

# TB DIAGNOSTICS: NEWER TOOLS AND OUTLOOK

- Bringing diagnostics to communities

22 March 2023



#### TB DIAGNOSTIC GAP



Covid impacts<sup>2</sup> further emphasize the urgent need for simpler tools to enable PHC and community-based screening and testing



18% (1.3M!)

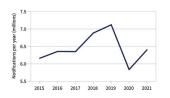
fewer people were notified in 2020 compared to 2019



The hardest hit countries are among the highest absolute TB incidence<sup>3</sup>

...India, Indonesia, China, Bangladesh, Nigeria, Pakistan.

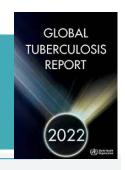
#### Global notified new TB cases



# Proportion subclinical (%) Africa Asia Overall

#### Testing remains the weakest link in the cascade of care<sup>1</sup>

- Of annual 10.6M cases, 4.0M remain undiagnosed<sup>1</sup>
- 1 in 3 TB patients are bacterially confirmed
- 1 in 5 TB patients are diagnosed with a WHO recommended mDx
- 1 in 3 with DR-TB are tested and put on relevant treatment



# Diagnostic gaps in TB have many root causes<sup>4</sup>



70% of patients initiate care at the community and PHC where there is no capacity to diagnose TB

Symptom screen miss 50% of TB cases in communities 5

 Reliance on sputum makes diagnosis difficult and selects patients with advanced disease

# The pandemic has opened new opportunities

Bringing diagnostics closer to the patients

Diverse MDx portfolio, the end of onesize-fits-all

Leveraging investments in Dx infrastructure, digital and connectivity

New tools for a comprehensive response with TBI test-and-treat strategies, scTB and personalized medicine in TB

- <sup>1</sup> WHO global TB report 2022
- <sup>2</sup> StopTB modelling
- <sup>1</sup> WHO global TB report 2021
- <sup>4</sup>Pai M et al, Nat.Microb. 2017
- <sup>5</sup>Francella et al, CID, 2021 DOI: 10.1093/cid/ciaa1402





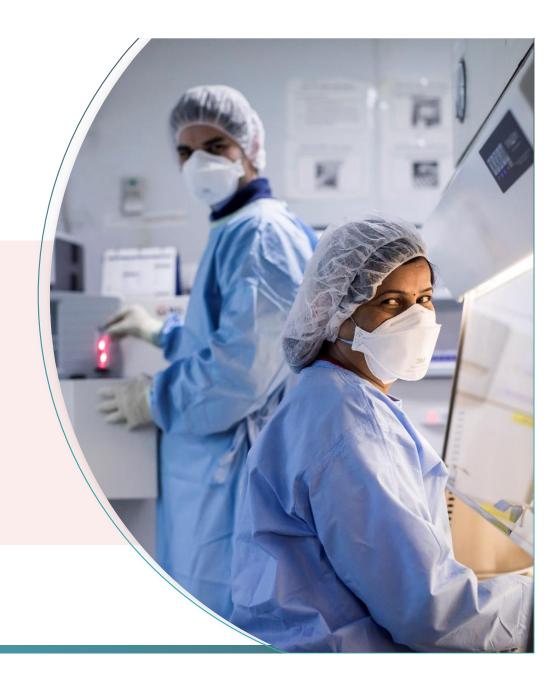
# **OUR MISSION**

FIND seeks to ensure equitable access to reliable diagnosis around the world

We connect countries and communities, funders, decision-makers, healthcare providers and developers to spur diagnostic innovation and make testing an integral part of sustainable, resilient health systems

GOAL:

