MDR) *Mycobacterium tuberculosis* complex strains not detected by commercial molecular drug susceptibility testing (mDST) assays due to the RpoB I491F resistance mutation are threatening the control of MDR tuberculosis (MDR-TB) in Eswatini.

Methods: We investigate the evolution and spread of MDR strains in Eswatini with a focus on bedaquiline (BDQ) and clofazimine (CFZ) resistance using whole-genome sequencing in two collections ((1) national drug resistance survey, 2009–2010; (2) MDR strains from the Nhlangano region, 2014–2017).

Results: MDR strains in collection 1 had a high cluster rate (95%, 117/123 MDR strains) with 55% grouped into the two largest clusters (gCL3, $n = 28$; gCL10, $n = 40$). All gCL10 isolates, which likely emerged around 1993 (95% highest posterior density 1987–1998), carried the mutation RpoB I491F that is missed by commercial mDST assays. In addition, 21 (53%) gCL10 isolates shared a Rv0678 M146T mutation that correlated with elevated minimum inhibitory concentrations (MICs) to BDQ and CFZ compared to wild type isolates. gCL10 isolates with the Rv0678 M146T mutation were also detected in collection 2.

Conclusion: The high clustering rate suggests that transmission has been driving the MDR-TB epidemic in Eswatini for three decades. The presence of MDR strains in Eswatini that are not detected by commercial mDST assays and have elevated MICs to BDQ and CFZ potentially jeopardizes the successful implementation of new MDR-TB treatment guidelines. Measures to limit the spread of these outbreak isolates need to be implemented urgently.

Keywords: Tuberculosis, Multidrug resistance, Resistance evolution, MDR outbreak strains, Diagnostice escape, Treatment escape, Treatment failure

Beckert et al. Genome Medicine (2020) 12:104https://doi.org/10.1186/s13073-020-00793-8

Emergence of bedaquiline resistance in a high tuberculosis burden country

Elena Chesov[1,2,3,4,12], Dumitru Chesov[1,3,4,12], Florian P. Maurer[5,6], Sönke Andres[5], Christian Utpatel[7], Ivan Barilar[7], Ana Donica[2], Maja Reimann[3,4,8], Stefan Niemann[3,5,7], Christoph Lange[2,3,8,9,10], Valeriu Crudu[2], Jan Heyckendorf[3,4,8,12] and Matthias Merker[3,7,11,12]

Methods In a cross-sectional cohort study, we employed patient data, whole-genome sequencing (WGS) and phenotyping of *Mycobacterium tuberculosis* complex (MTBC) isolates. We could retrieve baseline isolates from 30.5% (62 out of 203) of all MDR-TB patients who received bedaquiline between 2016 and 2018 in the Republic of Moldova. This includes 26 patients for whom we could also retrieve a follow-up isolate.

Measurements and main results At baseline, all MTBC isolates were susceptible to bedaquiline. Among 26 patients with available baseline and follow-up isolates, four (15.3%) patients harboured strains which acquired bedaquiline resistance under therapy, while one (3.8%) patient was re-infected with a second bedaquiline-resistant strain. Treatment failure and death were associated with cavitary disease (p=0.011), and any additional drug prescribed in the bedaquiline-containing regimen with WGS-predicted resistance at baseline (OR 1.92 per unit increase, 95% CI 1.15–3.21; p=0.012).

Conclusions MDR-TB treatments based on bedaquiline require a functional background regimen to achieve high cure rates and to prevent the evolution of bedaquiline resistance. Novel MDR-TB therapies with bedaquiline require timely and comprehensive drug resistance monitoring.

Chesov et al, Eur Respir J 2022; https://doi.org/10.1183/13993003.00621-2021

Emergence of bedaquiline-resistant tuberculosis and of multidrug-resistant and extensively drug-resistant *Mycobacterium tuberculosis* strains with *rpoB* Ile491Phe mutation not detected by Xpert MTB/RIF in Mozambique: a retrospective observational study

Ivan Barilar, Tatiana Fernando*, Christian Utpatel*, Cláudio Abujate, Carla Maria Madeira, Benedita José, Claudia Mutaquiha, Katharina Kranzer, Tanja Niemann, Nalia Ismael, Leonardo de Araujo, Thierry Wirth, Stefan Niemann†, Sofia Vieqas†*

