LOST IN TRANSLATION?

CONSIDERING USER NEEDS IN REPORTING CLINICAL MICROBIAL GENOMICS RESULTS

@JENNIFERGARDY
BC CENTRE FOR DISEASE CONTROL

SUCCESSFULLY IMPLEMENTING CLINICAL (META)GENOMICS REQUIRES HAPPY END USERS; THIS COMES FROM USER-CENTRED DESIGN

USER-CENTRED DESIGN IS NOT ASKING WHAT YOUR USERS NEED, NOR IS IT GIVING THEM WHAT YOU WANT

EVERYTHING* YOU ASSUME ABOUT YOUR USER AND THEIR ENVIRONMENT IS WRONG

* not really, but it makes for a snappy quote

DESIGN IS A PROCESS, NOT A PRODUCT,
AND DESIGN IS MORE THAN LOOK AND FEEL,
IT'S ABOUT HOW SOMETHING WORKS

AN EXAMPLE FROM CLINICAL TUBERCULOSIS WGS REPORT DESIGN

Rapid, comprehensive, and affordable mycobacterial diagnosis with whole-genome sequencing: a prospective study

Louise J Pankhurst, Carlos del Ojo Elias*, Antonina A Votintseva*, Timothy M Walker*, Kevin Cole, Jim Davies, Jilles M Fermont, Deborah M Gascoyne-Binzi, Thomas A Kohl, Clare Kong, Nadine Lemaitre, Stefan Niemann, John Paul, Thomas R Rogers, Emma Roycroft, E Grace Smith, Philip Supply, Patrick Tang, Mark H Wilcox, Sarah Wordsworth, David Wyllie, Li Xu, Derrick W Crook, for the COMPASS-TB Study Group†*

Summary

Background Slow and cumbersome laboratory diagnostics for *Mycobacterium tuberculosis* complex (MTBC) risk delayed treatment and poor patient outcomes. Whole-genome sequencing (WGS) could potentially provide a rapid and comprehensive diagnostic solution. In this prospective study, we compare real-time WGS with routine MTBC diagnostic workflows.

Methods We compared sequencing mycobacteria from all newly positive liquid cultures with routine laboratory diagnostic workflows across eight laboratories in Europe and North America for diagnostic accuracy, processing times, and cost between Sept 6, 2013, and April 14, 2014. We sequenced specimens once using local Illumina MiSeq platforms and processed data centrally using a semi-automated bioinformatics pipeline. We identified species or complex using gene presence or absence, predicted drug susceptibilities from resistance-conferring mutations identified from reference-mapped MTBC genomes, and calculated genetic distance to previously sequenced UK MTBC isolates to detect outbreaks. WGS data processing and analysis was done by staff masked to routine reference laboratory and clinical results. We also did a microcosting analysis to assess the financial viability of WGS-based diagnostics.

Findings Compared with routine results, WGS predicted species with 93% (95% CI 90–96; 322 of 345 specimens; 356 mycobacteria specimens submitted) accuracy and drug susceptibility also with 93% (91–95; 628 of 672 specimens; 168 MTBC specimens identified) accuracy, with one sequencing attempt. WGS linked 15 (16% [95% CI 10–26]) of 91 UK patients to an outbreak. WGS diagnosed a case of multidrug-resistant tuberculosis before routine diagnosis was completed and discovered a new multidrug-resistant tuberculosis cluster. Full WGS diagnostics could be generated in a median of 9 days (IQR 6–10), a median of 21 days (IQR 14–32) faster than final reference laboratory reports were produced (median of 31 days [IQR 21–44]), at a cost of £481 per culture-positive specimen, whereas routine diagnosis costs £518, equating to a WGS-based diagnosis cost that is 7% cheaper annually than are present diagnostic workflows.

Interpretation We have shown that WGS has a scalable, rapid turnaround, and is a financially feasible method for full MTBC diagnostics. Continued improvements to mycobacterial processing, bioinformatics, and analysis will improve the accuracy, speed, and scope of WGS-based diagnosis.

Lancet Respir Med 2016; 4: 49–58

Published Online December 3, 2015 http://dx.doi.org/10.1016/S2213-2600(15)00466-X

See Comment page 6

*Contributed equally

†Members listed in the appendix

Microbiology and Infectious Diseases, Nuffield Department of Clinical Medicine, John Radcliffe Hospital (L J Pankhurst PhD, C del Ojo Elias MSc, A A Votintseva PhD, T M Walker MRCP, D W Crook FRCPath, D Wyllie FRCPath), **Health Economics Research Centre, Nuffield Department of Population Health** (J M Fermont MSc, S Wordsworth PhD), **and Department of Computer Science** (Prof J Davies PhD), **University of Oxford, Oxford, UK; Brighton and Sussex University Hospitals NHS Trust, Brighton, UK** (K Cole BSc, J Paul MD); **Public Health England Regional Centre for**

1-DAY POSITIVE CULTURES ARE SEQUENCED

SPECIES, RESISTANCE, & CLUSTERING ARE REPORTED

Whole Genome Sequencing Report from MGIT Positive Samples

Not for diagnostic use

Sample Details			
Sequencing Location	Vancouver	Date Received in Lab	4th Nov 2013
Local LIMS Specimen ID	H4167	Run Date	18th March 2014
GUID			

Sample/Sequencing Quality	
Comments	Unable to perform resistotyping; evidence for contamination with non-mycobacterial DNA.

Organism Identification
Mycobacterium tuberculosis

Resistotype				
Drug	Prediction	HAIN Mutation	Extended Catalogue	Ambiguous
Isoniazid				
Rifampicin				
Ethambutol				
Pyrazinamide				
Streptomycin				
Moxifloxacin				
Amikacin				

Relatedness			
Nearest neighbour(s)	Based on 81% genome coverage		Genealogy
GUID	No. of SNPs Apart	Centre	
C00014793	272	Birmingham	

Authorised	
Signature:	Print name: Timothy Walker
Position:	Date: 3 April 2014

COMPASS-TB REPORT V.1 (2014)

VERSION 2 (2015)

Mycobacterium Whole Genome Sequencing Report from MGIT Positive Samples

Not for diagnostic use 01/02/1915

Sample Details

Sequencing Location	Oxford	**Date received in Lab**	
Local Lims Specimen ID	123456789	**Run date**	01/01/19150115
Guuid	123456-79aab-910abr-15243hg		

Organism Identification

Predicted/closest match	
TBCOMP/microti	100%
TBCOMP	100%
TBCOMP/TB	96.77%
TBCOMP/tuberculosis-canettii	35.71%
MACCOMP	21.21%

Sample/Sequencing Quality

Total reads (~millions)	**Mapped %**	**No reads mapped (~millions)**	**Coverage %**
4.73	99.47	4.7	91.99

Resistance Summary

INH	**RIF**	**EMB**	**PZA**	**QUI**	**SM**	**AG**
U	S	S	S	S	S	S

Resistotype

Drug	**Mutation**	**Nucleotides**	**Support (ACGT)**	**Source – (R/Total)**	**Prediction**
INH	katG_A727T	GCC->ACC	(160/0/1/0) (0/164/0/0) (0/167/0/0)	Unclassified	UNK

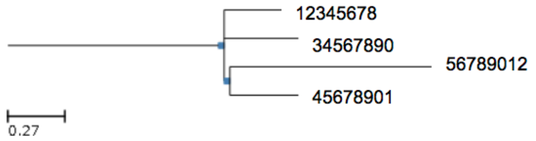
Relatedness

NB: This data may be added or updated at a later date

Nearest neighbour(s)

Sample -Plate Name	**Date received in Lab**	**Centre**	**No. of SNPs apart**
123456789		Oxford	0
34567890	1900-01-01		10
45678901	1015-01-31	Oxford	15
56789012		London	8

The alignment width is 285. Multiply this number by the tree metrics.