ACCELERATE GLOBAL EFFORTS TOWARDS
UNIVERSAL HEALTH COVERAGE AND
HEALTH EMERGENCY RESPONSE





TB

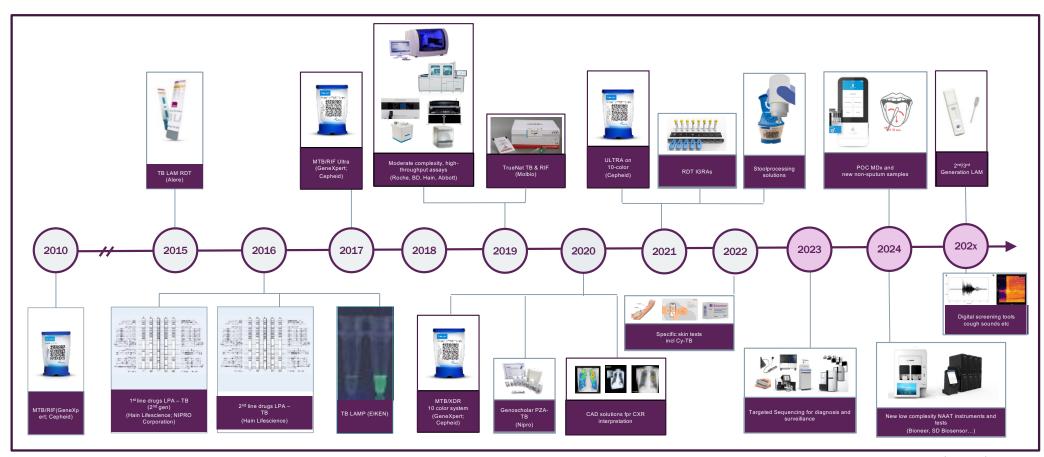
HOW WILL WE DELIVER ON THIS VISION?







19 WERE AT 7 GDG/TEGs SINCE 2019...BUT ALMOST ALL FIND EVIDENCE RELATED TO DX ACCURACY



...and many others

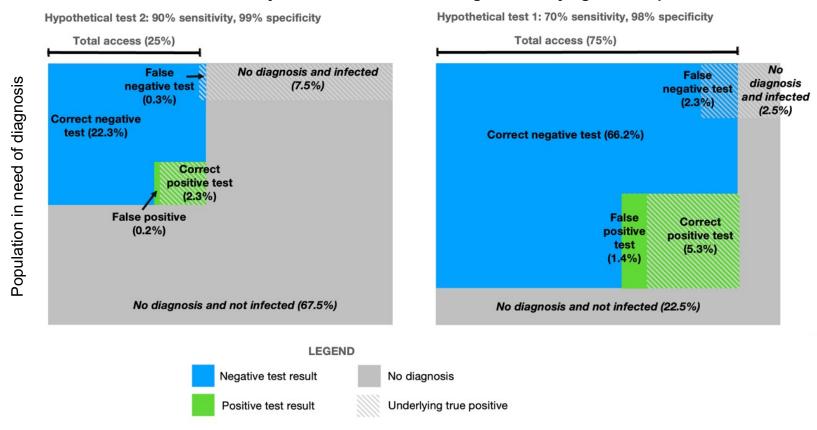




#### ADDRESSING THE 4.1M DETECTION GAP?

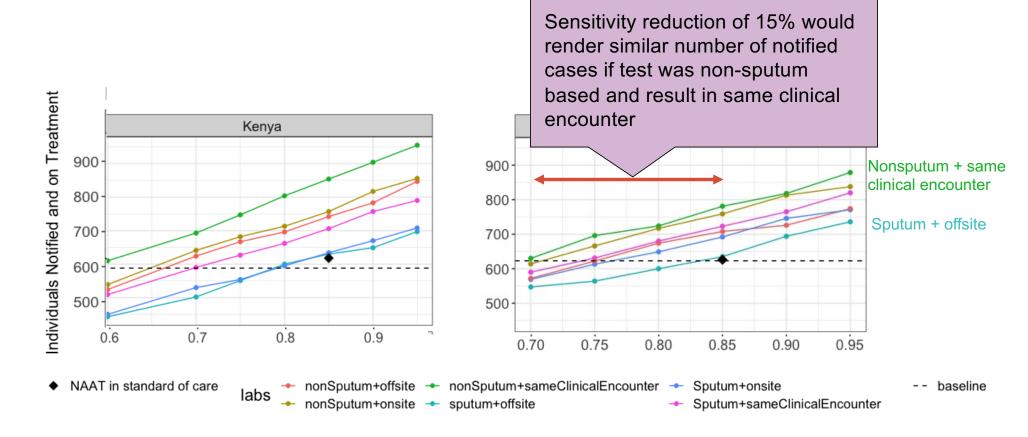
#### REPLACING NOTHING WITH SOMETHING PROBABLY MAKES 'SO-SO' 'GOOD ENOUGH'

#### Trade off between test accuracy and test access, assuming an underlying disease prevalence of 10%





# MODELLED IMPACT WITH VARIOUS ACCESS PARAMETERS





#### BRINGING mDX TO THE PEOPLE

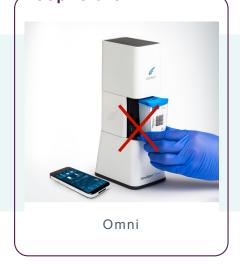
# POINT OF CARE MOLECULAR...