Findings Between Jan 1, 2015, and July 31, 2021, 2606 Mtbc isolates with an isoniazid or rifampicin resistance were identified in the NTRL biobank, of which, 1483 (56·9%) were from men, 1114 (42·7%) from women, and nine (0·4%) were unknown. Genome-based drug-resistant prediction classified 704 Mtbc strains as rifampicin resistant. 628 (89%) of the 704 Mtbc strains were classified MDR; of those, 146 (23%) were pre-extensively drug resistant (pre-XDR; additional fluoroquinolone resistance), and 24 (4%) extensively drug resistant (XDR; combined fluoroquinolone and bedaquiline resistance). Overall, 61 (9%) of 704 strains revealed resistance to bedaquiline: five (7%) of 76 rifampicin resistant plus bedaquiline resistant, 33 (7%) of 458 MDR plus bedaquiline resistant, and 24 (100%) of 24 XDR. Prevalence of bedaquiline resistance increased from 3% in 2016 to 14% in 2021. The cluster rate (12 single-nucleotide polymorphism threshold) was 42% for rifampicin resistant strains, 78% for MDR strains, 94% for pre-XDR strains, and 96% for XDR Mtbc strains. 31 (4%) of 704 Mtbc strains, belonging to a diagnostic escape outbreak strain previously described in Eswatini (group_56), had an *rpoB* Ile491Phe mutation which is not detected by Xpert MTB/RIF (no other *rpoB* mutation). Of these, 23 (74%) showed additional resistance to bedaquiline, 13 (42%) had bedaquiline and fluoroquinolone resistance, and two (6%) were bedaquiline, fluoroquinolone, and delamanid resistant.

Barilar et al. The lancet 2023, https://doi.org/10.1016/ S1473-3099(23)00550-9

Helios

Bedaquiline resistance mechanisms

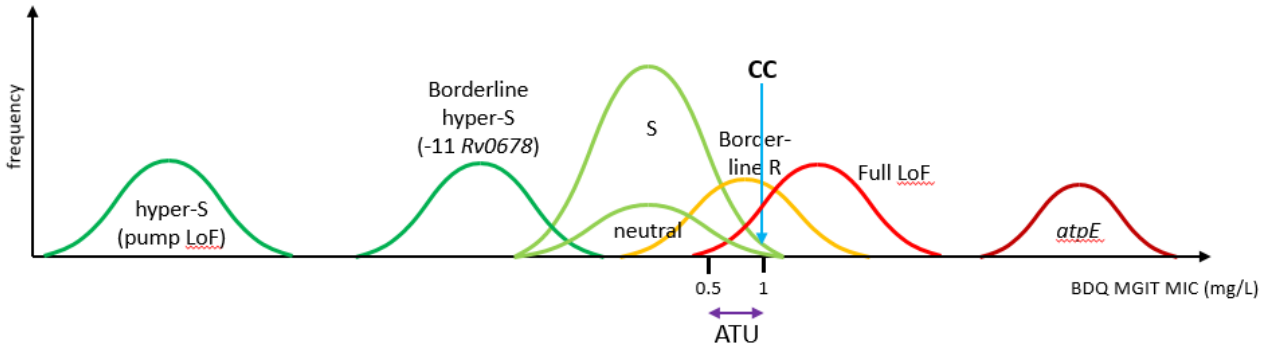
Table 1. Mechanisms of Bedaquiline Resistance

Genes	Gene Function	MIC Increase
*atp*E [4, 45]	Coding for a transmembrane protein of the ATP synthase, target of Bdq	8- to 133-fold increase in Bdq MIC
Rv0678 [16, 18]	Regulating the expression of the MmpS5-MmpL5 efflux pump	2- to 8-fold increase in Bdq MIC and 2- to 4-fold increase in clofazimine MIC
*pep*Q [24]	Unclear	4-fold increase in Bdq and clofazimine MICs

Nguyen et al 2018 DOI: 10.1093/cid/cix992

Bedaquilin-Resistenz

Bedaquiline



- Mutations in essential *atpE* target are easy to interpret and detect by pAST but are rare (NB: they are not always secondary resistance mutations).
- *Rv0678* dominant resistance mechanism but:
  - Large spectrum of mutations, which can have no (neutral), modest (borderline R – e.g. M146T from Eswatini) or full loss-of-function (LoF) effect with maximal overexpression of *mmpS5-mmpL5* efflux pump.
  - Epistasis: *Rv0678* mutations cannot confer resistance in *mmpS5-mmpL5* LoF background (rare globally, but frequent in Lima, Peru, and some South-East Asian countries).
  - Hetereroresistance plays a major role as a greater proposition of resistance is selected vs. transmitted.
  - Low PPV of pAST as true prevalence of resistance is low in most settings.
  - Associations studies with outcomes need to consider above confounders (retesting discordant results is key).