Comments

Authorised

Signature:	**Print name:**
Position:	**Date:**

Mycobacterium Whole Genome Sequencing Report from MGIT
Positive Samples

Report date: 23/02/2017 04:36:56

Report version: 1.6

Sample Details

Sequencing location: N/A

Local Lims Specimen ID: n12s258

Plate name: Canada_Mtub_nprefix_NickS

Guuid: e8cab4f7-a647-45cd-85d8-27d9d252e562

Collection Date (dd/mm/yyyy): 01/01/1900 00:00:00

Sequencing date: 01/01/1900 00:00:00

Pipeline start date: 23/02/2017 01:43:52

Organism Identification

Kraken (percentage)

Human 0.00

Mykrobe		Percentage	Median
Phylo_group:	Mycobacterium_tuberculosis_complex	99.55	104
Species:	Mycobacterium_tuberculosis	98.47	103
Lineage:	Beijing_East_Asia	100.00	101

Sequencing Quality

Mapped to: R00000039

Total reads (~millions	**Mapped %**	**No reads mapped** (~millions)	**Coverage %**
4.33	99.09	4.29	92.14

Resistance Summary

INH	**RIF**	**EMB**	**PZA**	**QUI**	**SM**	**AG**
S	S	S	S	S	S	S

Resistotype

Drug	**Mutation**	**Nucleotides**	**Support** (A/C/G/T)	**Source**	**Prediction**
ETH,PRO	ethA_S266R	AGC->AGG	(100/0/0/0) (0/0/98/0) (0/0/97/0)	novel	U
Results from sensitive Line Probe					
MOX	gyrA_*94*	GAC->GAC	(0/0/106/0) (107/0/0/0) (0/106/0/0	Line-probe	S
RIF	rpoB_*450*	TCG->TCG	(0/0/0/126) (0/125/0/0) (0/0/126/0	Line-probe	S
INH	fabG1_*-15*	C->C	(0/120/0/0)	Line-probe	S
SM	rpsL_*43*	AAG->AAG	(109/0/0/0) (109/0/0/0) (0/0/107/0	Line-probe	S
EMB	embB_*306*	ATG->ATG	(141/0/0/0) (0/0/0/140) (0/0/144/0	Line-probe	S
INH	katG_*315*	AGC->AGC	(97/0/0/0) (0/0/98/0) (0/95/0/2)	Line-probe	S

Relatedness

Samples related to: **n12s258_ Canada_Mtub_nprefix_Nick**

on 23/02/2017 04:36:56

Sample - Plate name	**Center**	**CollectionDate**	**ElephantWalk snp**
n12s258-Canada_Mtub_nprefix_NickS	N/A	1900-01-01	0
11s022-BC_UK_TB_nick	N/A	1900-01-01	20

VERSION 3 (CURRENT)

Overview | Research | Talks | Publications | Teaching | Blog | CV

News

- 22 Sep 2017 : Evidence Based Report Design
- 10 May 2017 : Presenting at ABPHM
- 1 May 2017 : Teaching at CBW Infectious Epi Workshop
- 30 Apr 2017 : Advanced to Candidacy!
- 27 Mar 2017 : Thesis Proposal Defence
- 24 Oct 2016 : IEEE VIS DC presentation
- 24 Oct 2016 : Presenting at IEEE Vis 2016 Workshop
- 1 Sep 2015 : I get to start my PhD today!

About me

As of September 2015 I am starting my doctoral studies with Dr. Jennifer Gardy and Dr. Tamara Munzner at the University of British Columbia.

For my doctoral project I will study how data from multiple clinical streams (laboratory, contact networks, and medical) can be integrated and visualized - with a specific emphasis on genomic data sources. My overarching goals are to develop frameworks and prototypes that illustrate how heterogeneous and complex data can be used to support knowledge translation between researchers, clinical teams, and policy makers.

A more detailed overview of doctoral research project is available on a separate page.

I am funded through a CIHR Vanier Scholarship.

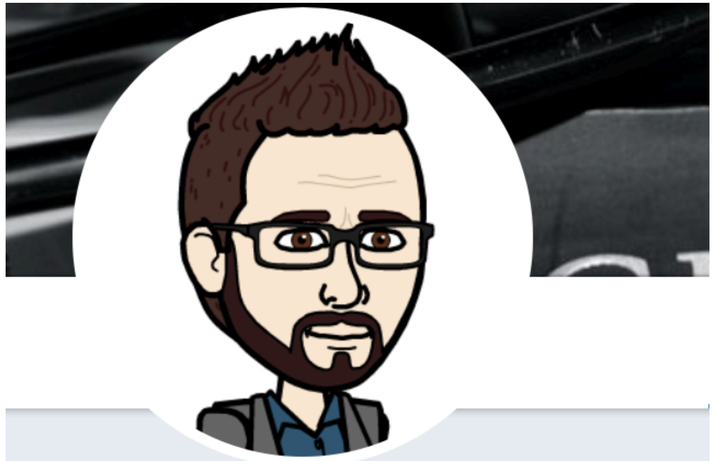
Background

I have over 5 years of experience in both industry and academic settings. I have developed pipelines and algorithms for the management and analysis of high-throughput genomic data (including next generation sequencing) and have lead translational projects that marry these technologies to clinical frameworks. My primary asset is the ability to envision, implement and especially communicate complex analyses pertaining to large amounts of heterogeneous data. In addition to my research pursuits, my goals are to also actively develop my leadership skills and work in environments that comprise multidisciplinary teams. You can either check out the publications or prior page research to learn more about my research background.

I presently hold a MSc in Bioinformatics and am also a Project Management Professional who is trained in both traditional and Agile practices and certified through the Project Management Institute.

Skill Set Summary

ANA CRISAN



Geoff McKee, MD/MPH

@DrGWM Follows you

#UBC #PHPM Resident | #PublicHealth Advocate | CD Enthusiast | Researcher | MedTech Nerd | Data Geek | Views my own, not medical advice.

GEOFF MCKEE

PeerJ

View 64 tweets

Related research

PEER-REVIEWED Bioinformatics and Genomics section ›

Evidence-based design and evaluation of a whole genome sequencing clinical report for the reference microbiology laboratory

Research article | Genomics | Microbiology | Infectious Diseases | Public Health

Anamaria Crisan [1], Geoffrey McKee [2], Tamara Munzner [1], Jennifer L. Gardy [2,3]

Published January 10, 2018 PubMed 29340235

peerj.com/articles/4218

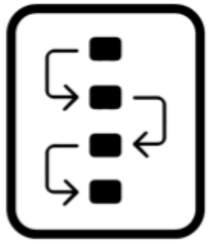
DESIGN STUDY METHODOLOGY

Discovery
Information Gathering

Design
Design & Evaluation

Implement
Finalize Design

Expert Consults

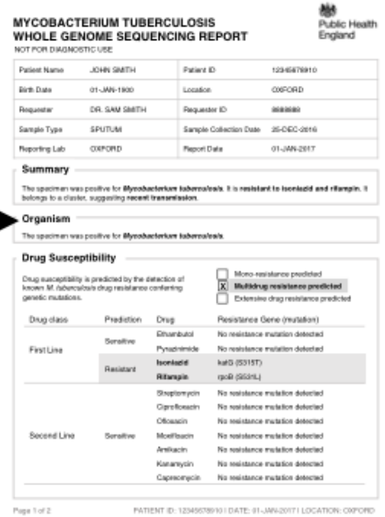


TB Workflow Map

Task & Data Questionnaire

Design Sprint

Design Choice Questionnaire



MYCOBACTERIUM TUBERCULOSIS
WHOLE GENOME SEQUENCING REPORT
NOT FOR DIAGNOSTIC USE

Public Health England

Patient Name	JOHN SMITH	Patient ID	1234567890
Birth Date	01-JAN-1900	Location	OXFORD
Requestor	DR. SAM SMITH	Requestor ID	888888
Sample Type	SPUTUM	Sample Collection Date	25-DEC-2016
Reporting Lab	OXFORD	Report Date	01-JAN-2017

Summary

The specimen was positive for ***Mycobacterium tuberculosis***. It is **resistant to isoniazid and rifampin**. It belongs to a cluster, suggesting **recent transmission**.

Organism

The specimen was positive for ***Mycobacterium tuberculosis***.

Drug Susceptibility

Drug susceptibility is predicted by the detection of known *M. tuberculosis* drug resistance conferring genetic mutations.

