THE REPUBLIC OF UGANDA
MINISTRY OF HEALTH

UGANDA Supranational® Reference Laboratory

Timely Accurate Diagonostics for a TB-Free Africa

THE TB SAMPLE REFERRAL SYSTEM (TSRS) TRAINING

Module 2

WHO recommended TB diagnostic assays & algorithms

xXth -xXth MONTH YEAR

NAME OF PRESENTER

OUTLINE

- End TB strategy
- WHO processes for new technology evaluation
- WHO endorsed TB diagnostic techniques until 2020
- Diagnostic techniques scheduled for evaluation 2019/2020
- The WHO TB diagnostic algorithms
- Example of country specicfic algorithm

Group exercise-10 minutes

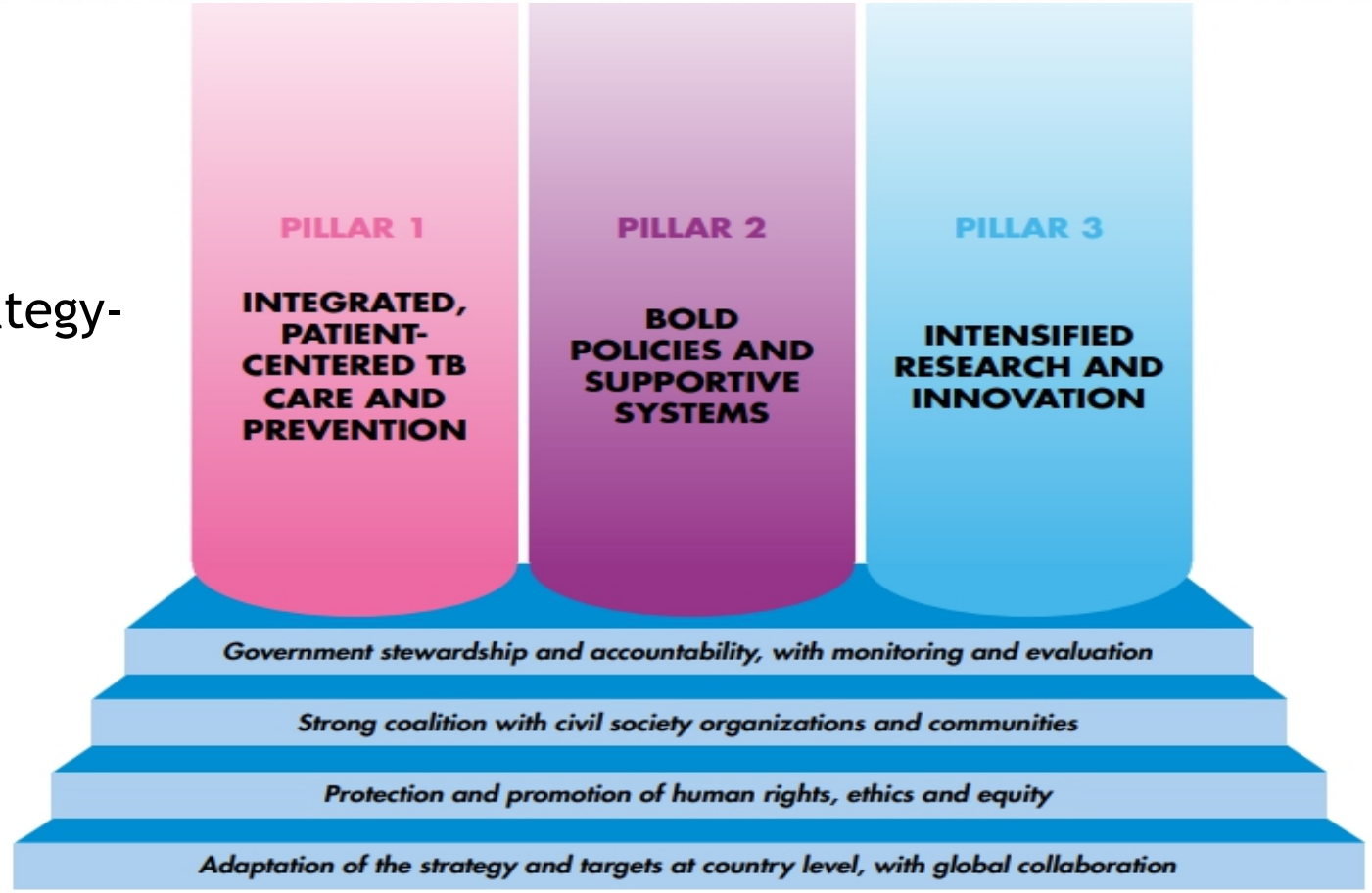
1. List all the WHO approved TB diagnostic tests that you know.