Merker et al. Genome Med. 2020 12:27
Li et al. Nat Microbiol. 2022 Jun;7(6):766-79
Villellas et al. J Antimicrob Chemother. 2017 72:684-90
Vargas et al. Antimicrob Agents Chemother. 2021 65:e0116421

Slide: Claudio Köser, WHO, ESM Tirana 2023

Befund aus dem NRZ Borstel

Material: Fluessig Kultur Andere

Differenzierung

- *Mycobacterium tuberculosis [1]*
  Im Zusendelabor identifiziert.

Molekulare Resistenzbestimmung

Bedaquilin: Rv0678-Gen: bp141 ins C Mutation vorhanden (VERMUTLICH RESISTENT)
Bedaquilin: atpE: Wildtyp (sensibel)

Für Pretomanid ist derzeit kein Referenzwert ("Clinical Breakpoint") zur Bewertung der Empfindlichkeit des Erregers ("S" / "R") seitens der WHO oder EUCAST definiert. Das Isolat zeigte bei 1 mg/l im MGIT 960 kein Wachstum. Die EMA nennt 1 mg/l als vorläufige kritische Konzentration. Bitte beachten Sie die geänderte kritische Konzentration für Rifampicin (vormals 1,0 mg/l, jetzt 0,5 mg/l; WHO 2021). Damit verbessert sich der Nachweis von "borderline" Resistenzen, die als klinisch relevant erachtet werden, jedoch nur mit geringfügigen Erhöhungen der minimalen Hemmkonzentration einhergehen. Unabhängig von dieser Anpassung sollte zum Ausschluss einer Rifampicinresistenz auch weiterhin grundsätzlich eine molekularbiologische Untersuchung des rpoB-Gens erfolgen.

Für Cycloserin ist aufgrund von ungenügenden Daten international keine kritische Konzentration etabliert. Das von uns berichtete Ergebnis beruht auf eigenen Erfahrungswerten und gilt daher unter Vorbehalt.

Kommentar

Antibiogramm		**[1]**
Levofloxacin	(1 mg/l)	S
Moxifloxacin	(0,25 mg/l)	S
Moxifloxacin	(1 mg/l)	S
Bedaquilin	(0,5 mg/l)	R
Bedaquilin	(1,0 mg/l)	R
Bedaquilin	(2,0 mg/l)	R
Bedaquilin	(4,0 mg/l)	S
Linezolid	(1 mg/l)	S
Clofazimin	(0,5 mg/l)	R
Clofazimin	(1,0 mg/l)	R
Clofazimin	(2,0 mg/l)	S
Clofazimin	(4,0 mg/l)	S
Cycloserin	(30 mg/l)	S
Pretomanid	(0,5 mg/l)	S
Pretomanid	(1 mg/l)	S
Amikacin	(1 mg/l)	S
Protionamid	(2,5 mg/l)	S
Delamanid	(0,06 mg/l)	S

S = sensibel R = resistent I = intermediär
K = keine Interpretation F = folgt

Neuer WHO Katalog (2nd. Edition)

