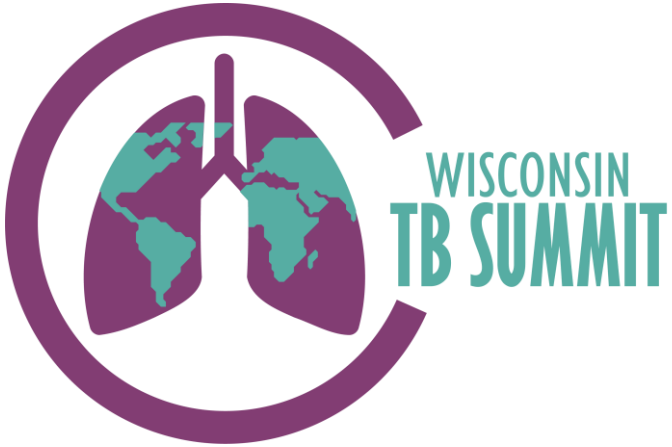


DIAGNOSTIC TESTING FOR MYCOBACTERIUM TUBERCULOSIS COMPLEX

LOCAL, STATE-WIDE, AND NATIONAL

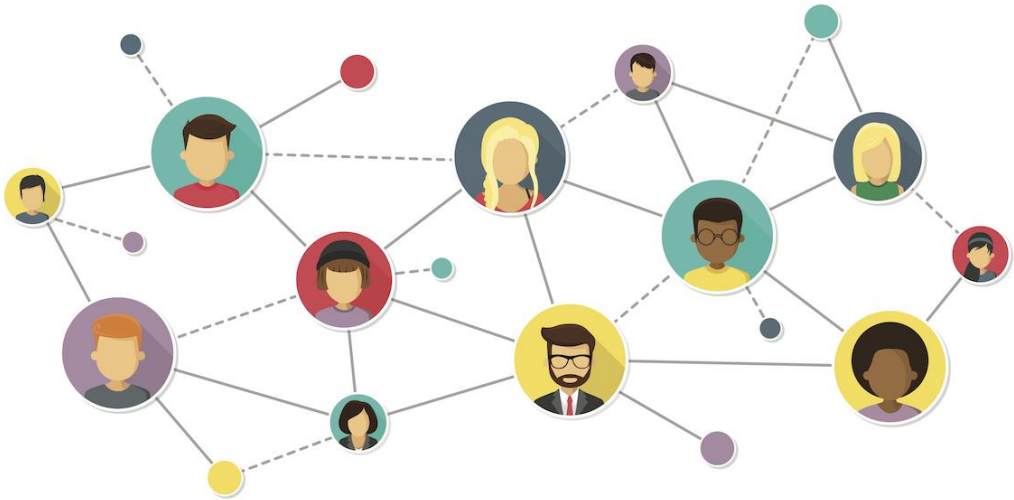
Nate Simon
WI TB Program Laboratory Coordinator
WI State Lab of Hygiene – Communicable Diseases Division
04/02/2024

OUTLINE

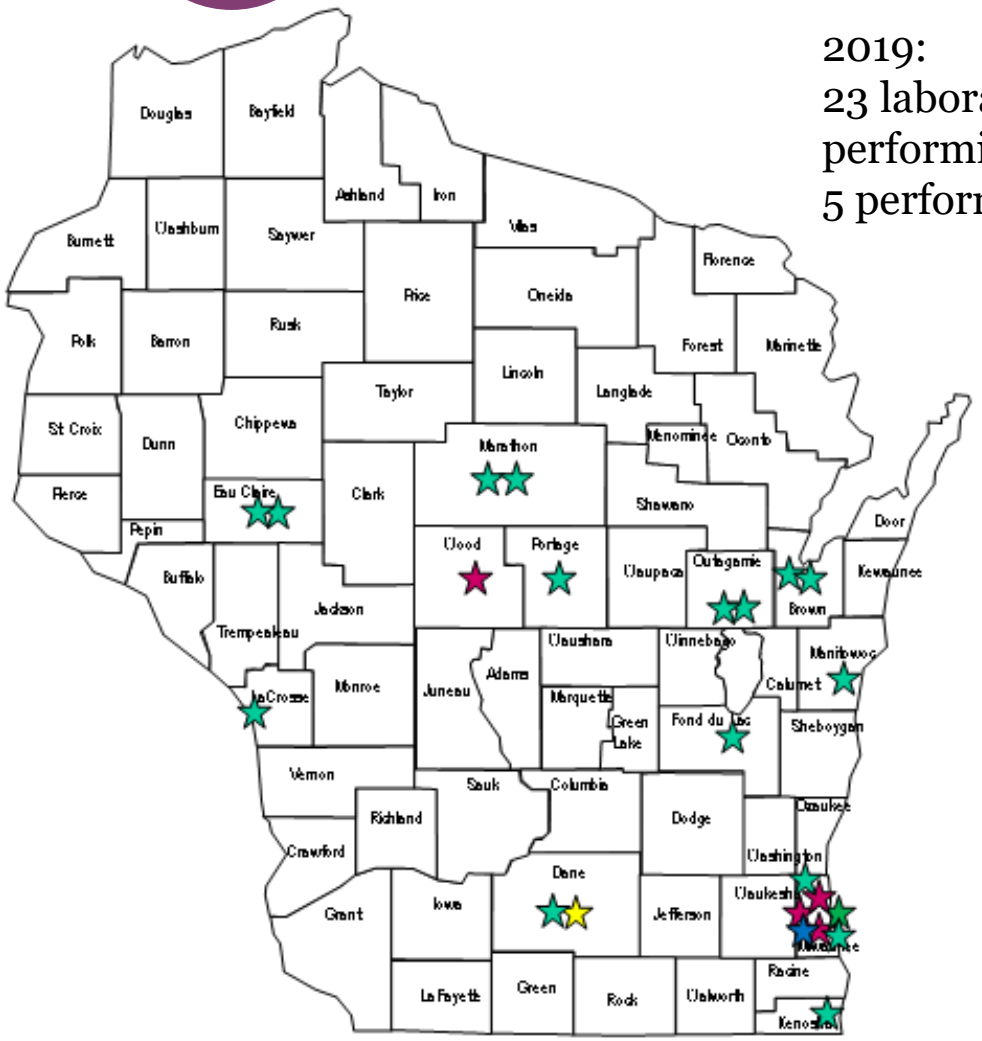
- TB diagnostic testing in WI
  - WMLN and current state of TB testing
  - WSLH TB testing
- Additional testing options outside WSLH
- WSLH testing updates and plans for the future

WISCONSIN MYCOBACTERIOLOGY LABORATORY NETWORK (WMLN)

- WMLN was started in 1998
  - **Mission: Ensure state-wide access to rapid and reliable TB testing**
- Coordinated by WSLH, collaboration between public health and clinical labs, local and state public health departments, and other healthcare professionals
  - Infrastructure for communication
  - Education and outreach activities
  - Assessment of state lab capacity
  - Annual conference
  - Laboratory-based surveillance