Onsite Xpert testing and access to same day treatment initiation leads to 56% increase in treatment start (measured a day 14)

(Xpel study, Katamba, Cattamanchi et al in press)



#### Cepheid Omni

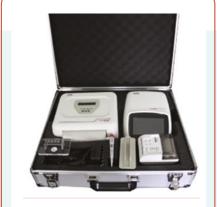


## Cepheid Edge



Edge

#### Molbio



TruePrep + TrueLab









#### EDCTP FUNDED TB-CAPT CONSORTIUM

**CORE TRIAL:** Molbio Truenat<sup>™</sup> TB platform combined with the Truenat TB assays for detection of tuberculosis and rifampicin resistance in adults with presumptive pulmonary tuberculosis at primary-level diagnostic centres in Tanzania and Mozambique: a pragmatic, cluster- randomized controlled trial

Katharina Kranzer, Adam Penn-Nicholson, Morten

Ruhwald, Elisa Tagliani and many others

**EXULTANT TRIAL:** Expanding Xpert Ultra for TB: diagnosis among HIV-positive patients admitted to hospitals in Tanzania and Mozambique Alberto García-Basteiro, Adam Penn-Nicholson, Laura de la

Torre, Morten Ruhwald, Elisa Tagliani, and many others

**Xpert MTB/XDR study:** Two-site laboratory-based diagnostic accuracy and feasibility study of the Xpert MTB/XDR assay for detection of isoniazid, fluoroguinolone, ethionamide and second-line injectable anti-tuberculosis drug





Helen Cox, Leslie Scott, Chad Cetner, Adam Penn-Nicholson, Morten Ruhwald, Elisa Tagliani, and many others

#### Mozambique

- Instituto Nacional de Saude
- Centro de Investigação em Saúde de Manhiça





#### Tanzania

- National Institute for Medical Research - Mbeya Medical Research
- Ifakara Health Institute Trust

#### **South Africa**

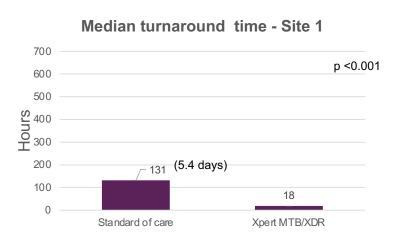
University of Cape Town Wits Health Consortium

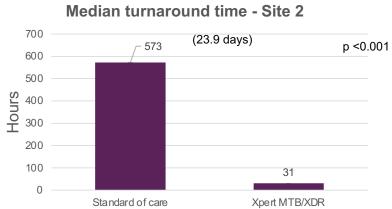
#### XPERT XDR



#### Diagnostic Accuracy and Feasibility study of Xpert MTB/XDR

- Two high throughput labs in South Africa (Cape Town and Gqeberha)
- Sputum from n=763 participants processed by Xpert Ultra and reflexed to Xpert XDR, vs pDST + WGS, compared to LPA
  - 86% of specimens were processed on Xpert XDR >4hrs of addition of SR buffer, with no significant impact on test validity rates for any drug target.
  - Median turn-around-time for resistance result was dramatically reduced by Xpert XDR vs SOC









Diagnostic accuracy was aligned to previously reported results

Next step: TRiAD study → To evaluate the effectiveness, operational feasibility, acceptability, and cost-effectiveness of implementing the Xpert MTB/XDR assay for rapid triage and selection of all-oral regimens for DR-TB



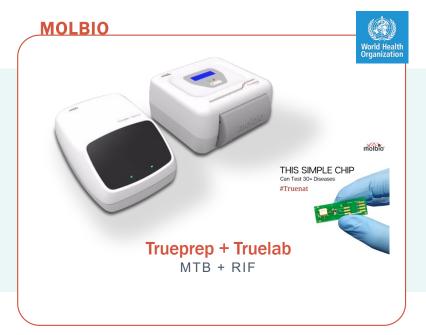




#### GROWING LANDSCAPE AND PIPELINE OF 'LOW COMPLEXITY AUTOMATED NAATS

# STATUS ON mDx assays







#### GROWING LANDSCAPE AND PIPELINE OF 'LOW COMPLEXITY AUTOMATED NAATS'

## **NEAR POC MDX**

#### SD BIOSENSOR, STANDARD M10



#### **BIONEER, IRON-qPCR**



- MTB assay
  - TB, RIF, INH, FQ, SLID
  - Result in 30 mins

#### **MOLBIO, TRUENAT**



- New Ultima, INH and FQ chips
- Combined TB and Covid-19 assay
- Clinical trials started in 2022