2. Identify the role of each of those tests in the TB diagnosis and follow up.

End TB strategy

THE END TB STRATEGY: PILLARS AND PRINCIPLES

Source: The end TB strategy- WHO



End TB Strategy Pillars and Components

1. **INTEGRATED, PATIENT-CENTERED CARE AND PREVENTION**

A. Early diagnosis of TB, including universal drug susceptibility testing and systematic screening of contacts and high-risk groups

B. Treatment of all people with TB, including drug-resistant TB, and patient support

C. Collaborative TB/HIV activities, and management of comorbidities

D. Preventive treatment of persons at high, and vaccination against TB

End TB Strategy Pillars and Components…cont

2. Bold policies and supportive systems

A. Political commitment with adequate resources for TB care and prevention

B. Engagement of communities, civil society organization, and public and private care givers

C. Universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicine, an infection control

D. Social protection, poverty alleviation and actions on other determinants of TB

End TB Strategy Pillars and Components…cont

3. Intensified research and innovation

A. Discovery, development and rapid uptake of new tools, interventions and strategies

B. Research to optimize implementation and impact, and promote innovation

Lab indicators and targets under End TB Strategy

- Three (3) Laboratory objectives and Twelve (12) indicators
- Objective 1: Increase access to rapid and accurate detection of TB
- Objective 2: Reach universal access to Drug Susceptibility Testing (DST)
- Objective 3: Strengthen quality of laboratory services

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Achieving early diagnosis and universal access to DST

- Requires rapid molecular diagnosis at the first entry point to the health system
- All bacteriologically confirmed cases require a rapid DST (at least rifampicin)
- All rifampicin-resistant TB or MDR-TB require rapid second-line DST
- Conventional microscopy monitoring and culture required for monitoring TB patients response to therapy
- This requires a functional laboratory network with strong sample referral mechanism

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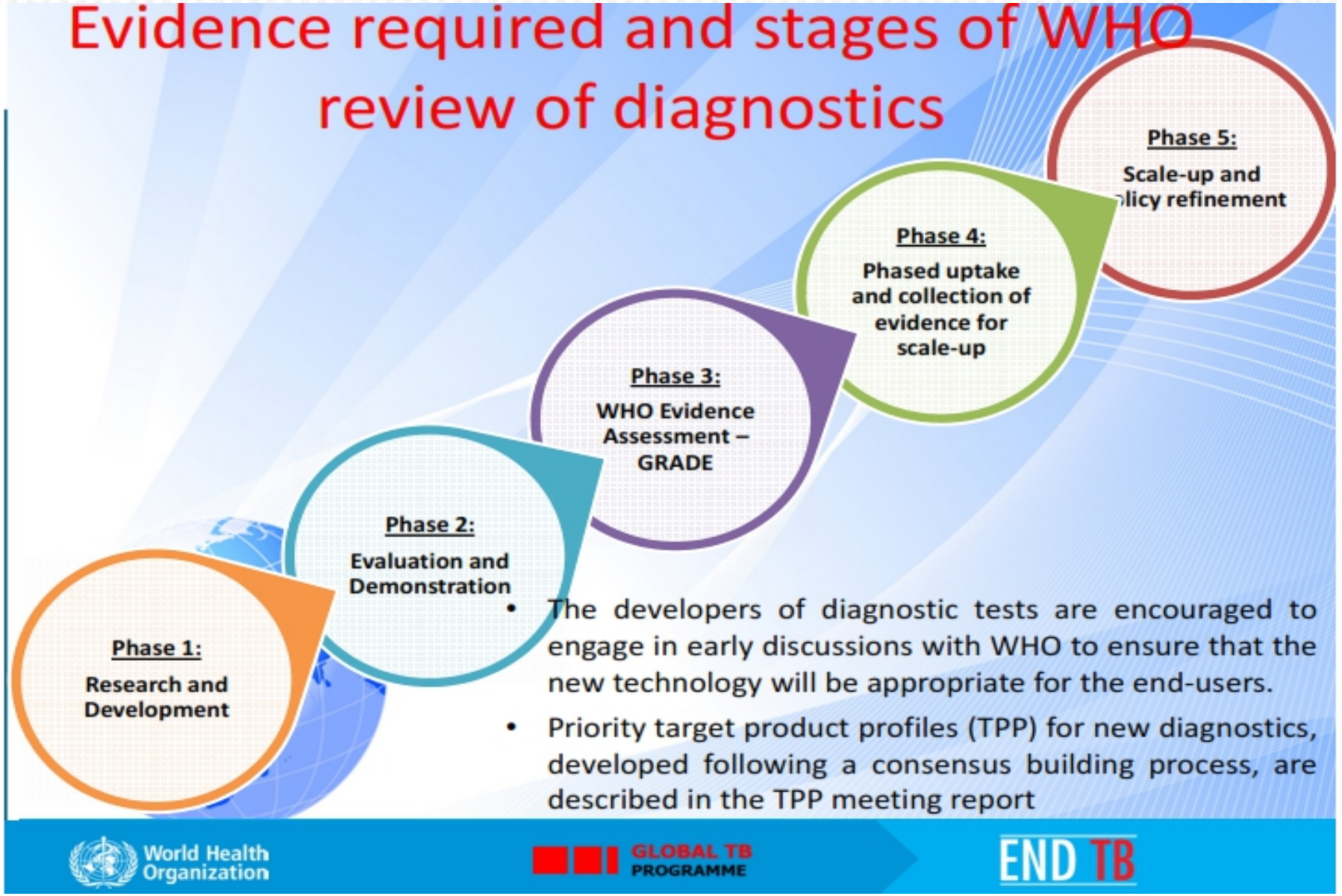
Challenges to considerer under these 12 indicators