- ☐ Mono-resistance predicted
- ☒ **Multidrug resistance predicted**
- ☐ Extensive drug resistance predicted

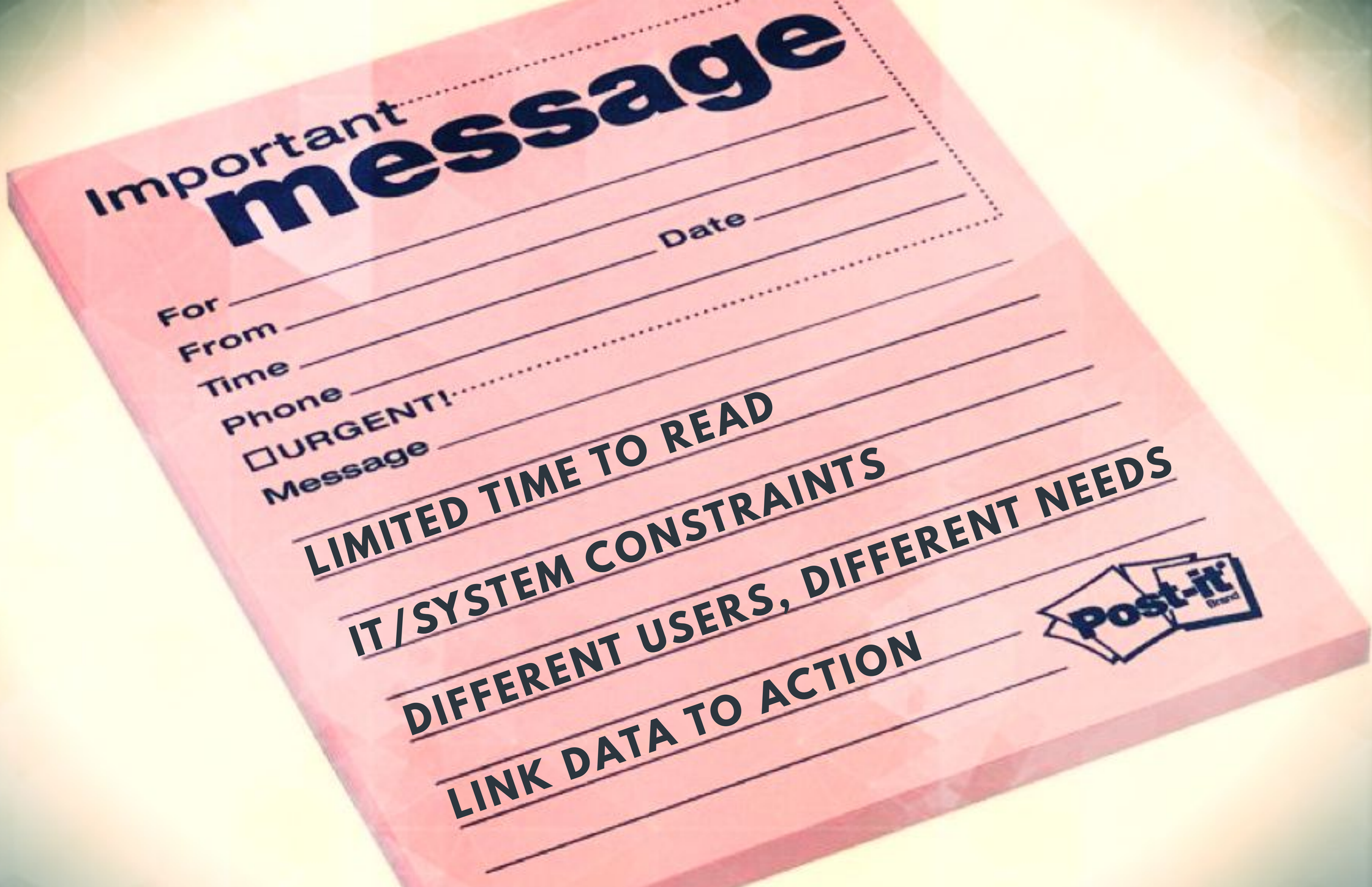
Drug class	Prediction	Drug	Resistance Gene (mutation)
First Line	Sensitive	Ethambutol	No resistance mutation detected
		Pyrazinimide	No resistance mutation detected
	Resistant	**Isoniazid**	katG (S315T)
		Rifampin	rpoB (S531L)
Second Line	Sensitive	Streptomycin	No resistance mutation detected
		Ciprofloxacin	No resistance mutation detected
		Ofloxacin	No resistance mutation detected
		Moxifloxacin	No resistance mutation detected
		Amikacin	No resistance mutation detected
		Kanamycin	No resistance mutation detected
		Capreomycin	No resistance mutation detected

Page 1 of 2 PATIENT ID: 1234567890 | DATE: 01-JAN-2017 | LOCATION: OXFORD

Data Gathered

Qualitative	○		○
Quantitative		○	○

Study Design Exploratory Sequential Model | Embedded Model

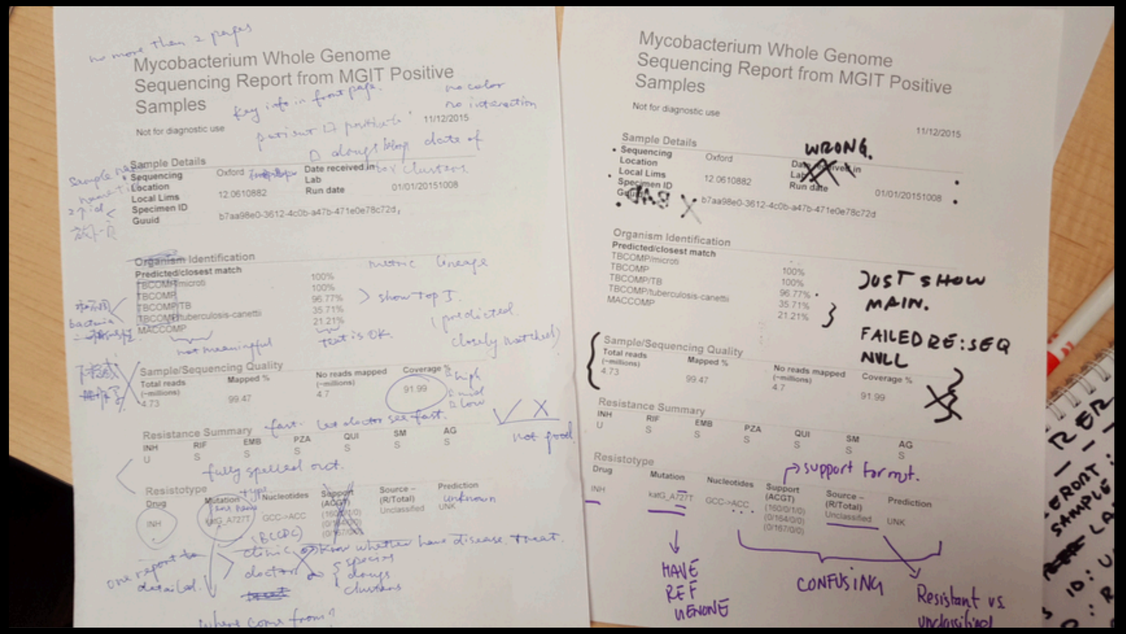

Important
message
For
From
Time
Phone
URGENT!
Message
Date
LIMITED TIME TO READ
IT/SYSTEM CONSTRAINTS
DIFFERENT USERS, DIFFERENT NEEDS
LINK DATA TO ACTION
Post-it

“10 SECONDS (TO REVIEW A REPORT) IS LIKELY, ONE MINUTE IS LUXURIOUS”

– INTERVIEWEE

“MY PATIENT’S ISOLATE IS 6 SNPS FROM ONE DIAGNOSED 3 YEARS AGO - WHAT IS THE CLINICAL ACTION?”