## READY TO LEVERAGE COVID-19 INVESTMENTS, MULTI-PATHOGENIZE MDX SERVICES

#### Enable

- Sputum based
- high-throughput testing
- upfront INH testing
- multi-disease testing

#### Performance

- Sensitivity similar to Xpert
- Resistance detection similar to LPA







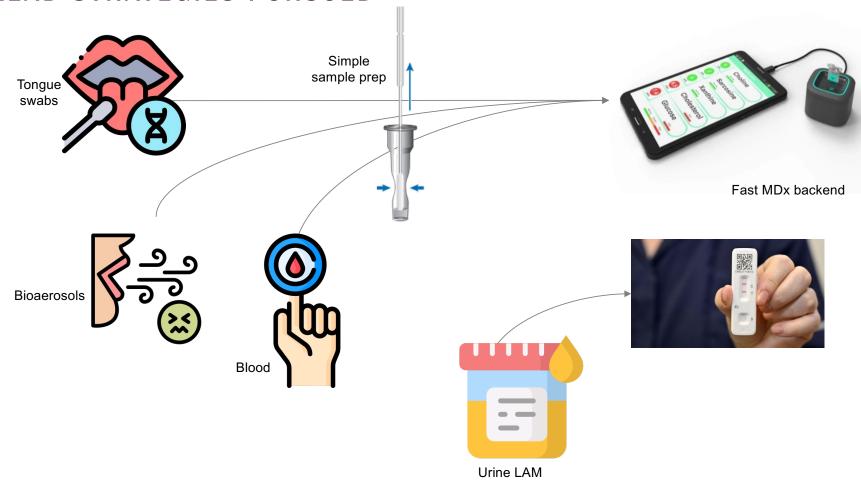






#### AN ALTERNATIVE TO SPUTUM - ADDRESS MAJOR ACCESS BARRIERS

# LEAD STRATEGIES PURSUED





#### NON-SPUTUM BASED SAMPLING WITH SWABS

#### TONGUE SWABS IS A POTENTIALLY DISRUPTIVE STRATEGY TO REPLACE SPUTUM



- Swab frozen in 1.2ml PBS
- Thawed, and 2.4ml SR buffer added
- 2ml loaded to Xpert Ultra



Tonque	

Cheek and gums

**Nostrils** 

Tongue, cheek and gum

Tongue swab Ultra, Method 2 (N=183) trace+ for all Microbiologic reference Sputum Xpert standard\* Sensitivity 77.8 (64.4-88.0) 73.4 (59.1-83.3) Specificity 100 (97.2-100) 100 (96.9-100)

FEND-TB consortium, in preparation \* = n=30 for nostril swabs



#### Some refinements underway

- The optimal swab?
- Sample prep?
- The optimal backend?
- Stability and optimal transport media...or dry?
- Simultaneous SARS-CoV2 testing?

"I got tested at home, the help came to me": acceptability and feasibility of home-based TB testing of household contacts using portable molecular diagnostics in South Africa

Andrew Medina-Marino<sup>1,2,3</sup>, Lindsey de Vos<sup>1</sup>, Dana Bezuidenhout<sup>1</sup>, Claudia M. Denkinger<sup>4,5</sup>, Samuel G. Schumacher<sup>4</sup>, Sanghyuk S. Shin<sup>6</sup>, Wendy Stevens<sup>7</sup>, Grant Theron<sup>8</sup>, Martie van der Walt<sup>9</sup> and Joseph Daniels<sup>1</sup>

#### **SWABS IN ACTIVE CASE FINDING PILOT**

ANALYZING SWABS IN REAL TIME IN THE COMMUNITY.

**POOLING SWABS** FROM HOUSEHOLD

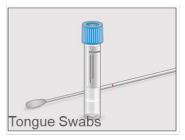
Andrew Medina-Marino and Bernard Fourie, in preparation





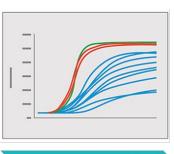


#### FIRST IN CLASS - SWAB BASED TB DETECTION ON MULTI-PATHOGEN PLATFORM AT POC











Sample Collection & Lysis

Insert Strip & Add Sample

Amplification 15 minutes

Analysis and Report





#### LumiraDx Smart Connectivity

- ☐ Step-by-step test instructions on screen
- ☐ Digital display of results and reporting
- ☐ Data analytics and decision support
- Seamless, secure connectivity to the cloud and health IT systems
- ☐ Platform launch 2018, in 2021 5k instruments installed in Africa, 20k globally
- ☐ TB assay enter policy trial 2023