- Approved diagnostic algorithm at country level
- Rapid test as initial diagnostic test for all the TB suspected cases
- Lab data transmitted electronically to clinicians and management
- All bacteriologically confirmed TB have DST at least for RIF

Challenges to considerer under these 12 indicators…cont

- All Rif resistant cases (by GeneXpert) have DST for FQ and SLI drugs
- Availability of Quality Assurance for all tests, QMS implementation towards accreditation
- Accreditation of the National TB Reference Laboratories

Evidence required and stages of WHO review of diagnostics



Source: The end TB strategy-WHO

WHO's recommended techniques for diagnosing TB until 2019

Molecular detection of TB and drug resistance

- Xpert MTB/RIF and Xpert Ultra as the initial diagnostic test for TB and rifampicin resistance, Cepheid, USA
- Line probe assay for the detection of Mycobacterium tuberculosis (MTB), isoniazid and rifampicin resistance in acid-fast bacilli smear positive sputum or MTB cultures (FL-LPA), Hain Lifescience, Germany
- Line probe assay for the detection of resistance to fluoroquinolones and second-line injectable agents (SL-LPA), Hain Lifescience, Germany
- TB LAMP for detection of TB, Eiken, Japan

Molecular methods for the diagnosis o DR-TB

- Molecular (genotypic) methods detect specific DNA mutations in the genome of *the M. tuberculosis*, which are associated with resistance to specific anti-TB drugs.

- Molecular methods have considerable advantages for programmatic management of drug-resistant TB, in particular with regard to their speed, the standardization of testing, their potentially high throughput and the reduced requirement for laboratory safety

Molecular methods for the diagnosis o DR-TB…cont

- Molecular tests for detecting drug resistance to rifampicin alone or in combination with isoniazid have been recommended for use by WHO since 2008

Xpert MTB/RIF

- Xpert MTB/RIF remains the only WHO recommended diagnostic test that can simultaneously detect TB and rifampicin resistance that is suitable for use at lower levels of the health system

Xpert MTB/RIF Ultra Assay

- Ultra has a higher sensitivity than Xpert MTB/RIF particularly in s-c+ specimens (+17%) and in specimen from HIV-infected patients with at least as good accuracy from rifampicin resistance detection

- Greatest benefit was in the increased yield for the detection of MTB in S-C+ specimens, pediatric specimens, extra-pulmonary specimens (notably cerebrospinal fluid) and especially for HIV+ patients whose specimens are frequently paucibacillary

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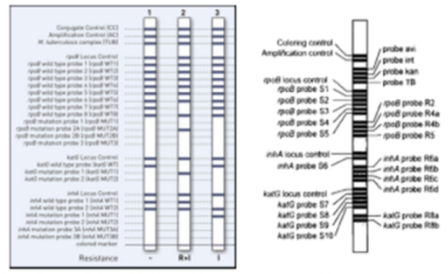
Xpert Areas of diagnostic integrations (Additional Xpert Assays)

- Xpert cartridges for other diseases and conditions can be used on the same GeneXpert_instrument_as for Xpert MTB/RIF
- WHO Prequalified: Xpert HIV-1 Qual assay (EID), Xpert Hepatitis C and HIV Viral Load assays
- Potential areas for integration: Testing site personnel, trainings, maintenance, supply systems, specimen referral, quality assurance, etc.