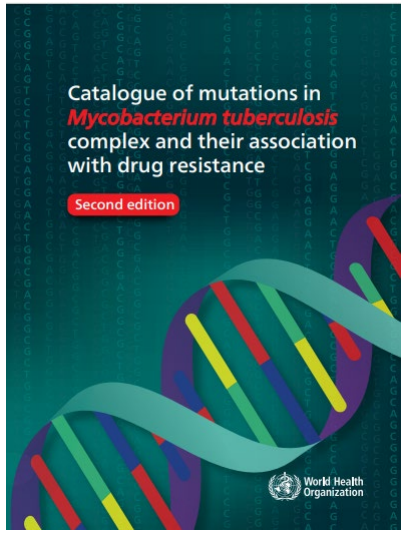


Table 12. Abridged variant classification for BDQ

Drug	Variant	MUT Present_pheno S	MUT Absent_pheno S	MUT Present_pheno R	MUT Absent_pheno R	Sensitivity	Specificity	PPV	PPV SOLO	PPV SOLO_ub	PPV|SOLO_lb	OR SOLO	Initial confidence grading	Supporting dataset	Additional grading criteria applied	Final confidence grading	Notes	Changes vs prev. ver.
BDQ	Rv0678_LoF	134	12817	424	611	41.0%	99.0%	76.0%	79.5%	82.9%	71.3%	81.1	1) AwR	ALL+WHO		1) Assoc w R	E	
BDQ	Rv0678_p.Glu49fs	26	12925	142	893	13.7%	99.8%	84.5%	85.7%	90.7%	77.6%	86.8	1) AwR	ALL+WHO		1) Assoc w R	E	
BDQ	Rv0678_p.Asp47fs	25	12926	61	974	5.9%	99.8%	70.9%	71.1%	80.5%	59.3%	32.6	1) AwR	ALL+WHO		1) Assoc w R	E	
BDQ	Rv0678_p.Ile67fs	35	12916	52	983	5.0%	99.7%	59.8%	76.1%	85.7%	48.2%	41.9	1) AwR	ALL+WHO		1) Assoc w R	E	
BDQ	Rv0678_p.Gly121Arg	1	12950	9	1026	0.9%	100.0%	90.0%	90.0%	99.7%	55.5%	113.6	1) AwR	ALL+WHO		1) Assoc w R	E	
BDQ	Rv0678_p.Leu117Arg	4	12947	8	1027	0.8%	100.0%	66.7%	66.7%	90.1%	34.9%	25.2	1) AwR	ALL+WHO		1) Assoc w R	E	
BDQ	Rv0678_p.Met146Thr	0	1249	11	890	1.2%	100.0%	100.0%	100.0%	100.0%	71.5%	Inf	1) AwR	WHO	Pot. infl. PPV	2) Assoc w R - Interim	C, E, O	
BDQ	Rv0678_p.Ile67Ser	0	12951	12	1023	1.2%	100.0%	100.0%	100.0%	100.0%	73.5%	Inf	1) AwR	ALL+WHO	Pot. infl. PPV	2) Assoc w R - Interim	C, E, O	
BDQ	Rv0678_p.Cys46Arg	1	12950	9	1026	0.9%	100.0%	90.0%	90.0%	99.7%	55.5%	113.6	1) AwR	ALL+WHO	Pot. infl. PPV	2) Assoc w R - Interim	C, E, O	
BDQ	pepQ_LoF	4	12947	8	1027	0.8%	100.0%	66.7%	63.6%	89.1%	30.8%	22.1	1) AwR	ALL	ALL only	2) Assoc w R - Interim	C	
BDQ	atpE_p.Ala63Pro	0	12951	7	1028	0.7%	100.0%	100.0%	100.0%	100.0%	47.8%	Inf	1) AwR	ALL	ALL only	2) Assoc w R - Interim	C	
BDQ	atpE_p.Ile66Met	0	12951	7	1028	0.7%	100.0%	100.0%	100.0%	100.0%	54.1%	Inf	1) AwR	ALL	ALL only	2) Assoc w R - Interim	C	
BDQ	Rv0678_p.Ala36Val	0	12951	6	1029	0.6%	100.0%	100.0%	100.0%	100.0%	54.1%	Inf	1) AwR	ALL	ALL only	2) Assoc w R - Interim	C, E, O	
BDQ	Rv0678_p.Asn70Asp	1	12950	6	1029	0.6%	100.0%	85.7%	85.7%	99.6%	42.1%	75.5	1) AwR	ALL	ALL only	2) Assoc w R - Interim	C, E, O	
BDQ	Rv0678_p.Leu32Ser	1	12950	5	1030	0.5%	100.0%	83.3%	83.3%	99.6%	35.9%	62.9	1) AwR	ALL	ALL only	2) Assoc w R - Interim	C, E, O	
BDQ	atpE_p.Glu61Asp	3	12948	2	1033	0.2%	100.0%	40.0%	50.0%	93.2%	5.3%	12.5	3) Uncertain	ALL+WHO	Selection	2) Assoc w R - Interim		
BDQ	atpE_p.Asp28Ala	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Selection	2) Assoc w R - Interim		
BDQ	atpE_p.Asp28Gly	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Selection	2) Assoc w R - Interim		
BDQ	atpE_p.Asp28Val	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Selection	2) Assoc w R - Interim		
BDQ	mmpL5_LoF	247	12704	0	1035	0.0%	98.1%	0.0%	0.0%	1.7%	0.0%	0.0	3) Uncertain	ALL+WHO		3) Uncertain significance	D	
BDQ	mmpL5_p.Ile948Val	1245	4	895	6	99.3%	0.3%	41.8%	7.7%	10.6%	2.0%	0.1	5) NotAwR	WHO	Lit. (PMID 28031270; 34503982)	4) Not assoc w R - Interim		
BDQ	Rv1979c_c.-129A>G	1238	11	893	8	99.1%	0.9%	41.9%	NA	NA	0.0%	NA	5) NotAwR	WHO	Lit. (PMID 28031270; 34503982)	4) Not assoc w R - Interim		
BDQ	mmpL5_p.Thr794Ile	760	489	635	266	70.5%	39.2%	45.5%	NA	NA	0.0%	NA	5) NotAwR	WHO	Lit. (PMID 28031270; 34503982)	4) Not assoc w R - Interim		
BDQ	Rv1979c_p.Asp286Gly	48	1201	71	830	7.9%	96.2%	59.7%	NA	NA	0.0%	NA	5) NotAwR	WHO	Lit. (PMID 28031270; 34503982)	4) Not assoc w R - Interim		
BDQ	mmpS5_c.-74G>T	3	1246	36	865	4.0%	99.8%	92.3%	NA	NA	0.0%	NA	5) NotAwR	WHO	Lit. (PMID 28031270; 34503982)	4) Not assoc w R - Interim		
BDQ	mmpL5_p.Asp767Asn	509	740	146	755	16.2%	59.2%	22.3%	NA	NA	0.0%	NA	5) NotAwR	WHO		5) Not assoc w R		