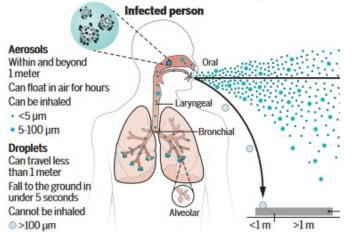




# BIOAEROSOLS POTENTIALLY DETECT SUBCLINICAL/MINIMAL DISEASE BETTER THAN SPUTUM-BASED METHODS



## TB AEROSOLS & CAPTURE TECHNOLOGIES









Face mask-type technologies









Blow tube-type technologies

- Higher in patients with pulmonary TB, declines with Rx
- Infectiousness is highly variable
- Aerosol output is better predictor of Mtb in households compared to smear positivity













#### ADDITIONAL USE CASES

#### SUBCLINICAL TB DETECTION

#### FMS performance for sub-clinical TB

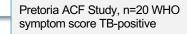
Exhaled Mycobacterium tuberculosis output and detection of subclinical disease by face-mask sampling: prospective observational studies



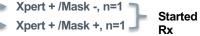
Caroline M Williams, Mohamad Abdulwhhab, Surinder S Birring, Elsabe De Kock, Natalie J Garton, Eleanor Townsend, Manish Pareek, Alaa Al-Taie, Iinazhe Pan, Rakesh Ganatra, Anton C Stoltz, Pranabashis Haldar, Michael R Barer

oa

 $\mathbb{Q}^{\dagger}$ 



Xpert - /Mask -, n=12 - 10mo FU, No TB



Xpert - /Mask +, n=6 =

Positivity rate: 7/8 for masks and 2/8 for sputum Xpert



# 6 weeks FU (n=5)

n=4 Xpert+ve/Mask+ve

all CXR-ve but PET-CT+ve

#### n=1 Xpert-ve/Mask+ve

- CXR-ve. PET-CT+ve
- Alternative Dx made at 20 week FU

#### TRANSMISSION

#### FMS performance for household contacts (transmission)

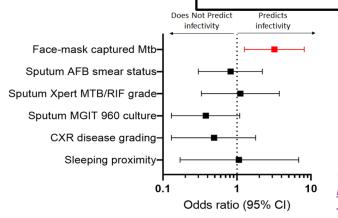
The Gambia, n=46 microbiologically confirmed TB patients each with at least 3 household contacts (n=181 household contacts)

#### **Index Cases**

1hr FMS at enrolment Sputum sample at enrolment

#### **Household Contacts**

QFT at enrolment Assessment for active TB at enrolment QFT at 6 months Assessment for active TB at 6 months



Williams CM et al. https://www.medrxiv.org/content/ 10.1101/2021.11.06.21266008v1

- A high mask Mtb level (≥20,000 IS6110 copies) observed in 45% of cases and associated with increased likelihood of incident Mtb infection in contacts
- Mask Mtb level was a better predictor of incident Mtb infection than sputum bacillary load, chest radiographic characteristics or sleeping proximity
- Follow-up studies in Pretoria, screening 321pts to date, found >25% positivity with FMS+Ultra



Williams CM et al. Lancet ID 2020



## FACE MASKS AND BREATH CAPTURE

FIND and the University of Leicester have developed the concept into a scalable product for tidal breath sampling (30min) and TB detection

Clinical performance for TB detection is currently being evaluated in FEND-TB

Once clinical evidence is available, production will be scaled up and face masks will be made available for clinical use via an RFP process

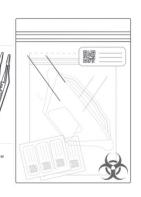












Wear 30mins

Remove PVA strip and backing from mask

Remove PVA strip from backing

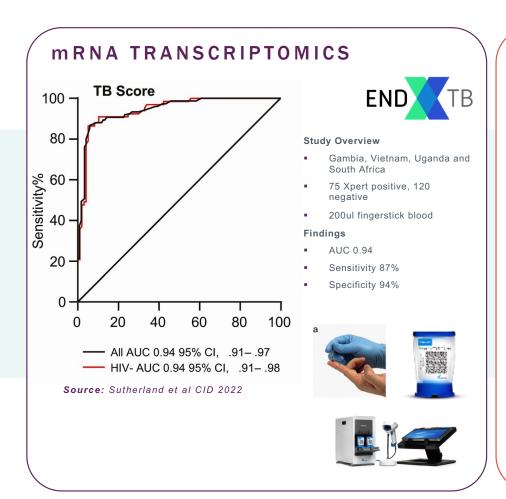
Dissolve PVA strip in 4ml H2O (tap)