First-line LPA

- New guidance recommends the use of LPA as the initial test for the detection of resistance to rifampicin and isoniazid in sputum smear positive specimens and culture of MTBC



Examples of different line probe assays strip readouts:
a) Hain GenoType MTBDR*plus* V1 and V2 strip readout
b) Nipro NTM+MDR Detection Kit 2 strip

Second-line LPAs

- Who recommends the use of the SL-LPA for patients with confirmed rifampicin-resistant TB or MDR-TB as the initial test to detect resistance to fluoroquinolones and the second line injectable drugs, instead of phenotypic culture based drug-susceptibility test

Lateral flow-Urine Lipoarabnomannin assay (LF-LAM)

- Recommended to help with the diagnosis of TB in two specific population groups:
- People living with HIV who have signs or symptoms of TB and a CD4 cell count less than or equal to 200 cells/µl
- People living with HIV who are “seriously ill” regardless of CD4 count or if the CD4 count is unknown.

Loop-mediated Isothermal Amplification Assay (TB-LAMP)

- TB-LAMP may be used as a replacement test for sputum smear microscopy for the diagnosis of pulmonary TB in adults with signs and symptoms consistent with TB

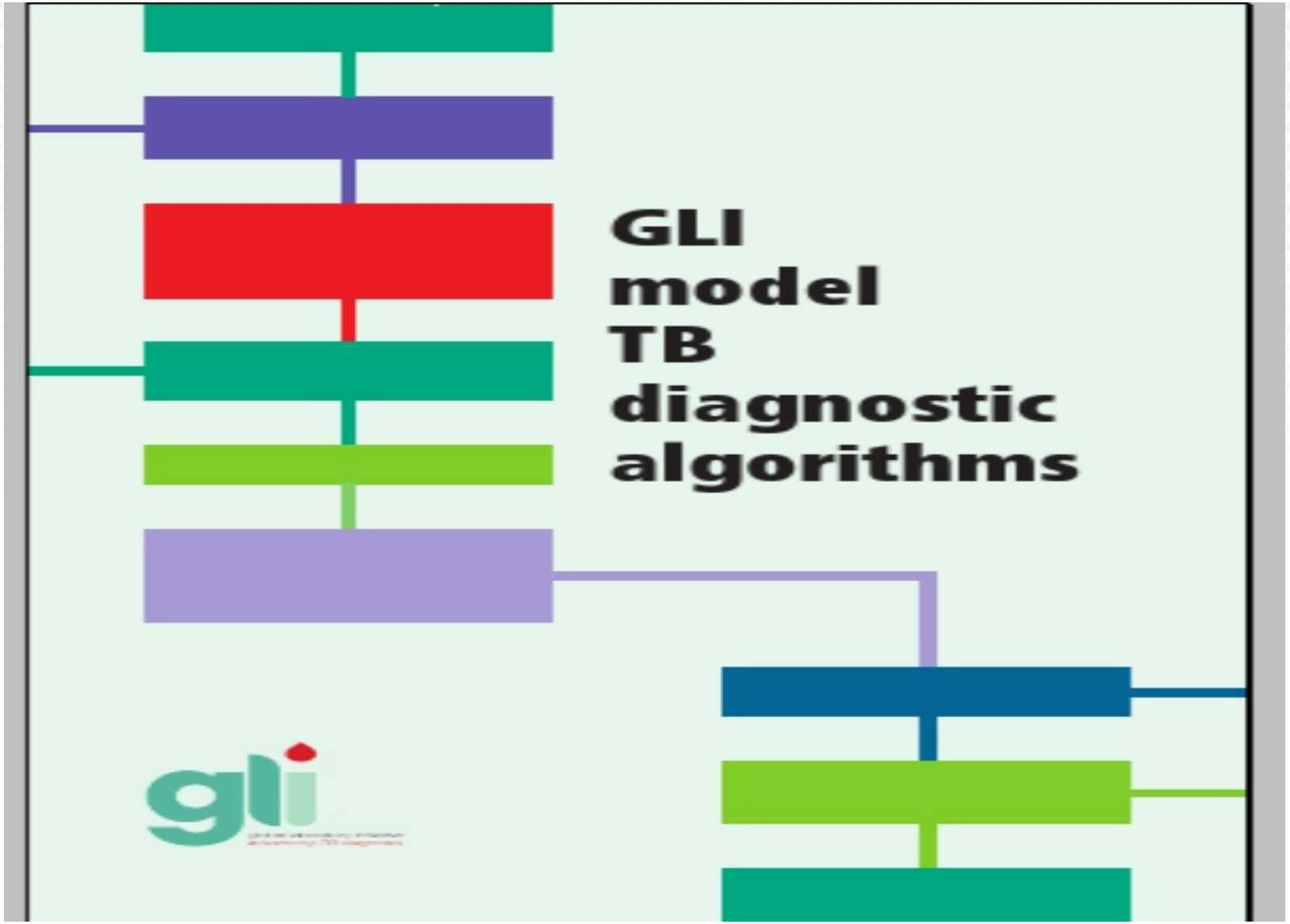
Molecular methods for the diagnosis of DR-TB-limitations