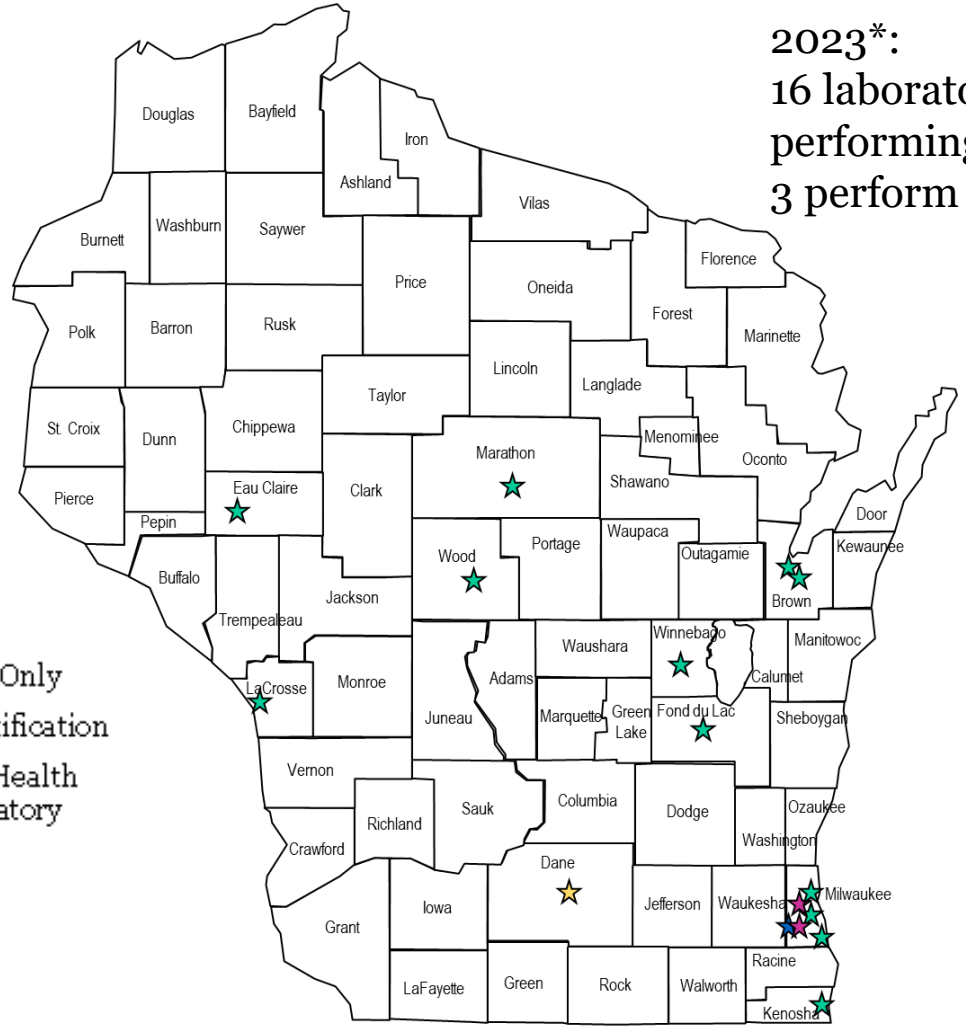


WMLN LABORATORIES: CONSOLIDATION OF TESTING



2019:
23 laboratories
performing AFB testing
5 perform AFB ID

- Smear and Culture Only
- Some level of Identification
- City of Milwaukee Health Department Laboratory
- WSLH



2023*:
16 laboratories
performing AFB testing
3 perform AFB ID

ISSUES FACING WI MYCOBACTERIOLOGY LABS

- Reagent shortages
  - Procurement of both liquid and solid media has been a recurring issue for WMLN labs and WSLH
- Discontinuation of AFB testing products
  - Despite global significance, mycobacteria testing is not financially attractive in the US
  - Discontinuation of Hologic Mycobacteria Accuprobes in late 2022

HOLOGIC®

AccuProbe®

MYCOBACTERIUM TUBERCULOSIS COMPLEX CULTURE IDENTIFICATION TEST

INTENDED USE

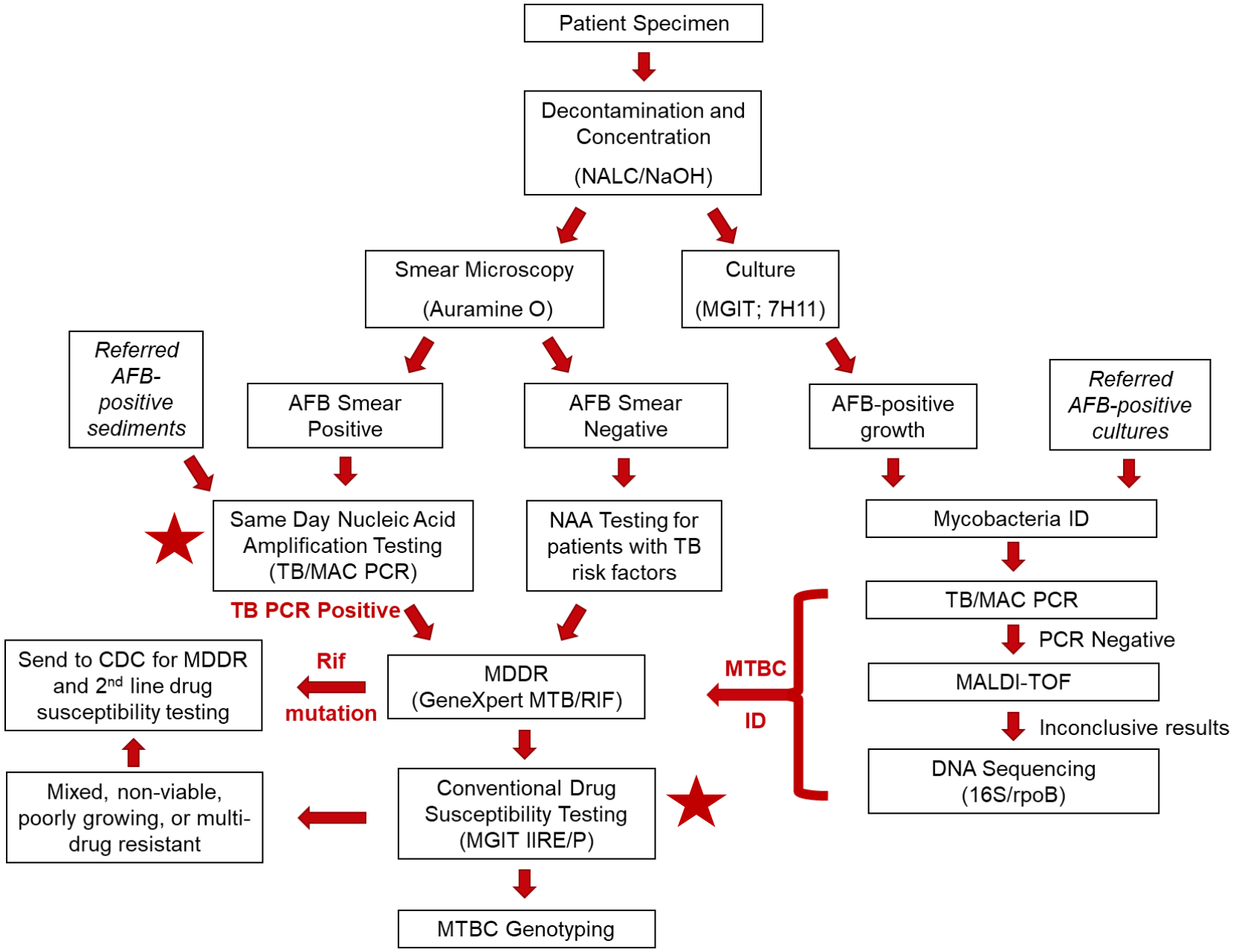
The ACCUPROBE MYCOBACTERIUM TUBERCULOSIS COMPLEX CULTURE IDENTIFICATION TEST is a rapid DNA probe test which utilizes the technique of nucleic acid hybridization for the identification of *Mycobacterium tuberculosis* (TB Complex) isolated from culture. The TB Complex consists of the following species: *M. tuberculosis, M. bovis, M. bovis BCG, M. africanum, M. microti* (8), and *M. canetti* (11).