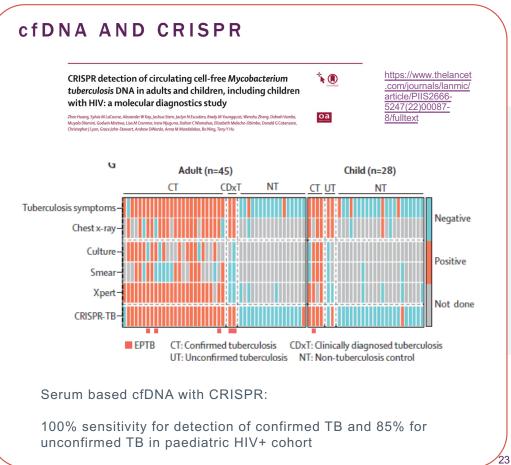
Run 5 drops of dissolved PVA on RDT (neat)

https://www.fend-tb.org/



# NON-SPUTUM-BASED TESTING USING BLOOD? BLOOD-BASED DX

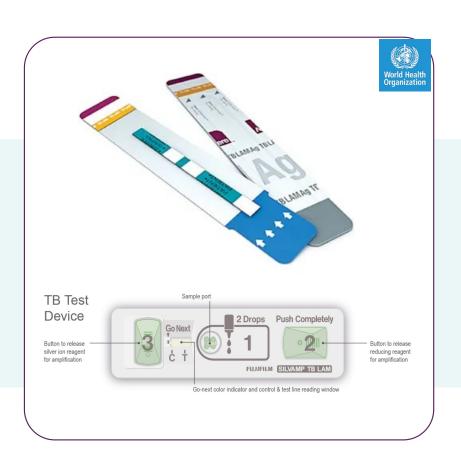






#### ANTIGEN DETECTION TESTS

# DETERMINE TB LAM Ag and Fujifilm SILVAMP TB LAM



## PLHIV (5 cohorts, n=1595)

	Sn [95% CI]	Sp [95% CI]
FujiLam	70.7 [59.0 – 80.8]	90.9 [87.2 – 93.7]
AlereLAM	34.9 [19.5 – 50.9]	95.3 [92.2 – 97.7]

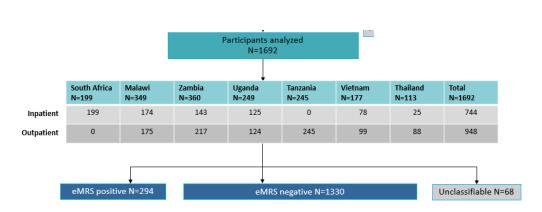
## HIV uninfected patients (n=372)

	Sensitivity (95% CI)	Specificity (95% CI)
FujiLAM	53.2% (43.9 to 62.2)	98.9% (96.7 to 99.6)
AlereLAM	10.8% (6.3 to 18.0)	92.3% (88.5 to 95.0)

Source: Broger et al. J Clin Invest 2020; Broger et al, PLOS Med 2020



# FIRST LARGE PROSPECTIVE ACCURACY EVALUATION OF FUJILAM RENDERS UNEXPECTED LOW SPECIFICITY AND VARIABILITY



	Sensitivity [95%CI]	Specificity[95%CI]
FujiLAM	54.8 [49.1-60.4]	85.1 [83.1-85.9]
Determine TB LAM Ag	30.5 [25.5-36.0]	90.7 [89.0-92.2]

		N	Sensitivity	Specificity
		N	[95%CI]	[95%CI]
				85·1 [83·1 –
	All	1615	54·8 [49·1–60·4]	86·9]
CD4	≤100	326	82·2 [73·6 –88·4]	80.4 [74.8–85.1]
	101 to ≤200	183	62.5 [47.0–75.8]	87.4 [81.0–91.9]
	201 to ≤500	502	44.9 [34.3–55.9]	83.5 [79.7–86.7]
	>500	588	22·1 [13·9–33·3]	87·7 [84·6–90·2]
Countires	South Africa	144	73·2 [60·4–83·0]	75.0 [65.0–82.9]
	Malawi	334	62·5 [45·2–77·1]	88·1 [83·9–91·3]
	Zambia	358	62·3 [48·8–74·1]	81.6 [76.9–85.6]
	Uganda	248	72.7 [58.1–83.7]	82·4 [76·5–87·0]
	Tanzania	245	26·5 [17·4–38·0]	87.0 [81.3–91.2]
	Viet Nam	176	33·3 [19·8–50·4]	96.5 [92.1–98.5]
	<u>Thai</u> land	110	83.3 [43.6–97.0]	81.7 [73.2–88.0]

