Drug	Variant	MUT Present_pheno S	MUT Absent_pheno S	MUT Present_pheno R	MUT Absent_pheno R	Sensitivity	Specificity	PPV	PPV SOLO	PPV SOLO_ub	PPV|SOLO_lb	OR SOLO	Initial confidence grading	Supporting dataset	Additional grading criteria applied	Final confidence grading	Notes	Changes vs prev. ver.
BDQ	Rv0678_p.Leu142Arg	2	12949	7	1028	0.7%	100.0%	77.8%	50.0%	93.2%	6.8%	12.6	3) Uncertain	ALL+WHO		3) Uncertain significance	O	
BDQ	Rv0678_p.Gly41Asp	0	12951	4	1031	0.4%	100.0%	100.0%	100.0%	100.0%	39.8%	Inf	3) Uncertain	ALL+WHO		3) Uncertain significance	O	
BDQ	Rv0678_p.Ser53Pro	0	12951	4	1031	0.4%	100.0%	100.0%	100.0%	100.0%	39.8%	Inf	3) Uncertain	ALL+WHO		3) Uncertain significance	O	
BDQ	Rv0678_p.Thr91Ile	0	12951	4	1031	0.4%	100.0%	100.0%	100.0%	100.0%	39.8%	Inf	3) Uncertain	ALL+WHO		3) Uncertain significance	O	
BDQ	Rv0678_p.Arg94Trp	1	12950	3	1032	0.3%	100.0%	75.0%	75.0%	99.4%	19.4%	37.6	3) Uncertain	ALL+WHO		3) Uncertain significance	O	
BDQ	Rv0678_p.Asp47dup	0	12951	3	1032	0.3%	100.0%	100.0%	100.0%	100.0%	29.2%	Inf	3) Uncertain	ALL+WHO		3) Uncertain significance	O	
BDQ	Rv0678_p.Gly65Glu	0	12951	3	1032	0.3%	100.0%	100.0%	100.0%	100.0%	29.2%	Inf	3) Uncertain	ALL+WHO		3) Uncertain significance	O	
BDQ	Rv0678_p.Leu60Pro	0	12951	3	1032	0.3%	100.0%	100.0%	100.0%	100.0%	15.8%	Inf	3) Uncertain	ALL+WHO		3) Uncertain significance	O	
BDQ	Rv0678_p.Pro48Leu	1	12950	3	1032	0.3%	100.0%	75.0%	75.0%	99.4%	19.4%	37.6	3) Uncertain	ALL+WHO		3) Uncertain significance	O	
BDQ	Rv0678_p.Ser2Ile	1	12950	3	1032	0.3%	100.0%	75.0%	75.0%	99.4%	19.4%	37.6	3) Uncertain	ALL+WHO		3) Uncertain significance	O	
BDQ	Rv0678_p.Ser63Gly	0	12951	3	1032	0.3%	100.0%	100.0%	100.0%	100.0%	29.2%	Inf	3) Uncertain	ALL+WHO		3) Uncertain significance	O	
BDQ	Rv0678_p.Ala102Thr	0	12951	2	1033	0.2%	100.0%	100.0%	100.0%	100.0%	15.8%	Inf	3) Uncertain	ALL+WHO		3) Uncertain significance	O	
BDQ	Rv0678_p.Ala99Pro	0	12951	2	1033	0.2%	100.0%	100.0%	100.0%	100.0%	15.8%	Inf	3) Uncertain	ALL+WHO		3) Uncertain significance	O	
BDQ	Rv0678_p.Arg107Cys	1	12950	2	1033	0.2%	100.0%	66.7%	66.7%	99.2%	9.4%	25.1	3) Uncertain	ALL+WHO		3) Uncertain significance	O	