- There remains imperfect correlation between phenotypic and genotypic methods
- Molecular methods have high specificity but lower sensitivity which varies for different drugs
- The predictive values of imperfect test depend on the pre-test probability of resistance

Phenotypic methods for the diagnosis of DR-TB

- Phenotypic, culture methods are based on assessment of the ability of M. tuberculosis to growth in culture media (solid or liquid) containing a critical concentration of specific anti-TB agents (which indicates resistance) or, conversely, its inability to grow in the same media (which is susceptible

- Commercial liquid culture systems for DST reduce the time to result to as little as 14 days, compared with 6 weeks needed for DST using solid media


GLI
model
TB
diagnostic
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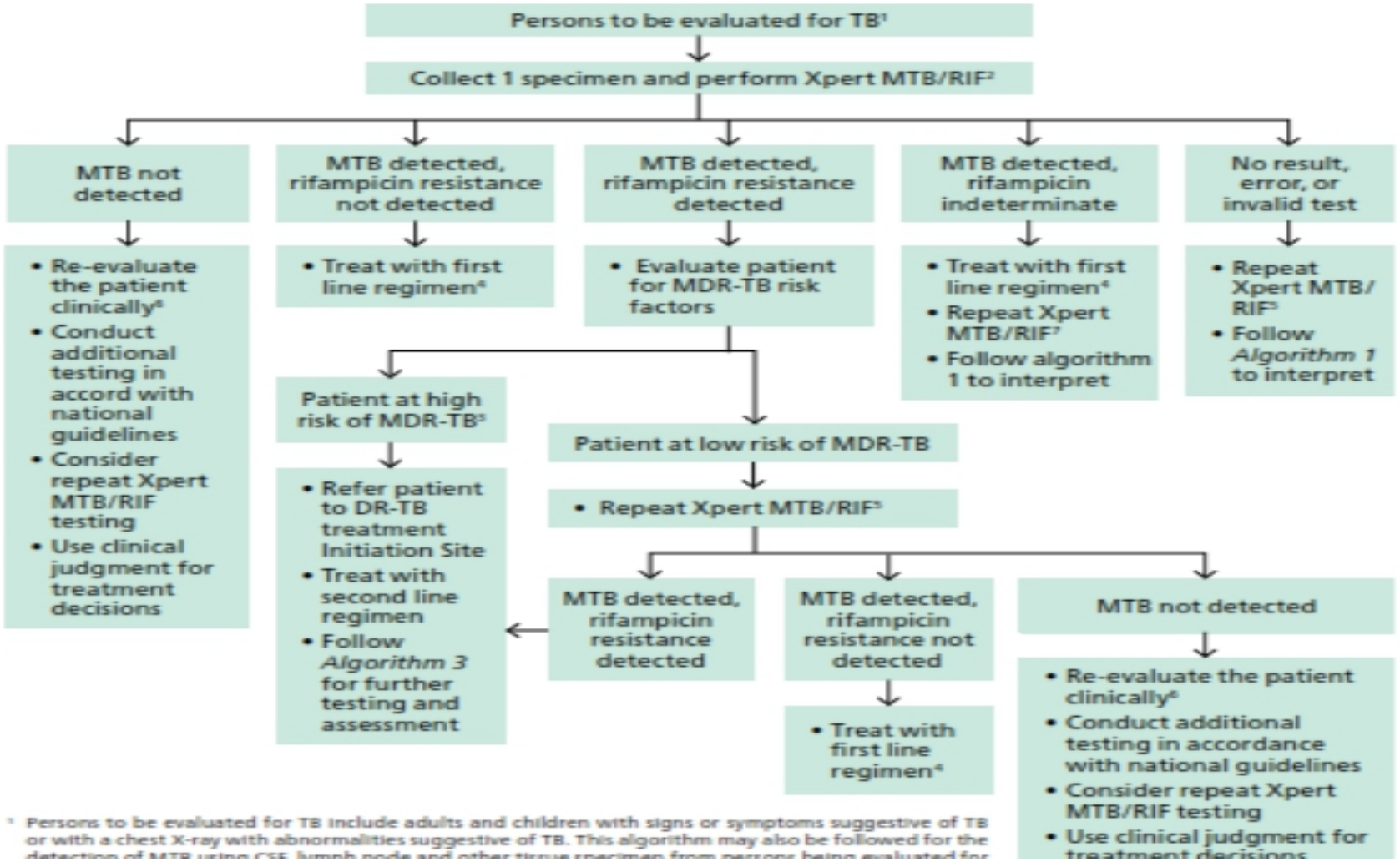
Algorithm 1: Preferred algorithm for universal patient access to rapid testing to detect MTB and rifampicin resistance