https://www.hologic.com/package-inserts/diagnostic-products/accuprobe-culture-identification-tests

MYCOBACTERIOLOGY AT THE WI STATE LAB OF HYGIENE

- **Full-service mycobacteriology laboratory**
  - Fully commissioned BSL-3 lab space
  - Primary diagnostic facility receiving clinical specimens from:
    - 2 large Madison-area hospitals
    - Public Health Departments state-wide
  - Reference laboratory
    - Mycobacteria ID and NAAT testing for clinical labs in WI
  - Public health laboratory

MYCOBACTERIOLOGY TESTING AT WSLH



RAPID MTBC ID: WSLH MTBC NAAT TESTING

- Detect *M. tuberculosis* complex and *M. avium* complex directly from processed sediment
- Automatically performed on all new smear-positive specimens from WI
  - Respiratory and **non-respiratory sources**
  - Fee-exempt testing for up to 2 specimens per patient
- Testing of AFB smear-negative **respiratory** specimens at request of WI TB Program
- Diagnostic testing only!
  - Positive TB PCR results are confirmatory for tuberculosis disease
  - Testing not acceptable on patients with mycobacterial diagnosis in last 12 months or patients on TB treatment for >7 days

MTBC DRUG SUSCEPTIBILITY TESTING (DST)

- WI has low TB rate with low levels of drug-resistant TB
- Guide for choosing treatment plan—provide the best chance of a cure and lower development of resistance
- Initiate appropriate treatment for contacts of infectious cases

FROM PAGE ONE

TB Strain in India Resists All Drugs

Continued from Page One

trol program, said the government was "seriously addressing" the widening drug-resistance problem. However, he refuted Dr. Udwadia's description of a "totally drug-resistant" TB strain—not because there is a treatment, but because the term isn't internationally re[illegible]nized and a new cure could [illegible]ored.

Dr. Kur[illegible]adia and his h[illegible] ported t[illegible] author[illegible] tional [illegible] cern [illegible] sai[illegible]

kill the disease provide favorable conditions for mutation of new, stronger strains.

Experts of the World Health Organization met in Geneva to discuss untreatable TB in March, according to documents reviewed by the Journal. They decided against creating a "totally drug-resistant" category because the condition was difficult to confirm in a lab. Some participants also worried about the [illegible]ological effect on patients [illegible]ss was declared "to[illegible]ant."

[illegible]lab chief at [illegible]st of

India in Race to Con[illegible] Untreatable Tuberculo[illegible]

By Geeta Anand

MUMBAI—India's slow response to years of medical warnings now threatens to turn the country into an incubator for a mutant strain of tuberculosis that is proving resistant to all known treatments, raising alarms of a new global health hazard.

"We finally have ended up with a virtually [illegible] treatable strain" of tuberculosis in India, [illegible] arir Udwadia, one of the country's l[illegible] writes.

documents reviewed by The W[illegible] Spread of the strain could re[illegible] to the fatal plague that killed [illegible] afflicted, before mode[illegible] oped in the 1940[illegible] tor of the S[illegible] Organ[illegible]

In December, Dr. Udwad[illegible] al that he had [illegible] to all [illegible]

Alarming levels of drug-resistant TB found worldwide

Thu, Aug 30 2012

By Kate Kelland

LONDON (Reuters) - Scientists have found an alarming number of cases of the lung disease tuberculosis in Africa, Asia, Europe and Latin America that are resistant to up to four powerful antibiotic drugs.

In a large international study published in the Lancet medical journal on Thursday, researchers found rates of both multi drug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) were higher than previously thought and were threatening global efforts to curb the spread of the disease.

"Most international recommendations for TB control have been developed for MDR-TB prevalence of up to around 5 percent. Yet now we face prevalence up to 10 times higher in some places, where almost half of the patients ... are transmitting MDR strains," Sven Hoffner of the Swedish Institute for Communicable Disease Control, said in a commentary on the study.

TB is already a worldwide pandemic that infected 8.8 million people and killed 1.4 million in 2010.

Drug-resistant TB is more difficult and costly than normal TB to treat, and is more often fatal.

MDR-TB is resistant to at least two first-line drugs — isoniazid and rifampicin - while XDR-TB is resistant to those two drugs as well as a powerful antibiotic type called a fluoroquinolone and a second-line injectable antibiotic.

Treating even normal TB is a long process, with patients needing to take a cocktail of powerful antibiotics for six months. Many patients fai[illegible] complete their treatment correctly, a factor which has fuelled a rise in the drug-resistant forms.

Researchers who studied rates of the disease in Estonia, Latvia, Peru, the Philippines, Russia, South Africa, South Korea and Thailand fo[illegible] almost 44 percent of cases of MDR TB were also resistant to at least one second-line drug.

Tom Evans, chief scientific officer at Aeras, a non-profit group working to develop new TB vaccines, told Reuters treatment options for XDR[illegible] patients were "limited, expensive and toxic".

Treatments for drug-resistant TB can cost 200 times more than those for normal TB, he said in an emailed statement. They can also cause[illegible] severe side effects like deafness and psychosis, and can take two years to complete, he added.

In the United States, MDR-TB treatment can cost $250,000 or more per patient, and in many poorer countries costs can be catastrophic to[illegible] health systems and patients' families.