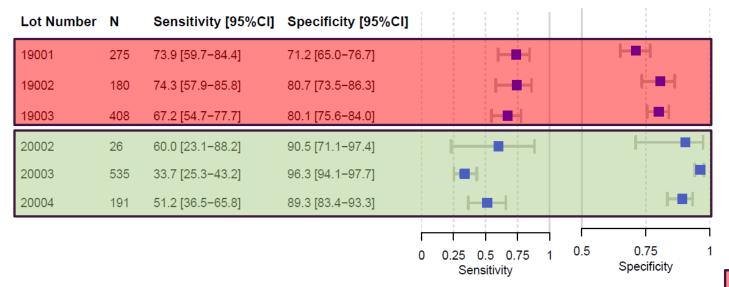
Expected

Spec>97%



# **FIND**

# LOT-TO-LOT VARIABILITY





n =1575 all PLHIV, 4 countries, outpatient sympt, asymptomatic with advanced HIV

_	Sensitivity	Specificity
	% (95% CI)	% (95% CI)
Lot 19003	76 (57-89)	77 (72-81)
Lot 20002	75 (41-93)	91 (81-96)
Lot 20003	59 (36-79)	98 (93-99)
Lot 20004	48 (34-62)	97 (94-99)

Huerga et al preprint, http://dx.doi.org/10.2139/ssrn.417522



ASTIIE study, n =600 all PLHIV, 2 countries.

Sensitivity Specificity

Lot 19002/3 56.3% (29.9 - 80.2) 86.4% (80.3 - 91.2)

Lot 20003 35.0% (15.4 - 59.2) 97.4% (95.3 - 98.8)

Tiemersma E et al in preparation



























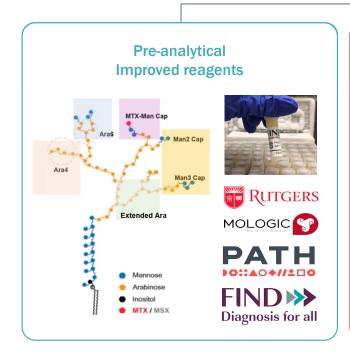






# PATHWAYS TO 3RD GENERATION LAM TESTS

3<sup>rd</sup> Generation LAM assay
Ultra sensitive (<10 pg/mL) to detect LAM in all TB patients









#### DIAGNOSING TB IN CHILDREN

## UPDATED POLICY RECOMMENDATION FOR STOOL



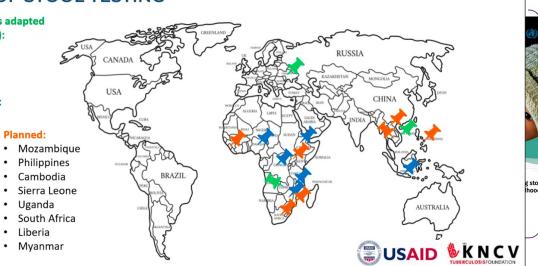
#### **UPTAKE OF STOOL TESTING**

# Routine (policies adapted for stool testing):

- Vietnam
- Zambia
- Ukraine

#### Pilot or scale up:

- 1 1100 01 300
- EthiopiaDR Congo
- Malawi
- Zimbabwe
- Indonesia
- Nigeria





Source: https://www.kncvtbc.org/en/sos-stoolbox/



# CAD/CXR - AUTOMATED CHEST X-RAY INTERPRETATION WITH AI SOFTWARE AND PORTABLE AND SAFER INSTRUMENTS

#### Al enabled solutions

Input:

Digital AP CXR





Abnormality score



#### A fast-moving field

- · CXR remains the most sensitive screening and triage tool for TB
- · CXR is underutilized due to global shortage of radiologists, infrastructure and logistical restraints
- Portable x-ray instruments are now on the market and WHO endorsed
- 8 CE marked CAD products in 2022 (only 3 in 2019) www.ai4hlth.org

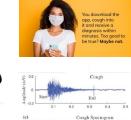
**POCUS** 

dStethoscopes

Cough apps

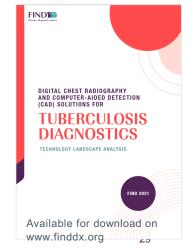






Portable x-ray instruments takes CXR to where no x-ray has gone before!