– SURVEY RESPONDENT



Mycobacterium Whole Genome Sequencing Report from MGIT Positive Samples

Not for diagnostic use

11/12/2015

Sample Details

Sequencing Location	Oxford	Date received in Lab	
Local Lims Specimen ID	12.0610882	Run date	01/01/20151008
Guuid	b7aa98e0-3612-4c0b-a47b-471e0e78c72d		

Organism Identification

Predicted/closest match

TBCOMP/micro6	100%
TBCOMP	100%
TBCOMP/TB	96.77%
TBCOMP/tuberculosis-canettii	35.71%
MACCOMP	21.21%

Sample/Sequencing Quality

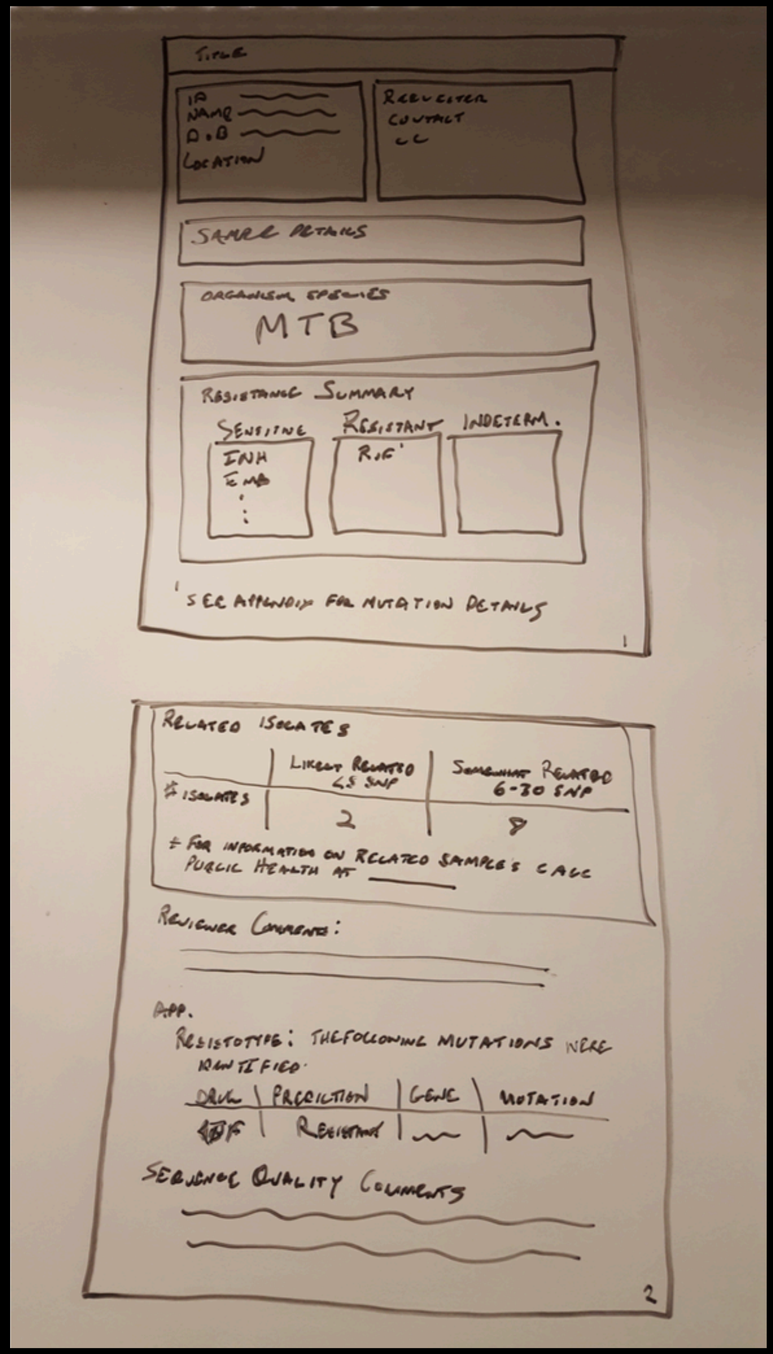
Total reads (~millions)	Mapped %	No reads mapped (~millions)	Coverage %
4.73	99.47	4.7	91.99

Resistance Summary

INH	RIF	EMB	PZA	QUI	SM	AG
U	S	S	S	S	S	S

Resistotype

Drug	Mutation	Nucleotides	Support (ACGT)	Source – (R/Total)	Prediction
INH	katG_A727T	GCC->ACC	(160/0/1/0) (0/164/0/0) (0/167/0/0)	Unclassified	UNK



1

01-01-1900 / Bob Johnson Not for diagnostic Use

Public Health England

Mycobacterium Whole Genome Sequencing Report

Report Date	01-01-1900
Laboratory	Oxford
Reviewed by	Dr. John Smith

Patient Details

Patient Name	Bob Johnson
Patient ID	123456789
Patient DoB	01-01-1900
Location	Oxford

Requester Details

Requester	Dr. Paul 1234 Smith St Birmingham, UK
Copy to	

Sample Details

Sample Type	Sputum	Sample Date	01-01-1900
Sample Site	-	Specimen ID	123456789

Speciation

Organism Species	Mycobacterium Tuberculosis

Drug Sensitivities

SUSCEPTIBLE	RESISTANT	INDETERMINATE
Ethambutol Pyrazinamide	Isoniazid[1] Rifampin[1]	

[1]Details about the mutation(s) used to predict resistance can be found in the technical section on page 2

Relatedness

	Likely Related (less than 5 SNP Difference)	Possibly Related (6-30 SNP Differences)
Number of isolates	2	6

For further information on related isolates and existing clusters, please contact the Public Health lab at 123-456-7890

01-01-1900 / Bob Johnson Not for diagnostic Use

Resistotype

Drug	Prediction	Gene	Mutation
Isoniazid	Resistant	katG	S315T
Rifampin	Resistant	rpoB	S531L

Sequence Quality

The whole genome sequence analysis of the isolate was considered HIGH QUALITY as the number of reads was greater than 4.7 million with 99.47% mapped and a coverage of 91.99% .

Reviewer Comments

No additional comments

Authorization

Signature		Print Name	Dr. John Smith
Date	01-01-1900	Position	Lab Director

2

Public Health England

Tuberculosis Genome Sequencing Results

NOT FOR DIAGNOSTIC PURPOSES

Page 1 of 2

Patient Information

Patient Name	Bob Johnson	Sample Type	Sputum
Patient ID	123456789	Sample Site	-
Patient DoB	01-01-1900	Sample Date	01-01-1900
Location	Oxford	Specimen ID	123456789

Summary of Findings

Based upon an analysis of the specimen's genomic data, this patient has **mycobacterium tuberculosis** that is predicted to be resistant to **2** antibiotics **(Isoniazid, Rifampin).** This case belongs to **a cluster** of cases with similar genomic findings.

Diagnosis

Methodology: genomic data from the specimen was compared to mycobacterium and non-mycobatercium tuberculosis genomes for speciation(reference published paper) .

The specimen was speciated as **mycobacterium tuberculosis**

Treatment

Methodology: Drug sensitivities were predicted using the genomic sequence data in accordance to the method reported in published paper ref.

The specimen was consider to be **multi-drug resistant (MDR) TB.**

Summary of sensitive findings

Drugs	Prediction	Status	Comment
Isoniazid	Resistant	!	Gene: katG, Amino Acid Change: S315T
Rifampin	Resistant	!	Gene: rpoB, Amino Acid Change: S531L
Ethambutol	Sensitive	✓	-
Pyrazinamide	Sensitive	✓	-
QUI	Sensitive	✓	-
SM	Sensitive	✓	-
AG	Sensitive	✓	-

Page 1 of 2

Public Health England

Tuberculosis Genome Sequencing Results

NOT FOR DIAGNOSTIC PURPOSES

Page 2 of 2

Epidemiologic Summary

Methodology: Patients are automatically assigned to clusters based upon based upon single nucleotide polymorphism differences. Clustering thresholds are defined according to cite referenced paper.

The specimen belongs to a **previously existing cluster**

Similarity	SNP difference	Cluster trend (past 5 years)	Membership (#cases)
Highly	0 to 5		2
Peripheral	6 to 12		6

Quality Summary

The whole genome sequence analysis of the isolate was considered HIGH QUALITY as the number of reads was greater than 4.7 million with 99.47% mapped and a coverage of 91.99% .

Comments

References
1. Ref 1
2. Ref 2
3. Ref 3

Authorized By	Dr. John Smith	Signature	
Position	Laboratory Director	Date	01-01-1901

Page 2 of 2

3

Mycobacterial Genome Sequencing Results

Public Health England

PATIENT NAME	BOB JOHNSON			PATIENT ID	123456789
BIRTH DATE	1 JAN 1900	GENDER	M	LOCATION	OXFORD
SAMPLE TYPE	SPUTUM			SAMPLE DATE	1 JAN 1900
REPORTING LAB	OXFORD			REPORT DATE	1 JAN 1900

SUMMARY

The specimen from **Bob Johnson** is positive for ***Mycobacterium tuberculosis***. It is predicted to be **resistant to isoniazid and rifampin**. It **belongs to a cluster** of genetically related cases.