"Without a robust pipeline of new drugs to stay one step ahead, it will be nearly impossible to treat our way out of this epidemic," Evans sa[illegible]

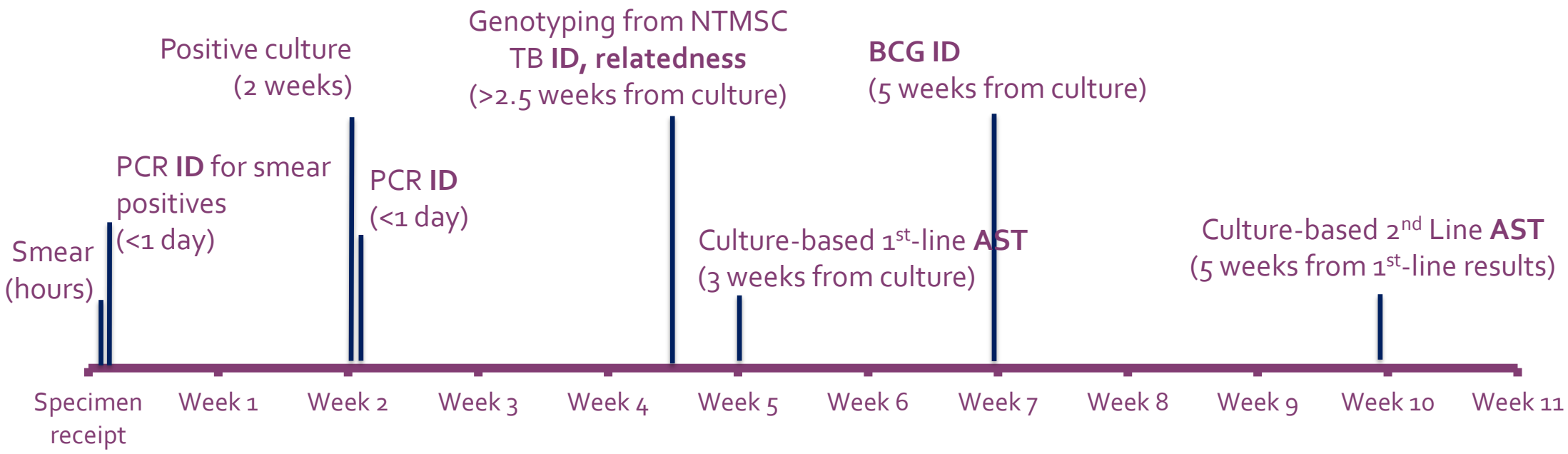
SPREADS THROUGH AIR

Tracy Dalton from the United States Centers for Disease Control and Prevention, who led the Lancet study, said that so far, XDR-TB has b[illegible] reported in 77 countries worldwide.

DISPATCHES

Bedaquiline Resistance after Effective Treatment of Multidrug-Resistant Tuberculosis, Namibia

TESTING FOR TB DRUG RESISTANCE IS SLOOOOOOW



Phenotypic AST: Incubate a standardized concentration of *M. tuberculosis* complex isolate with a known concentration of a drug

- Does the isolate grow?

WSLH DRUG SUSCEPTIBILITY TESTING: METHODS

- Phenotypic – BD MGIT IIRE/P
  - Performed weekly as needed, one isolate tested per patient
  - Resistant isolates confirmed by repeat testing
  - Rifampin-resistance, or resistance to multiple drugs, is reflexed to CDC for additional molecular testing
  - 4-13 days from when AST is set up to results
- Molecular – GeneXpert MTB/RIF
  - Performed on newly identified TB PCR-positive sediment (respiratory sources only) or TB-positive cultures (in-house or referred)
  - Rifampin-resistance prediction reflexed to CDC for additional molecular testing

MTBC DIAGNOSTIC TESTING OUTSIDE WI

- National Reference Laboratories
  - Mayo Clinic Laboratories
  - National Jewish Health Advanced Diagnostic Laboratories
  - ARUP Laboratories
- Regional or National Public Health Laboratories
  - Centers for Disease Control and Prevention TB Reference Laboratory
  - California Department of Public Health Microbial Diseases Laboratory
  - New York Department of Health at Wadsworth Center

Centers for Disease Control and Prevention

National Tuberculosis Reference Laboratory

- **Molecular Detection of Drug Resistance**
  - Targeted next-generation sequencing (tNGS)
  - 15 gene targets covering 11+ drugs
    - RIF, INH, EMB, PZA, FQ, AMK, CAP, KAN, BDQ, CLF, LZD
  - Molecular data confirmed with phenotypic testing for majority of drugs

**Pre-approval required for all testing

MTBC Agar Proportion Susceptibility*	% Resistant	Interpretation
Isoniazid 0.2 µg/mL	100 %	Resistant
Isoniazid 1.0 µg/mL	100 %	Resistant
Isoniazid 5.0 µg/mL	67 %	Resistant
Rifampin 1.0 µg/mL	0 %	Susceptible
Ethambutol 5.0 µg/mL	33 %	Resistant
Streptomycin 2.0 µg/mL	100 %	Resistant
Streptomycin 10.0 µg/mL	33 %	Resistant
Rifabutin 2.0 µg/mL	0 %	Susceptible
Ciprofloxacin 2.0 µg/mL	0 %	Susceptible
Kanamycin 5.0 µg/mL	0 %	Susceptible
Ethionamide 10.0 µg/mL	0 %	Susceptible
Capreomycin 10.0 µg/mL	0 %	Susceptible
PAS 2.0 µg/mL	0 %	Susceptible
Ofloxacin 2.0 µg/mL	0 %	Susceptible
Amikacin 4.0 µg/mL	0 %	Susceptible

CDC INFECTIOUS DISEASES PATHOLOGY BRANCH

- **Pathologic or Molecular Evaluation of Fixed Tissues for Possible Infectious Etiologies**
  - MTBC PCR from fixed specimens (FFPE blocks)
  - If MTBC is detected, will forward DNA for MDDR testing
  - Useful in cases where patients are culture-negative, but may have tissue blocks available from biopsy and MTBC confirmation is important to care

**Recommend working with State Lab to submit these specimens, as the requirements and paperwork are very specific

California Department of PublicHealth

MICROBIAL DISEASES LABORATORY BRANCH

- National MTBC Drug Susceptibility Testing Reference Center
- Phenotypic MTBC DST
  - Standard first-line drugs
  - 4-month rifapentine-moxifloxacin regimen
  - Second-line drugs AMK, CAP, ETA, KAN, RFB
- MDDR by whole-genome sequencing

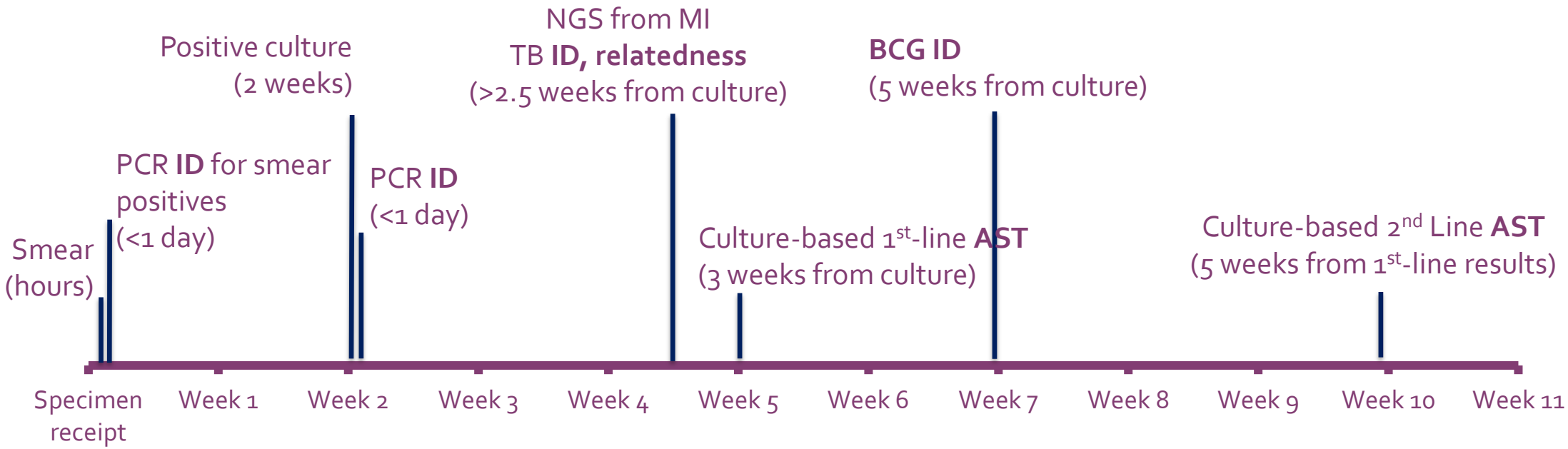
**Enrollment restricted to public health laboratories performing MTBC DST on fewer than 50 isolates per year OR requires pre-approval from APHL