#### AN EXPLOSION IN NEW DX FOR TBI

#### >15 NEW PRODUCTS ENTERING THE MARKET

#### AUTOMATED/HIGH THROUGHPUT

Qiagen-Diasorin



BioMeriéux, Vidas TB-IGRA





Qiagen, QIAreach



SD Biosensor, Standard F TB-Feron

#### **RDT BASED IGRA**



Boditech, iCHROMA IGRA-TB



R-Biopharm, IP-10 release assay



Lionex LIOFeron®TB-LTBI



LGchem Avansure TB



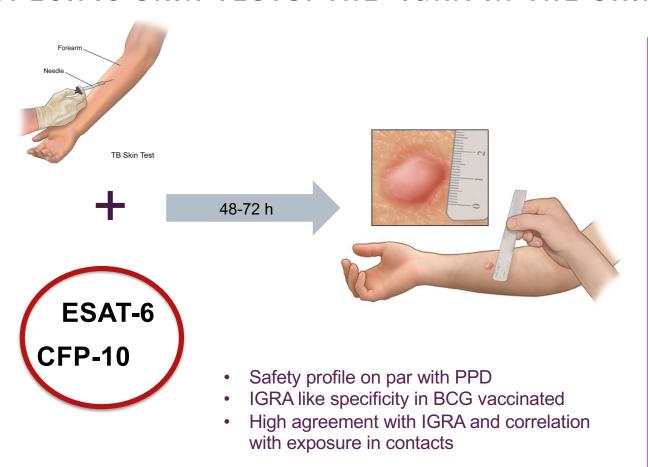
SD Biosensor Standard E TB Ferron

**ELISA BASED IGRA** 





# SPECIFIC SKIN TESTS: THE 'IGRA IN THE SKIN'





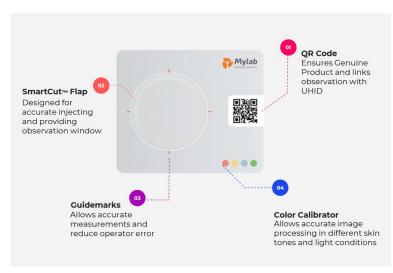


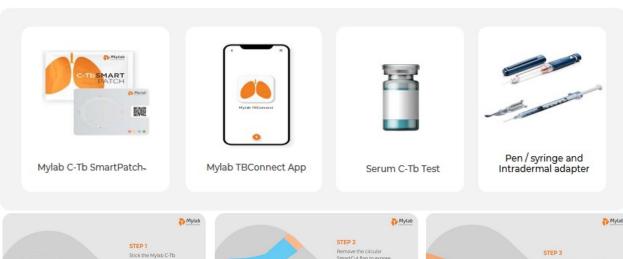




# CONNECTING THE CENTURY OLD SKIN TEST

# SMART PATCH AND COMPANION APP FOR CY-TB



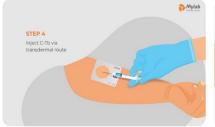






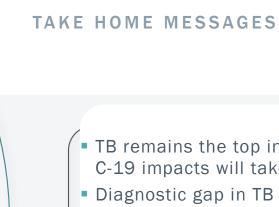












图图8周9

@ SD BIOS

TB Ina Tiba, Pimwa, Tibiwa, Ishi Poa



- TB remains the top infectious disease killer; C-19 impacts will take decades to recover from
- Diagnostic gap in TB is a disaster...but
- ...unprecedented opportunities coming through COVID-19 and we need to build on the momentum
- New instruments and alternative sampling strategies are showing promise to bring the diagnostics close to the patients
  - trade off in accuracy for yield is expected and impact is unknown
- Plenty of new diagnostics that can be partnered with communities and treatment regimens and digital solution for a comprehensive package to support patients



## ACKNOWLEDGEMENTS - FIND'S TEAM

# Thank you to the participants and their families

Thank you to the FIND TB team!





Sergio Carmona Morten Ruhwald Adam Penn-Nicholson Kavi Velen Margaretha De Vos Vinzeigh Leukes Mikashmi Kohli Rita Szekely Andrea Cavellini Laure Martine Mary Gaichiri Dennis Walusimbi Alex Ogwal
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Sandra Kik
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Harisha Ramachandraiah
Anita Suresh
Swapna Uplekar
Andres de la Rossa
Lauri Koivula
Tim Rodwell
Rebecca Colman

Sacha Laurent

Pamela Nabeta
Agnes Malobela
Luz Villa
Sunita Singh
Kavi Ramjeet
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Sarah-Jane Loveday

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Contact: adam.penn-nicholson@finddx.org