DIAGNOSIS

The specimen is positive for ***Mycobacterium tuberculosis***

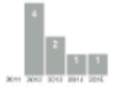
TREATMENT

Based on predicted antibiotic sensitivities, this individual has **multidrug-resistant (MDR) TB.**

First-Line Drugs	
Isoniazid	**Resistant (katG S315T)**
Rifampin	**Resistant (rpoB S531L)**
Ethambutol	Sensitive
Pyrazinamide	Sensitive
Second-Line Drugs	
Streptomycin	Sensitive
Ciprofloxacin	Sensitive
Ofloxacin	Sensitive
Moxifloxacin	Sensitive
Amikacin	Sensitive
Kanamycin	Sensitive
Capreomycin	Sensitive

EPIDEMIOLOGY

This isolate belongs to a cluster of **8** genetically related cases, suggesting recent transmission.



COMMENTS

This sample was sequenced twice; the initial sequencing run did not provide high quality data for further analysis.

AUTHORIZED BY	DR. JOHN SMITH	SIGNATURE	
POSITION	LABORATORY DIRECTOR	DATE	1 JAN 1900

Page 1 of 2

PATIENT NAME	BOB JOHNSON			IDENTIFIER	123456789
BIRTH DATE	1 JAN 1900	GENDER	M	LOCATION	OXFORD

DIAGNOSIS DETAILS

Species	% Identity
Mycobacterium tuberculosis	100%
Mycobacterium avium complex	40%
Mycobacterium canetti	20%

Species are identified by comparing sequenced genomic DNA against a database of known reference Mycobacterial species. % identity refers to how closely the DNA from the patient sample matches the DNA from the reference species.

TREATMENT DETAILS

Drug	Gene	Mutation	Catalog	Coverage	Support
Isoniazid	katG	S315T	Mykrobe v2	47x	46/47 reads
Rifampin	rpoB	S531L	Walker et al	38x	38/38 reads

Resistance is predicted by identifying known resistance conferring mutations in the genomic data. Coverage refers to how many sequence reads map to a mutation site, with Support indicating how many of those contain the resistance mutation.

EPIDEMIOLOGY DETAILS

Isolate	Year	SNP Distance
2015_A	2015	3
2014_A	2014	4
2013_A	2013	8
2013_B	2013	7
2012_A	2015	10
2012_B	2015	9
2012_C	2015	10
2012_D	2015	9

Clusters of related isolates are defined as those within 12 single nucleotide polymorphisms (SNPs) of another isolate, a threshold suggestive of recent transmission. The table displays those previously sequenced isolates within 12 SNPs of the current isolate, with the results arranged first by year, then by SNP distance.

GENOME SEQUENCING DETAILS

LOCAL LIMS ID	12.0010882	GUUID	07aa9880-3012-403b-
RUN DATE	1 JAN 1900	RUN INSTRUMENT	ILLUMINA MISEQ
TOTAL READS	4.73M	MAPPED READS (%)	4.70M (99.47%)
REFERENCE GENOME	H37RV (NC000962.2)		

Page 2 of 2

4

MYCOBACTERIAL GENOME SEQUENCING REPORT

Report Issued By: **OXFORD** Report Date: 1 **JAN 1900**

Public Health England

1 PATIENT INFORMATION

Name: **Bob Johnson** Identifier: **123456789**
Birth Date: **1 Jan 1900** Sample Date: **1 Jan 1900**
Location: **Birmingham** Gender: **M**

2 SPECIES IDENTIFIED BY SEQUENCING

100% identical to ***Mycobacterium tuberculosis***

3 PREDICTED ANTIBIOTIC RESISTANCE

Resistant to **isoniazid, rifampin.**

4 EPIDEMIOLOGICAL RELATIONSHIPS

Belongs to a cluster of **8 genetically related cases**, suggesting **recent transmission.**

5 SEQUENCING QUALITY

Sequenced **4 Aug 2016** on an **Illumina MiSeq**, yielding **4.73M reads**. **4.70M (99.47%)** mapped to the **H37Rv (NC000962.2)** reference genome.

6 COMMENTS

The sample was sequenced twice; the initial sequencing run did not provide high quality data for analysis.

MYCOBACTERIAL GENOME SEQUENCING REPORT

Report Issued By: **OXFORD** Report Date: 1 **JAN 1900**

Public Health England

7 Technical Details

This section of the report provides the technical details for the summaries presented on the first page.

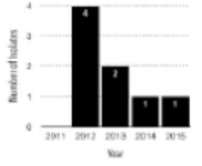
Resistotype

The resistotype describes the mutations that are predicted to confer drug resistance.

Drug	Gene	Mutation	Catalog	Coverage	Support
Isoniazid	katG	S315T	Mykrobe v2	47x	46/47 reads
Rifampin	rpoB	S531L	Walker et al	38x	38/38 reads

Related Isolates

The following graph and table describe isolates that have been identified as being genetically similar to this patient's isolate.



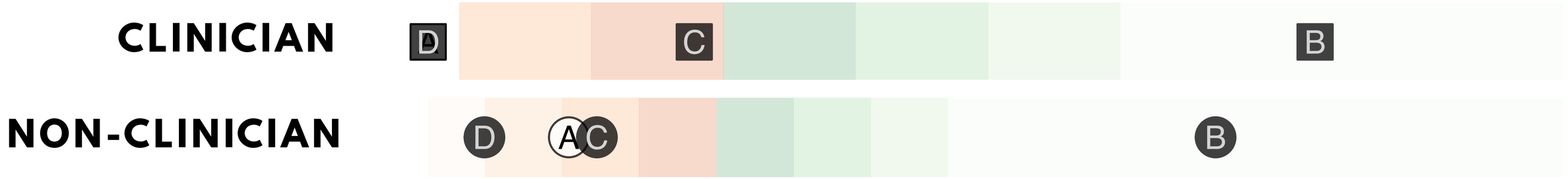
Isolate	Year	SNP Distance
2015_A	2015	3
2014_A	2014	4
2013_A	2013	8
2013_B	2013	7
2012_A	2015	10
2012_B	2015	9
2012_C	2015	10
2012_D	2015	9