WSLH MTBC NAAT TESTING UPDATES: GENEXPERT

- WSLH currently performs GeneXpert MTB/RIF assay on all new TB patients in WI
  - Sputum, BAL sediments
  - Broth or solid media culture isolates
  - Reflex testing only!
- Coming soon: validation of GeneXpert MTB/RIF from tissue specimens
  - Don't currently have a fee-exempt referral lab able to test extra-pulmonary specimens

Cepheid

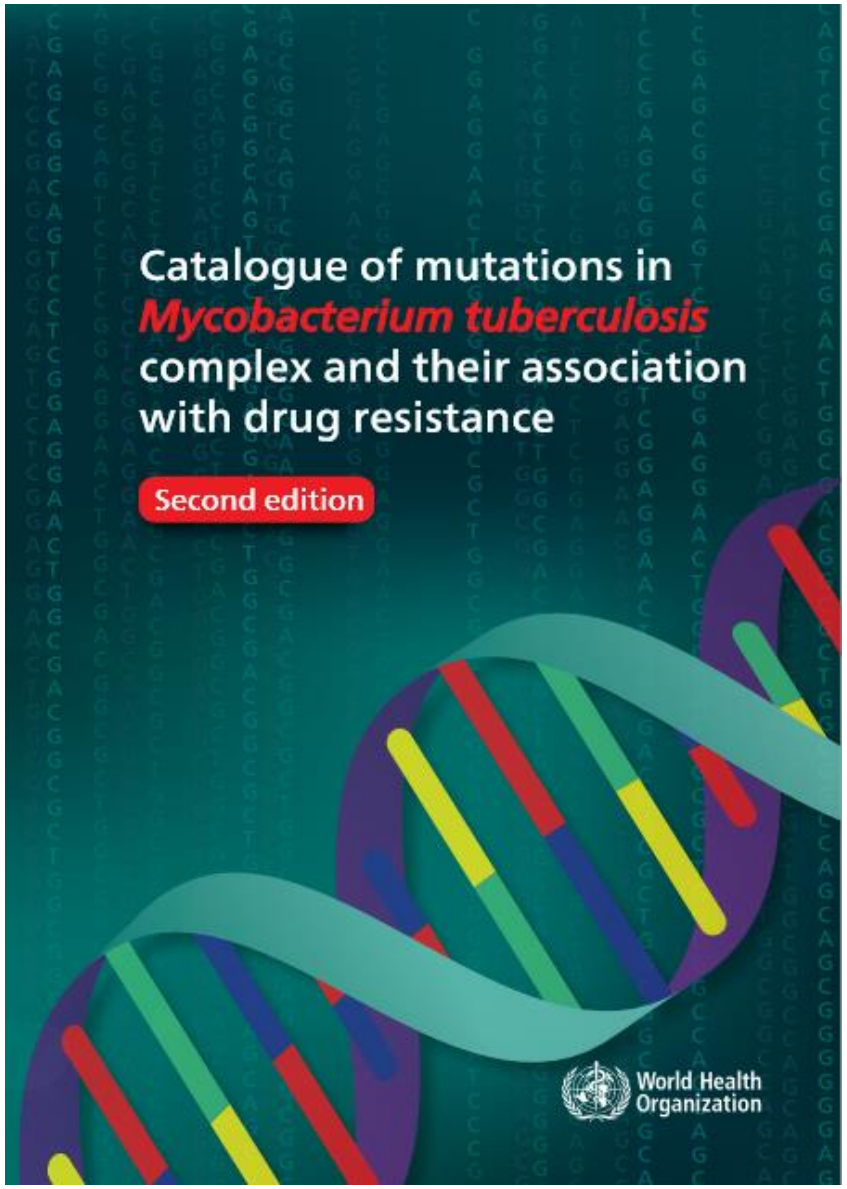
TESTING FOR TB DRUG RESISTANCE IS SLOOOOOOW



HOWEVER…

MTBC is an excellent organism for molecular drug resistance prediction

- TB mutation rate is very slow (0.3-0.5 SNP/genome/year)
- No evidence of recombination or plasmid transfer
- WHO has compiled extensive list of MTBC mutations and their significance
  - 144 pp, >52,000 isolates sequenced



WSLH TESTING UPDATES: MTBC WGS

- WSLH was one of ten Antibiotic Resistance Lab Network pilot sites for validation of MTBC WGS for prediction of drug resistance

- Currently working through a CLIA-level validation for use of WGS for diagnostic TB DST prediction
  - Results reported for individual patient care
    - **MTBC ID**- including *M. bovis*/BCG
    - **Drug susceptibility prediction-** 1st line drugs (INH, RIF, EMB, PZA)
  - Relatedness/genotyping reported to public health only