[1] Persons to be evaluated for TB include adults and children with signs or symptoms suggestive of TB or with a chest X-ray with abnormalities suggestive of TB. This algorithm may also be followed for the

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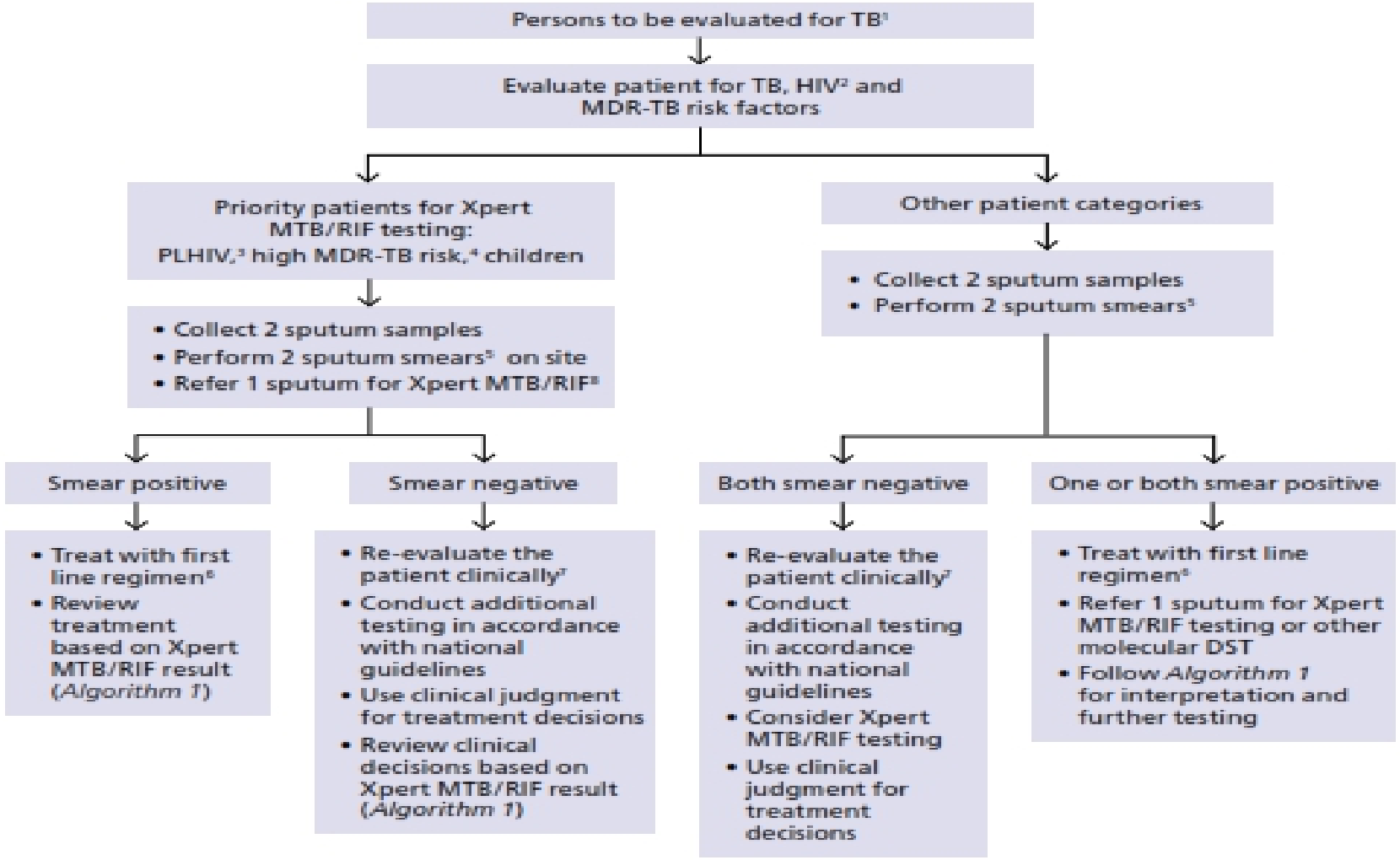
Algorithm 2: Interim algorithm moving towards universal access, with rapid testing for priority populations