TEST EACH ELEMENT (WORDING, DATA VIS, LAYOUT) INDIVIDUALLY

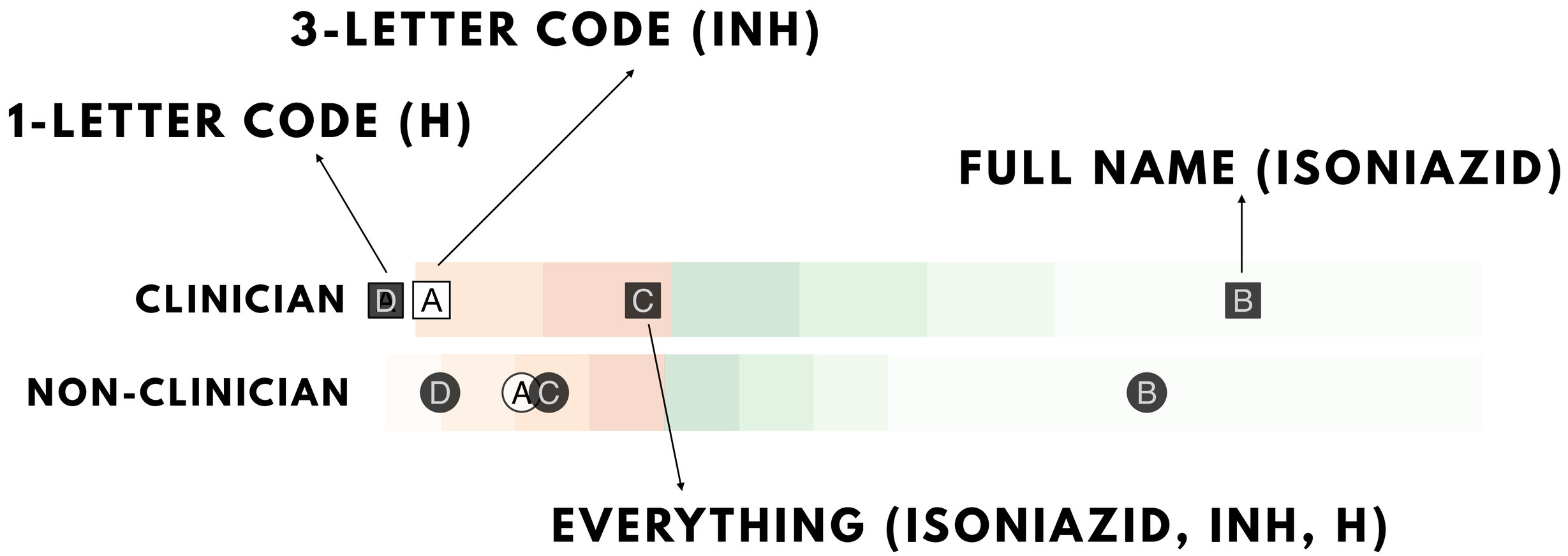
COMPARE CLINICIANS TO NON-CLINICIANS

COMPARE NEW DESIGNS TO ORIGINAL REPORT FORMAT

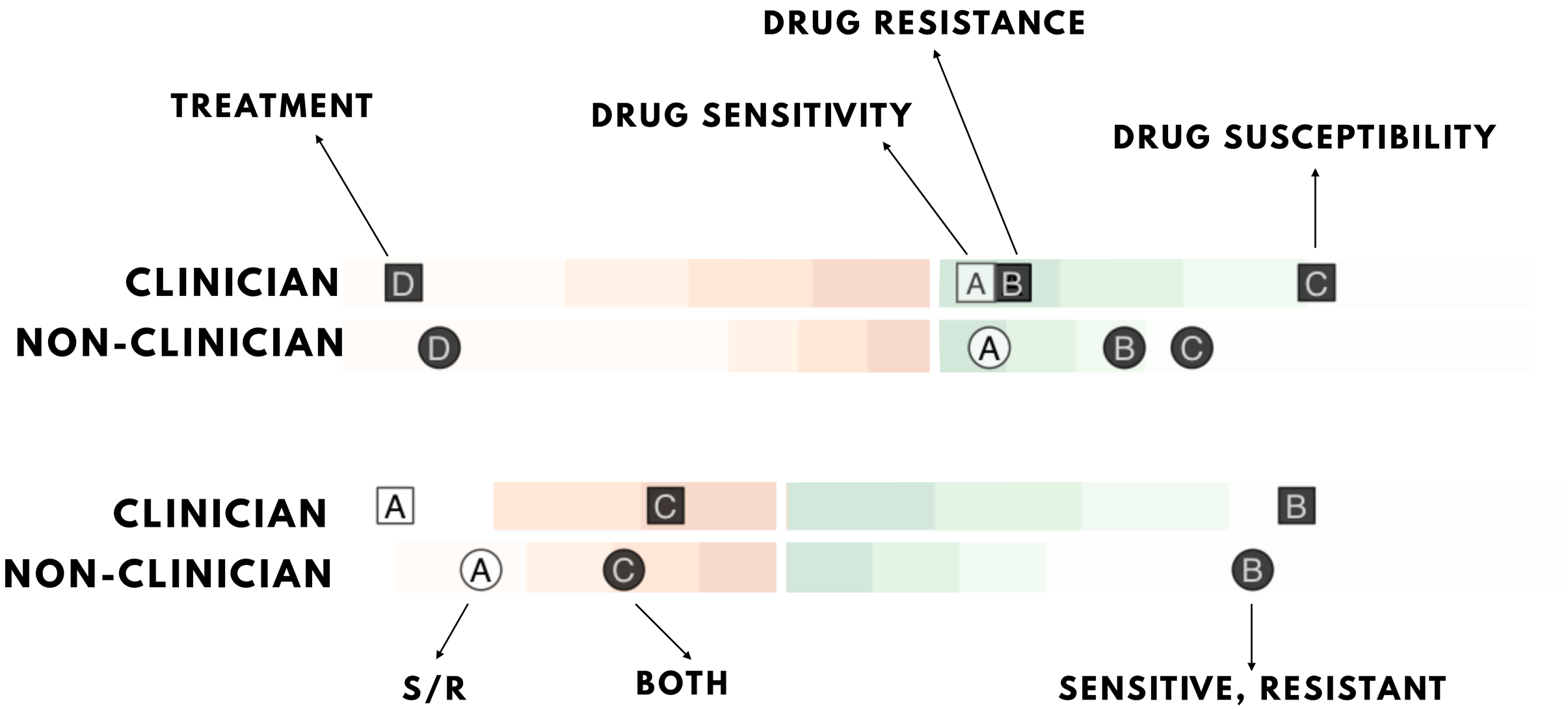
54



RESPONSES SPLIT BY ROLE
SHADING = LEAST TO MOST PREFERRED
WHITE CIRCLE = CONTROL/CURRENT DESIGN
BLACK CIRCLE = ALTERNATIVE DESIGNS FROM DESIGN SPRINT



WHAT WORDING DO WE USE FOR DRUGS?



WHAT WORDING DO WE USE FOR RESISTANCE?

NO HIGHLIGHT

Drug Susceptibility

Drug	Prediction
Isoniazid	Resistant
Rifampin	Resistant
Ethambutol	Sensitive
Pyrazinimide	Sensitive

SHADING

Drug Susceptibility

Drug	Prediction
Isoniazid	Resistant
Rifampin	Resistant
Ethambutol	Sensitive
Pyrazinimide	Sensitive

CLINICIAN

NON-CLINICIAN

BOLDING

Drug Susceptibility

Drug	Prediction
Isoniazid	**Resistant**
Rifampin	**Resistant**
Ethambutol	Sensitive
Pyrazinimide	Sensitive

ALERT GLYPH

Drug Susceptibility

Drug	Prediction
Isoniazid	Resistant ⚠
Rifampin	Resistant ⚠
Ethambutol	Sensitive
Pyrazinimide	Sensitive

HOW DO WE EMPHASIZE KEY RESULTS?

NO SUMMARY

Drug Susceptibility

Drug	Prediction
Isoniazid	Resistant
Rifampin	Resistant
Ethambutol	Sensitive
Pyrazinimide	Sensitive

SENTENCE

Drug Susceptibility

Based on predicted antibiotic sensitivities, this individual has **multidrug-resistant (MDR) TB.**

Drug	Prediction
Isoniazid	Resistant
Rifampin	Resistant
Ethambutol	Sensitive
Pyrazinimide	Sensitive

TICK BOXES

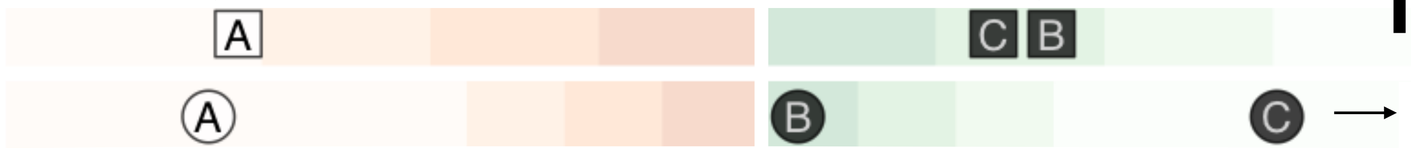
Drug Susceptibility

- Mono-resistant ☐
- Multidrug-resistant (MDR) ☑
- Extremely Drug Resistant (XDR) ☐

Drug	Prediction
Isoniazid	Resistant
Rifampin	Resistant
Ethambutol	Sensitive
Pyrazinimide	Sensitive

CLINICIAN

NON-CLINICIAN



HOW DO WE SUMMARIZE SUSCEPTIBILITY?

BASIC TABLE

Drug Susceptibility

INH	RIF	EMB	PZE
R	R	S	S

SENTENCE

Drug Susceptibility

The specimen is resistant to isoniazid, rifampin. It is sensitive to ethambutol and pyrazinamide.