MTBC DRUG SUSCEPTIBILITY PREDICTIONS

```
Taxonomic report:

Unclassified reads:      0.09%

Mycobacterium tuberculosis complex       99.89%
Mycobacterium bovis      7.77%
Mycobacterium bovis BCG 2.72%

RD1 region absent, likely Mycobacterium bovis BCG


Mycobacterium Species detected : Mycobacterium bovis BCG
```

```
Mapping Statistics (Downsampled ratio 0.980630565600288) :

Total # of mapped reads :        2240834
Percent of mapped reads:         99.40%
Genome Coverage =        0.969308
Average Depth =  111.326

# Homozygous positions = 4213184
# Heterozygous positions = 331
Percentage of Heterozygous Positions: 0.0079%
```

```
rpoB: PASS
katG: PASS
furA-katG promoter region: PASS
oxyR-ahpC promoter region: PASS
inhA: PASS
mabA-inhA promoter region: PASS
mabA: PASS
pncA: PASS
pncA promoter region: PASS
embB: PASS
embC-embA promoter region: PASS
rpsL: PASS
rrs 512, 513, 516, 906: PASS
rrs 1400: PASS
eis promoter region: PASS
gyrA: PASS
gyrB: PASS
ethA: PASS
panD: PASS
rrl: PASS
rplC: PASS
ndh: PASS
gidB: PASS
fbiD: PASS
fbiA: PASS
fbiB: PASS
fbiC: PASS
Rv0678: PASS
atpE: PASS
pepQ: PASS
```

```
All Mutations in screened loci:

5750    171     GTG -> GTA      Val -> Val      Rv0005  gyrB    Fluoroquinolones        1/1 (Pure) (Silent)
6404    389     AAC -> AAT      Asn -> Asn      Rv0005  gyrB    Fluoroquinolones        1/1 (Pure) (Silent)
6446    403     GCG -> TCG      Ala -> Ser      Rv0005  gyrB    Fluoroquinolones        1/1 (Pure) (Neutral)
7362    21      GAG -> CAG      Glu -> Gln      Rv0006  gyrA    Fluoroquinolones        1/1 (Pure) (Neutral)
7584    95      AGC -> ACC      Ser -> Thr      Rv0006  gyrA    Fluoroquinolones        1/1 (Pure) (Neutral)
8283    328     ATC -> ATT      Ile -> Ile      Rv0006  gyrA    Fluoroquinolones        1/1 (Pure) (Silent)
8622    441     CGG -> CGT      Arg -> Arg      Rv0006  gyrA    Fluoroquinolones        1/1 (Pure) (Silent)
8739    480     CGC -> CGT      Arg -> Arg      Rv0006  gyrA    Fluoroquinolones        1/1 (Pure) (Silent)
9141    614     ATT -> ATC      Ile -> Ile      Rv0006  gyrA    Fluoroquinolones        1/1 (Pure) (Silent)
9303    668     GGC -> GAC      Gly -> Asp      Rv0006  gyrA    Fluoroquinolones        1/1 (Pure) (Neutral)
491740  320     TTT -> TTC      Phe -> Phe      Rv0407  fgd1    Delamanid/Pretomanid    1/1 (Pure) (Silent)
763029  1075    GCT -> GCC      Ala -> Ala      Rv0667  rpoB    Rifampin        1/1 (Pure) (Silent)
763574  69      CGC -> CCC      Arg -> Pro      Rv0668  rpoC    Rifampin compensatory   1/1 (Pure) (Neutral)
776101  794     ACC -> ATC      Thr -> Ile      Rv0676c mmpL5   Clofazimine/Bedaquiline 1/1 (Pure) (Neutral)
775639  948     ATT -> GTT      Ile -> Val      Rv0676c mmpL5   Clofazimine/Bedaquiline 1/1 (Pure) (Neutral)
781566  3       ACC -> ACT      Thr -> Thr      Rv0682  rpsL    Streptomycin    1/1 (Pure) (Silent)
1417554 -207    C -> G          intergenic Rv1268c-embR Rv1268c-embR promoter region    Ethambutol      1/1 (Pure) (Neutral)
1917970 11      CTA -> CTG      Leu -> Leu      Rv1694  tlyA    Aminoglycosides 1/1 (Pure) (Silent)
2102106 313     GGG -> CGG      Gly -> Arg      Rv1854c ndh     Isoniazid       1/1 (Pure) (Neutral)
2103174 -131    Intergenic deletion     -G      intergenic ndh  ndh promoter region     Isoniazid       1/1 (Pure) (Unknown)
2156027 29      CCC -> CCA      Pro -> Pro      Rv1908c katG    Isoniazid       1/1 (Pure) (Silent)
2155505 203     ACC -> ACT      Thr -> Thr      Rv1908c katG    Isoniazid       1/1 (Pure) (Silent)
2154725 463     CGG -> CTG      Arg -> Leu      Rv1908c katG    Isoniazid       1/1 (Pure) (Neutral)
2156466 43      GCC -> GTC      Ala -> Val      Rv1909c furA    Isoniazid       1/1 (Pure) (Neutral)
2289073 57      CAC -> GAC      His -> Asp      Rv2043C pncA    Pyrazinamide    1/1 (Pure) (HC mutation)
3336825 365     ACA -> GCA      Thr -> Ala      Rv2981c ddlA    D-Cycloserine   1/1 (Pure) (Neutral)
4038403 768     TTG -> CTG      Leu -> Leu      Rv3596c clpC1   Pyrazinamide    1/1 (Pure) (Silent)
4240670 270     ACC -> ATC      Thr -> Ile      Rc3793  embC    Ethambutol      1/1 (Pure) (Neutral)
4242029 723     CTG -> TTG      Leu -> Leu      Rc3793  embC    Ethambutol      1/1 (Pure) (Silent)
4242641 927     CGC -> CGT      Arg -> Arg      Rc3793  embC    Ethambutol      1/1 (Pure) (Silent)
4242968 1036    ACC -> ACT      Thr -> Thr      Rc3793  embC    Ethambutol      1/1 (Pure) (Silent)
4244220 330     CTG -> TTG      Leu -> Leu      Rv3794  embA    Ethambutol      1/1 (Pure) (Silent)
4246550 13      AAT -> AGT      Asn -> Ser      Rv3795  embB    Ethambutol      1/1 (Pure) (Neutral)
4246862 117     GTC -> GTT      Val -> Val      Rv3795  embB    Ethambutol      1/1 (Pure) (Silent)
4247171 220     CTG -> CTA      Leu -> Leu      Rv3795  embB    Ethambutol      1/1 (Pure) (Silent)
4247645 378     GAG -> GCG      Glu -> Ala      Rv3795  embB    Ethambutol      1/1 (Pure) (Neutral)
4407590 205     GCA -> GCG      Ala -> Ala      RV3919c gidB    Streptomycin    1/1 (Pure) (Silent)


Number of mutation(s) found in screened loci = 37
```

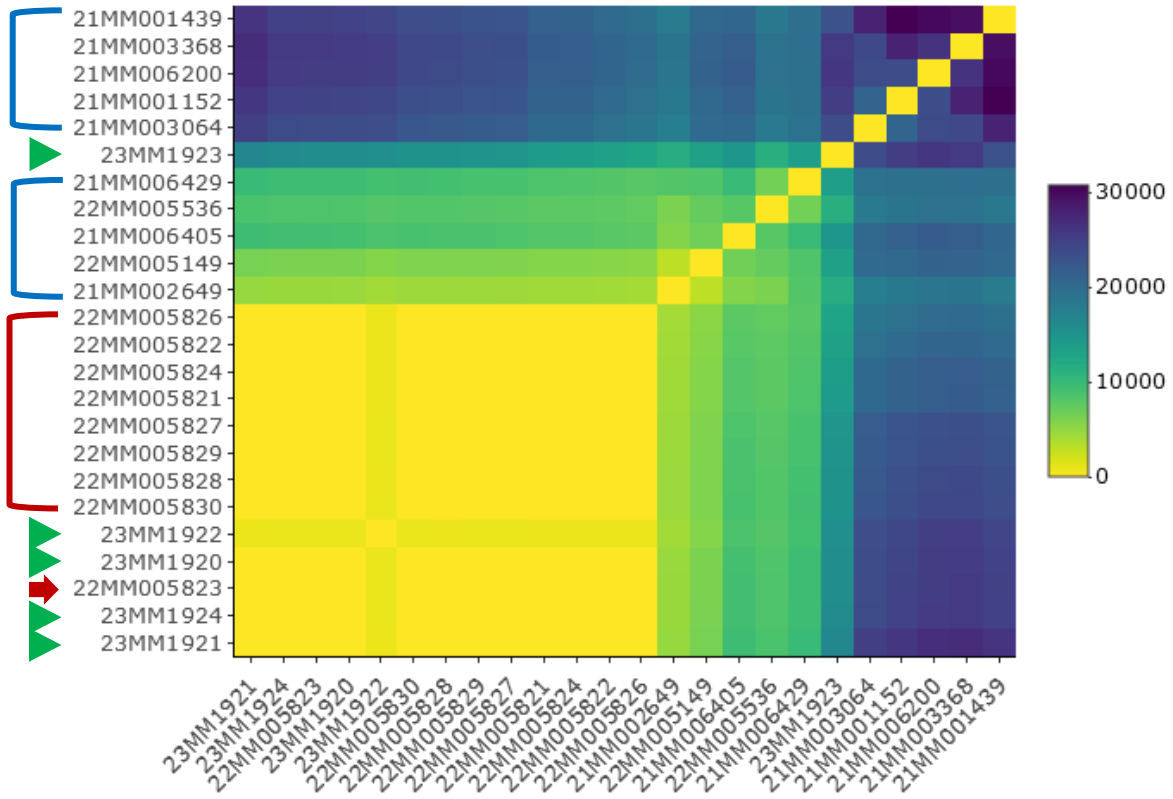
CLIMS SECTION:

Sample ID WI257
Analysis Date 12/21/2023

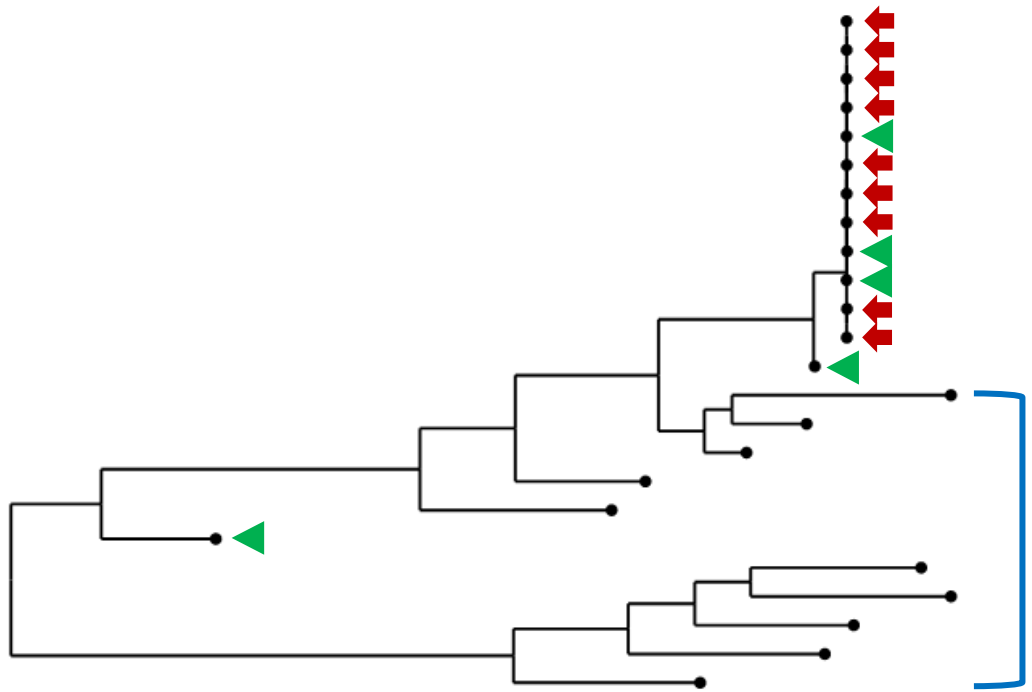
Test	Property	Notation	Result
WGS_HI_CONF_MUTATION	rpoB	PASS	No high-confidence mutation
WGS_HI_CONF_MUTATION	katG	PASS	No high-confidence mutation
WGS_HI_CONF_MUTATION	oxyR-ahpC promoter region	PASS	No high-confidence mutation
WGS_HI_CONF_MUTATION	inhA	PASS	No high-confidence mutation
WGS_HI_CONF_MUTATION	mabA-inhA promoter region	PASS	No high-confidence mutation
WGS_HI_CONF_MUTATION	mabA	PASS	No high-confidence mutation
WGS_HI_CONF_MUTATION	pncA	PASS	His57Asp
WGS_HI_CONF_MUTATION	pncA promoter region	PASS	No high-confidence mutation
WGS_HI_CONF_MUTATION	embB	PASS	No high-confidence mutation
WGS_HI_CONF_MUTATION	embC-embA promoter region	PASS	No high-confidence mutation
WGS_HI_CONF_MUTATION	rpsL	PASS	No high-confidence mutation
WGS_HI_CONF_MUTATION	rrs 512, 513, 516, 906	PASS	No high-confidence mutation
WGS_HI_CONF_MUTATION	rrs 1400	PASS	No high-confidence mutation
WGS_HI_CONF_MUTATION	eis promoter region	PASS	No high-confidence mutation
WGS_HI_CONF_MUTATION	gyrA	PASS	No high-confidence mutation
WGS_HI_CONF_MUTATION	gyrB	PASS	No high-confidence mutation
WGS_HI_CONF_MUTATION	ethA	PASS	No high-confidence mutation
WGS_HI_CONF_MUTATION	rrl	PASS	No high-confidence mutation
WGS_HI_CONF_MUTATION	rplC	PASS	No high-confidence mutation
WGS_TB_RESISTANCE	Rifampin	PASS	Susceptible
WGS_TB_RESISTANCE	Isoniazid	PASS	Susceptible
WGS_TB_RESISTANCE	Pyrazinamide	PASS	RESISTANT (predicted)
WGS_TB_RESISTANCE	Ethambutol	PASS	Susceptible
WGS_TB_RESISTANCE	Streptomycin	PASS	Susceptible
WGS_TB_RESISTANCE	Kanamycin/Amikacin	PASS	Susceptible
WGS_TB_RESISTANCE	Fluoroquinolones	PASS	Susceptible
WGS_TB_RESISTANCE	Ethionamid	PASS	Susceptible
WGS_TB_RESISTANCE	Linezolid	PASS	Susceptible
WGS_TB_RESISTANCE	Delamanid/Pretomanid	PASS	Susceptible
WGS_TB_RESISTANCE	Clofazimine/Bedaquiline	PASS	Susceptible
WGS_TB_RESISTANCE	Bedaquiline	PASS	Susceptible

NON-TUBERCULOUS MYCOBACTERIA: OUTBREAK INVESTIGATION *A*

RELATEDNESS HEATMAP (# SNP)



PHYLOGENETIC TREE



Suspect patient isolates

Environmental isolates (surgical equipment/suite)

Outgroup (species-matched; from other hospitals in WI)

WSLH TESTING UPDATES: MOXIFLOXACIN DST

- Phenotypic moxifloxacin susceptibility testing for MTBC
  - 4 month HPMZ regimen

- WSLH has begun validation of phenotypic moxifloxacin testing by MGIT
  - Will become part of the standard TB DST performed at WSLH; no need to order separately!