BDQ	Rv0678_p.Arg109Pro	0	12951	2	1033	0.2%	100.0%	100.0%	100.0%	100.0%	15.8%	Inf	3) Uncertain	ALL+WHO		3) Uncertain significance	O	
BDQ	Rv0678_p.Arg34Gln	0	12951	2	1033	0.2%	100.0%	100.0%	100.0%	100.0%	15.8%	Inf	3) Uncertain	ALL+WHO		3) Uncertain significance	O	
BDQ	Rv0678_p.Arg34Trp	0	12951	2	1033	0.2%	100.0%	100.0%	100.0%	100.0%	15.8%	Inf	3) Uncertain	ALL+WHO		3) Uncertain significance	O	
BDQ	Rv0678_p.Arg50Gln	1	12950	2	1033	0.2%	100.0%	66.7%	66.7%	99.2%	9.4%	25.1	3) Uncertain	ALL+WHO		3) Uncertain significance	O	
BDQ	Rv0678_p.Asn70Ile	0	12951	2	1033	0.2%	100.0%	100.0%	100.0%	100.0%	15.8%	Inf	3) Uncertain	ALL+WHO		3) Uncertain significance	O	
BDQ	Rv0678_p.Cys46Trp	0	12951	2	1033	0.2%	100.0%	100.0%	100.0%	100.0%	15.8%	Inf	3) Uncertain	ALL+WHO		3) Uncertain significance	O	
BDQ	Rv0678_p.Gln115Pro	0	12951	2	1033	0.2%	100.0%	100.0%	100.0%	100.0%	15.8%	Inf	3) Uncertain	ALL+WHO		3) Uncertain significance	O	
BDQ	Rv0678_p.Gly78Arg	0	12951	2	1033	0.2%	100.0%	100.0%	100.0%	100.0%	15.8%	Inf	3) Uncertain	ALL+WHO		3) Uncertain significance	O	
BDQ	Rv0678_p.Ile67Leu	0	12951	2	1033	0.2%	100.0%	100.0%	100.0%	100.0%	15.8%	Inf	3) Uncertain	ALL+WHO		3) Uncertain significance	O	
BDQ	Rv0678_p.Leu122Pro	0	12951	2	1033	0.2%	100.0%	100.0%	100.0%	100.0%	15.8%	Inf	3) Uncertain	ALL+WHO		3) Uncertain significance	O	
BDQ	Rv0678_p.Leu35Trp	0	12951	2	1033	0.2%	100.0%	100.0%	100.0%	100.0%	15.8%	Inf	3) Uncertain	ALL+WHO		3) Uncertain significance	O	
BDQ	Rv0678_p.Leu40Phe	0	12951	2	1033	0.2%	100.0%	100.0%	100.0%	100.0%	15.8%	Inf	3) Uncertain	ALL+WHO		3) Uncertain significance	O	
BDQ	Rv0678_p.Leu60Gln	0	12951	2	1033	0.2%	100.0%	100.0%	100.0%	100.0%	15.8%	Inf	3) Uncertain	ALL+WHO		3) Uncertain significance	O	
BDQ	Rv0678_p.Leu95Ser	1	12950	2	1033	0.2%	100.0%	66.7%	66.7%	99.2%	9.4%	25.1	3) Uncertain	ALL+WHO		3) Uncertain significance	O	
BDQ	Rv0678_p.Met139Ile	1	12950	2	1033	0.2%	100.0%	66.7%	66.7%	99.2%	9.4%	25.1	3) Uncertain	ALL+WHO		3) Uncertain significance	O	
BDQ	Rv0678_p.Phe79Leu	0	12951	2	1033	0.2%	100.0%	100.0%	100.0%	100.0%	15.8%	Inf	3) Uncertain	ALL+WHO		3) Uncertain significance	O	

Helios

Vielen Dank