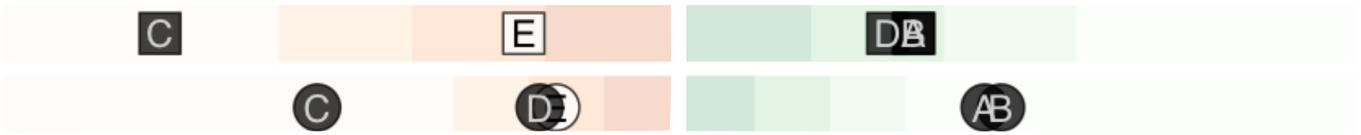
BY PHENOTYPE

Drug Susceptibility

Prediction	Drugs
Sensitive	Ethambutol, Pyrazinimide
Resistant	Isoniazid, Rifampin
Indeterminate	-

CLINICIAN

NON-CLINICIAN



BINNED BY PHENOTYPE

Drug Susceptibility

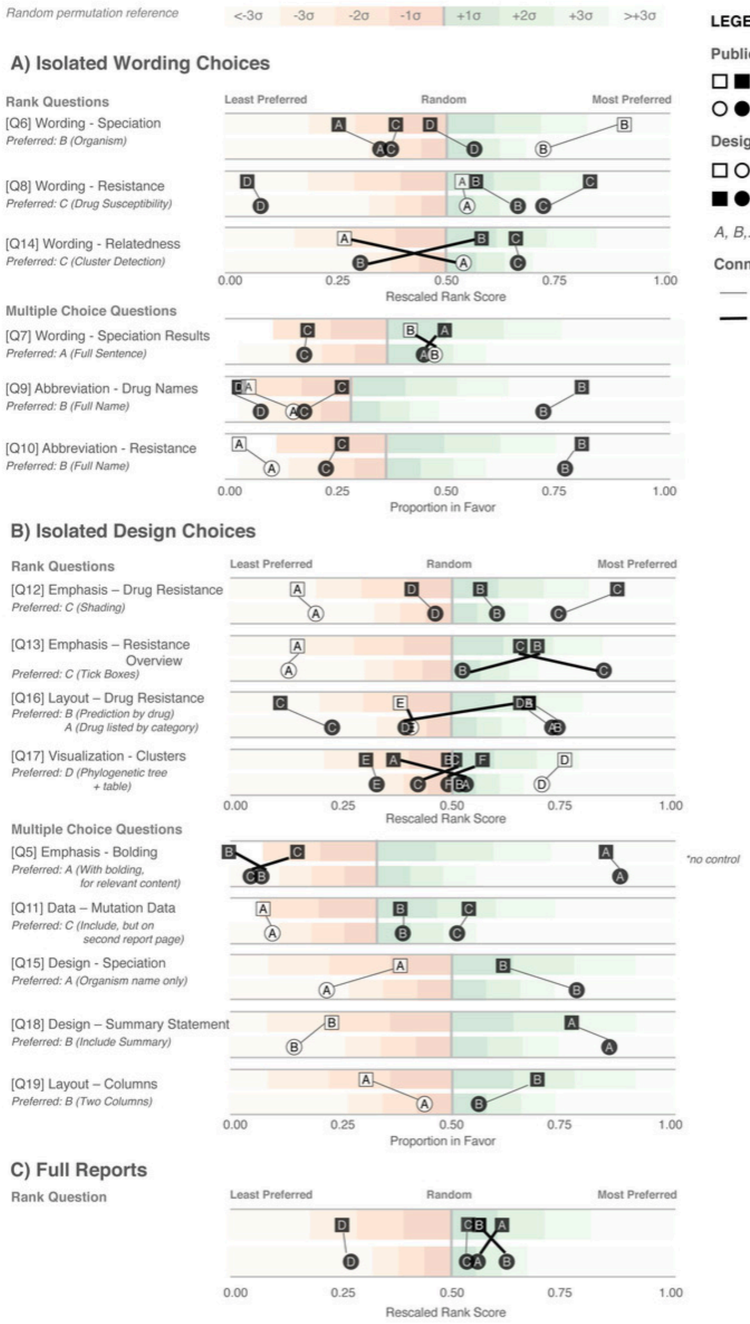
SUSCEPTIBLE	RESISTANT	INDETERMINATE
Ethambutol Pyrazinimide	Isoniazid Rifampin	

BY DRUG

Drug Susceptibility

Drug	Prediction
Isoniazid	Resistant
Rifampin	Resistant
Ethambutol	Sensitive
Pyrazinimide	Sensitive

HOW DO WE PRESENT SUSCEPTIBILITY?



NEW DESIGNS USUALLY OUTPERFORMED THE OLD

RESPONSES VARY BY ROLE

SUMMARIES, EMPHASIS, AND CLARITY ARE VALUED

MYCOBACTERIUM TUBERCULOSIS
WHOLE GENOME SEQUENCING REPORT
NOT FOR DIAGNOSTIC USE

See `https://github.com/amcrisan/TB-WGS-MicroReport` for how to automatically fill the contents of this template

Patient Name	JOHN DOE	Patient ID	12345678910
Birth Date	2000-01-01	Location	SOMEPLACE
Sample Type	SPUTUM	Sample Date	2016-12-25
Reporting Lab	LAB NAME	Report Date/Time	2017-01-01, 15:36
Requested By	REQUESTER NAME	Requester Contact	REQUESTER@EMAIL.COM

Summary

The specimen was positive for **Mycobacterium tuberculosis**. It is **resistant to isoniaizd and rifampin**. It belongs to a cluster, suggesting **recent transmission**.

Organism

The specimen was positive for **Mycobacterium tuberculosis**

Drug Susceptibility

Drug susceptibility is predicted by the presence of mutations known to confer drug resistance in *M. tuberculosis*.

- ☐ No drug resistance predicted
- ☐ Mono-resistance predicted
- ☑ Multi-drug resistance predicted
- ☐ Extensive drug resistance predicted

Drug class	Prediction	Drug	Resistance Gene (Amino Acid Mutation)
First Line	Sensitive	Ethambutol	No resistance mutation detected
		Pyrazinimide	No resistance mutation detected
	Resistant	Isoniazid	katG (S315T)
		Rifampin	rpoB (S531L)
Second Line	Sensitive	Streptomycin	No resistance mutation detected
		Ciprofloxacin	No resistance mutation detected
		Ofloxacin	No resistance mutation detected
		Moxifloacin	No resistance mutation detected
		Amikacin	No resistance mutation detected
		Kanamycin	No resistance mutation detected
		Capreomycin	No resistance mutation detected

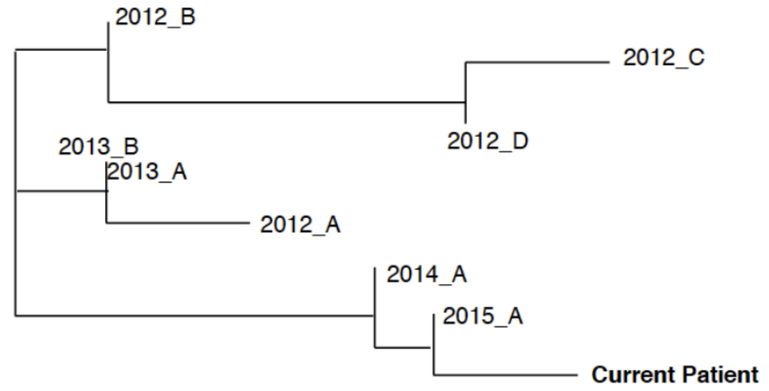
https://goo.gl/nmtayL

MYCOBACTERIUM TUBERCULOSIS
WHOLE GENOME SEQUENCING REPORT
NOT FOR DIAGNOSTIC USE

Cluster Detection

The current isolate was clustered with previously sequenced isolates, suggesting **recent transmission**.

Relatedness	Number of prior matching isolates
Closely Related (< 5 mutations apart)	**2** isolates
Related (6 to 30 mutations apart)	**6** isolates



Comments

No additional comments

Authorised

Signature	Name
Position	Date

TB-WGS-report-for-reference-lab

Open as Template | View Source | Download PDF

Author Anamaria Crisan

Abstract This is a template we have designed to facilitate the reporting of whole genome sequencing-based results for Mycobacterium tuberculosis diagnosis, phenotyping, and epidemiologcal clustering. A manuscript describing how we arrived at this template is being submitted to PeerJ in October, 2017. We will update this document with a link to the article – "Evidence-Based Design and Evaluation of a Whole Genome Sequencing Clinical Report for the Reference Microbiology Laboratory" – when it comes online.