WSLH TESTING UPDATES: RIFAMPIN DST

- In 2021, WHO published updated critical concentrations for phenotypic susceptibility testing
  - Most phenotypic testing using current critical concentration (1µg/ml) misses low-level rifampin resistant strains
  - Treatment outcomes for patients with these strains is generally worse
- Change has not been adopted by CLSI or other US regulatory agencies
- WSLH has begun validation of the lower RIF critical concentration in preparation for potential switch

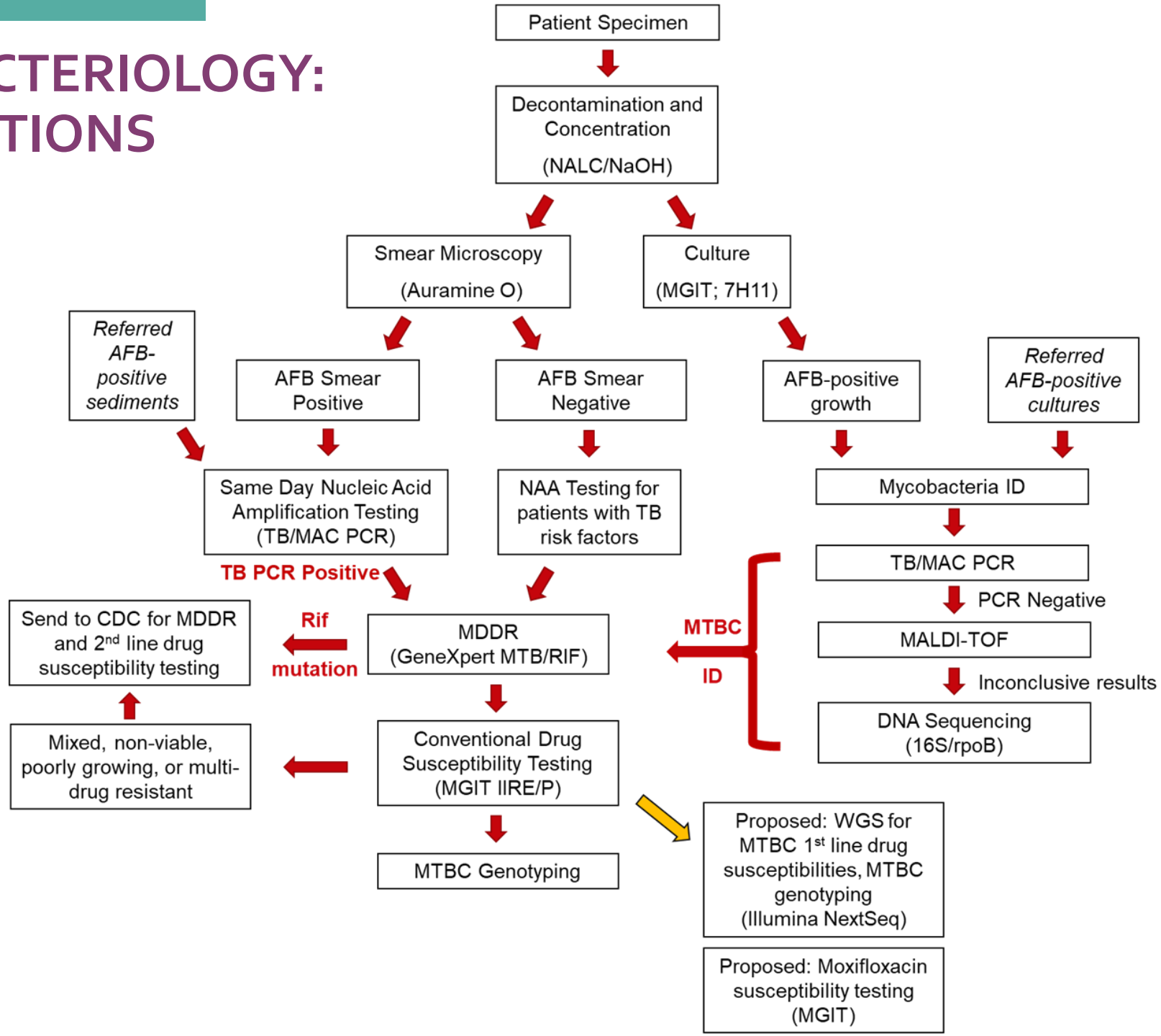
Technical Report on critical concentrations for drug susceptibility testing of isoniazid and the rifamycins (rifampicin, rifabutin and rifapentine)

World Health Organization

FIND
Because diagnosis matters

WHO Collaborating Centre for Tuberculosis Laboratory Strengthening and Diagnostic Technology Evaluation

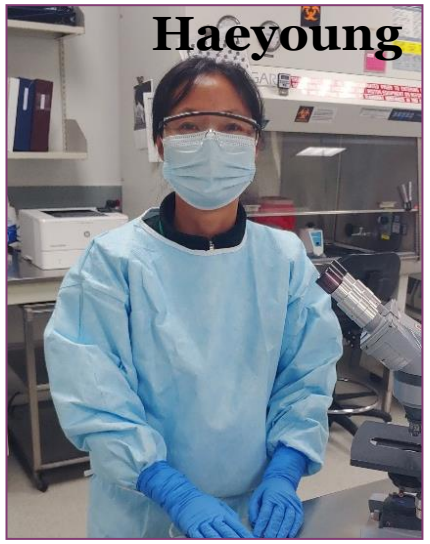
WSLH MYCOBACTERIOLOGY: FUTURE VALIDATIONS

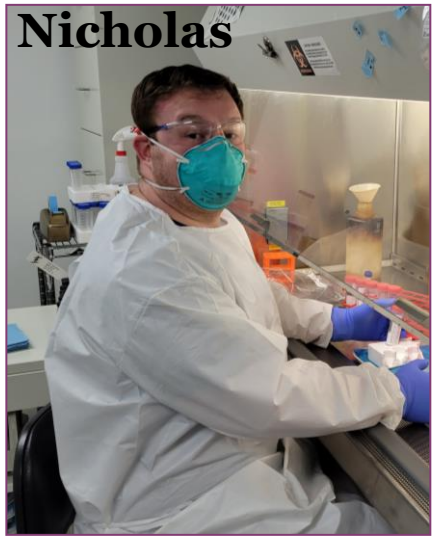


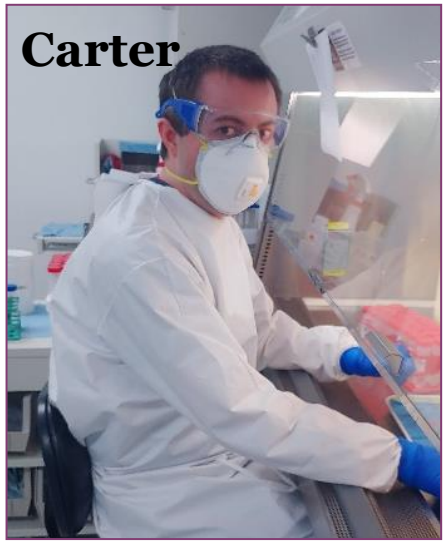
ACKNOWLEDGEMENTS

- *PHMDC and Mayo Clinic*
- *WI TB Program*
- *WSLH Mycobacteriology Laboratory Staff*
- *WSLH Sequencing Group*
- *WSLH Bioinformatics Group*

WSLH TB LABORATORY TEAM







QUESTIONS & ANSWERS

APRIL 2, 2024 SESSION EVALUATION

Please complete the session evaluation using the QR Code or link below. We appreciate your feedback!

http://tinyurl.com/WITBApril2