Tags Project / Lab Report

Find More Templates

MYCOBACTERIUM TUBERCULOSIS GENOME SEQUENCING REPORT
NOT FOR DIAGNOSTIC USE

Patient Name	JOHN DOE	Barcode	
Birth Date	2000-01-01	Patient ID	12345678910
Location	SOMEPLACE	Sample Type	SPUTUM
Sample Source	PULMONARY	Sample Date	2016-12-25
Sample ID	A12345678	Sequenced From	MGIT CULTURED ISOLATE
Reporting Lab	LAB NAME	Report Date/Time	2017-01-01, 15:36
Requested By	REQUESTER NAME	Requester Contact	REQUESTER@EMAIL.COM

Summary

The specimen was positive for **Mycobacterium tuberculosis**. It is **resistant to isoniaizd and rifampin**. It belongs to a cluster, suggesting **recent transmission**.

Organism

The specimen was positive for ***Mycobacterium tuberculosis***, lineage 2.2.1 (**East-Asian Beijing**).

Drug Susceptibility

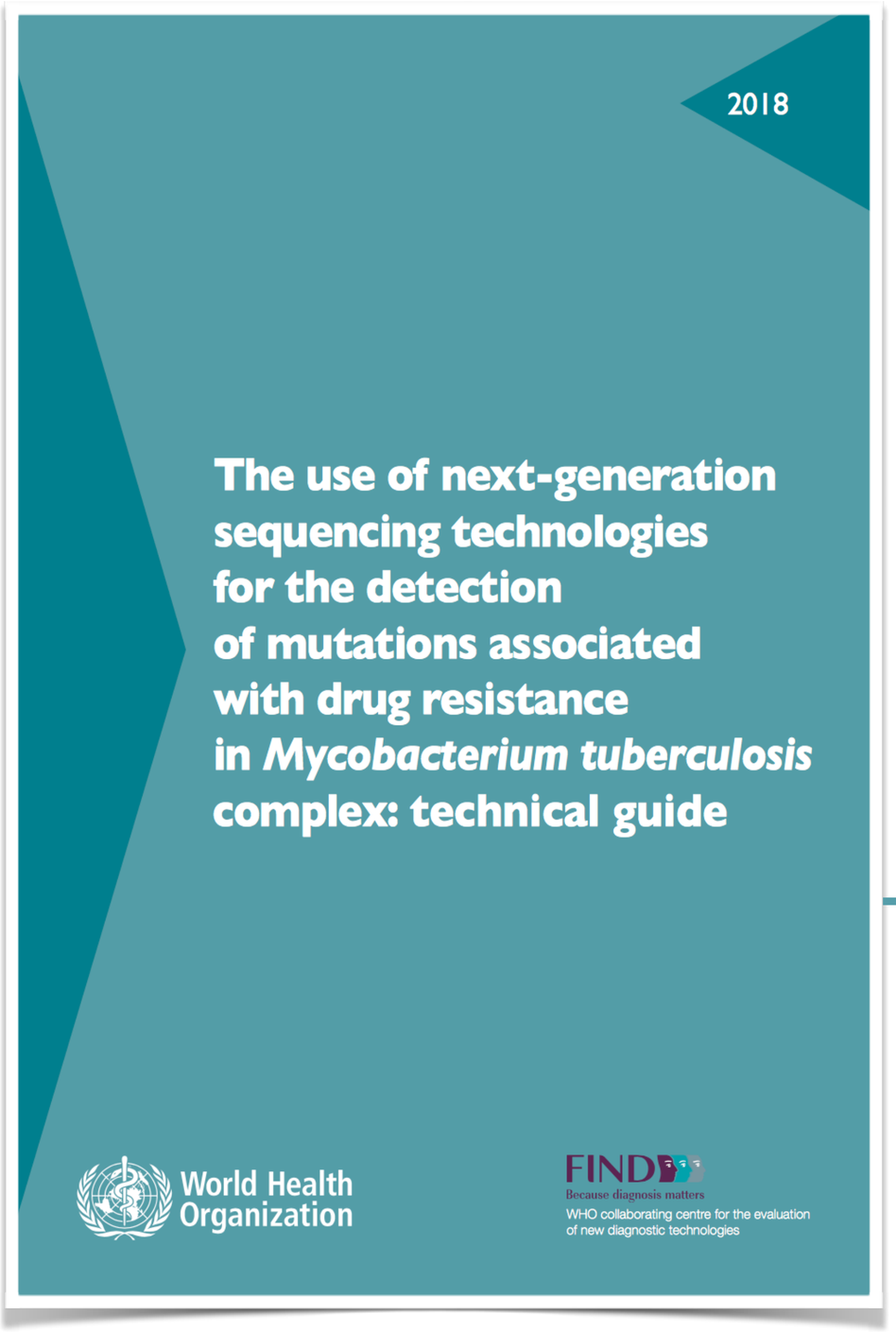
Resistance is reported when a high-confidence resistance-conferring mutation is detected. **"No mutation detected" does not exclude the possibility of resistance.**

☐ No drug resistance predicted
☐ Mono-resistance predicted
☑ Multi-drug resistance predicted
☐ Extensive drug resistance predicted

Drug class	Interpretation	Drug	Resistance Gene (Amino Acid Mutation)
First Line	Susceptible	Ethambutol	No mutation detected
		Pyrazinimide	No mutation detected
	Resistant	Isoniazid	katG (S315T)
		Rifampin	rpoB (S531L)
Second Line	Susceptible	Streptomycin	No mutation detected
		Ciprofloxacin	No mutation detected
		Ofloxacin	No mutation detected
		Moxifloxacin	No mutation detected
		Amikacin	No mutation detected
		Kanamycin	No mutation detected
		Capreomycin	No mutation detected

Page 1 of 2 Patient ID: 12345678910 | Date: 2017-01-01 | Location: Someplace

https://goo.gl/nmtayL



...THIS EMPHASIZES THE NEED FOR COMMON TERMINOLOGY AND STANDARDIZATION IN THE REPORTING OF GENOMIC INFORMATION TO MAXIMIZE ITS UTILITY. IT ALSO HIGHLIGHTS THE NEED FOR TRAINING OF HEALTH PRACTITIONERS IN THE INTERPRETATION OF THESE STANDARDIZED GENOMIC REPORTS IN ORDER TO TRANSLATE THIS INFORMATION INTO ACTIONABLE INFORMATION...

2018

The use of next-generation sequencing technologies for the detection of mutations associated with drug resistance in *Mycobacterium tuberculosis* complex: technical guide

World Health Organization

FIND
Because diagnosis matters
WHO collaborating centre for the evaluation of new diagnostic technologies

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
	Sensitive	Ethambutol		No mutation detected
		Pyrazinamide		***Expert consultation advised***
Second Line	Resistant	Capreomycin	*rrs* (C1402T, nucleotide 100%)	At least low-level resistance predicted
		Kanamycin	*rrs* (C1402T, nucleotide 100%)	
		Moxifloxacin	*gyrA* (Ala90Val, 14%)	
		Ofloxacin	*gyrA* (Ala90Val, 14%)	
	Sensitive	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

SUCCESSFULLY IMPLEMENTING CLINICAL (META)GENOMICS REQUIRES HAPPY END USERS; THIS COMES FROM USER-CENTRED DESIGN

USER-CENTRED DESIGN IS NOT ASKING WHAT YOUR USERS NEED, NOR IS IT GIVING THEM WHAT YOU WANT

EVERYTHING* YOU ASSUME ABOUT YOUR USER AND THEIR ENVIRONMENT IS WRONG

* not really, but it makes for a snappy quote

DESIGN IS A PROCESS, NOT A PRODUCT,
AND DESIGN IS MORE THAN LOOK AND FEEL,
IT'S ABOUT HOW SOMETHING WORKS

Thank you: Anamaria Crisan, Geoff McKee, Grace Smith, Ana cruz, Jeff Tornheim, Marco Schito, The ReSeqTB Consortium, FIND, Genome BC.