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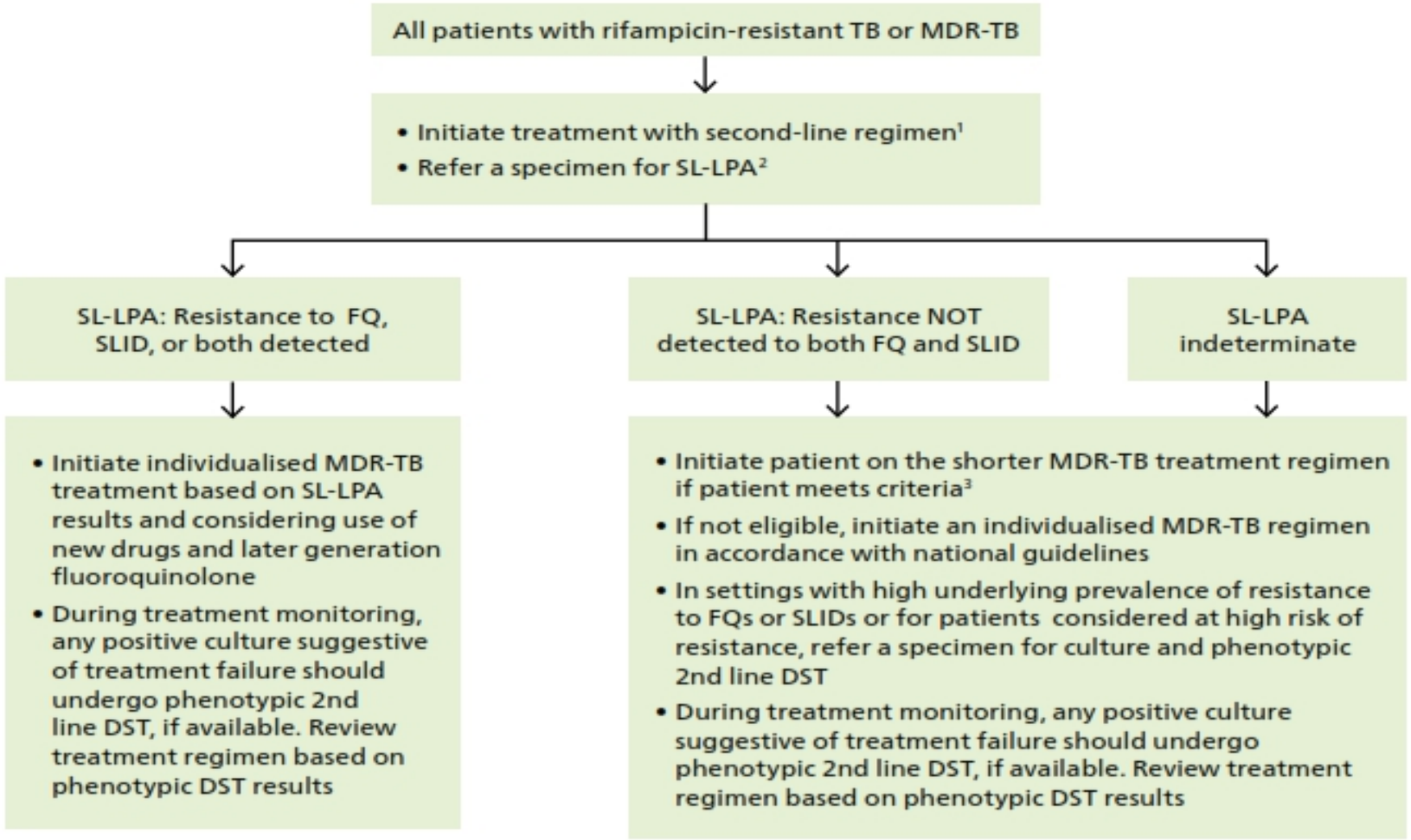
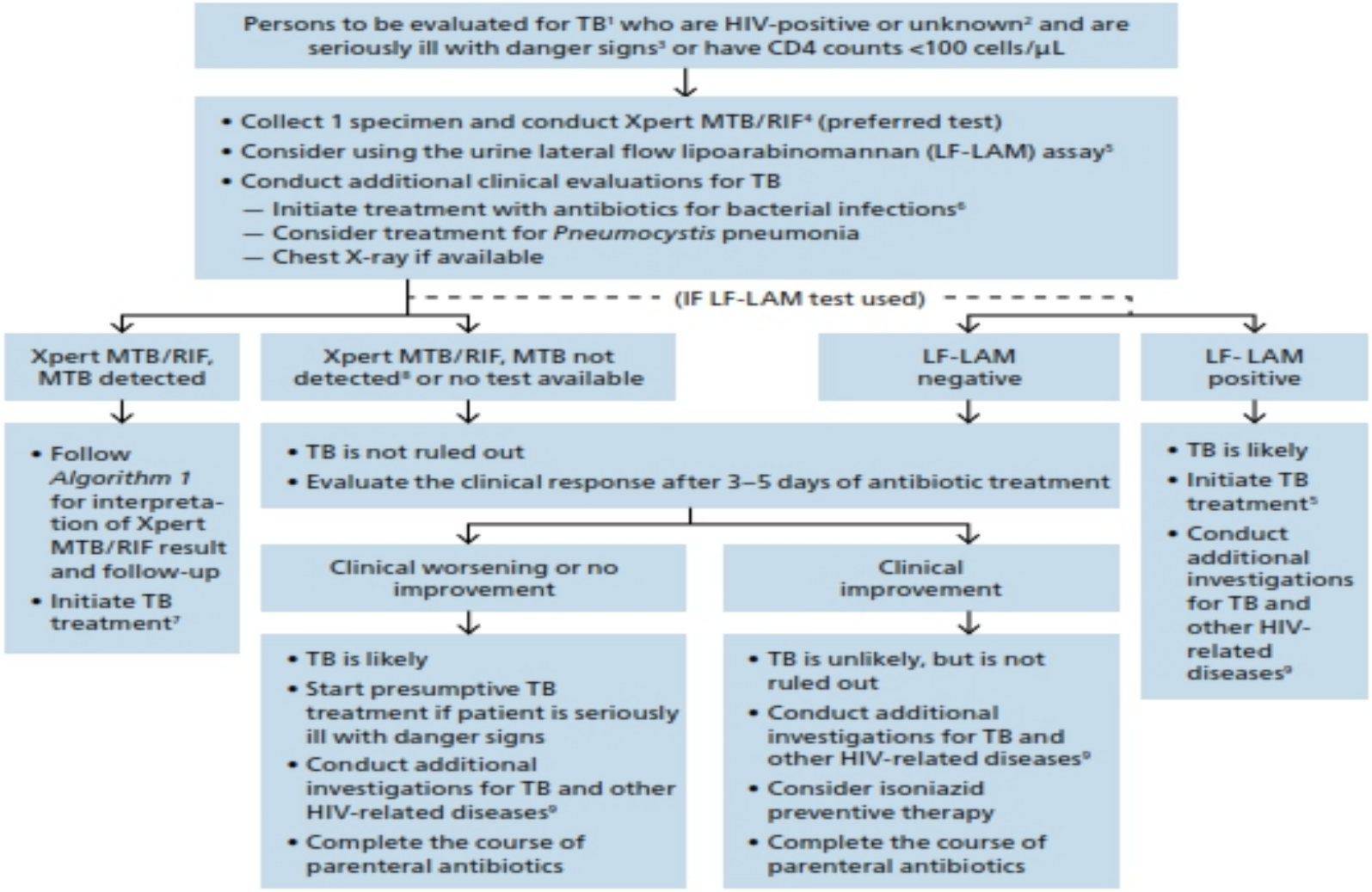
Algorithm 3: Algorithm for testing for second-line drug resistance among rifampicin-resistant TB or MDR-TB patients



Algorithm 4: Algorithm for evaluating persons for TB, among PLHIV who are seriously ill with danger signs or have CD4 counts ≤ 100 cells/µl



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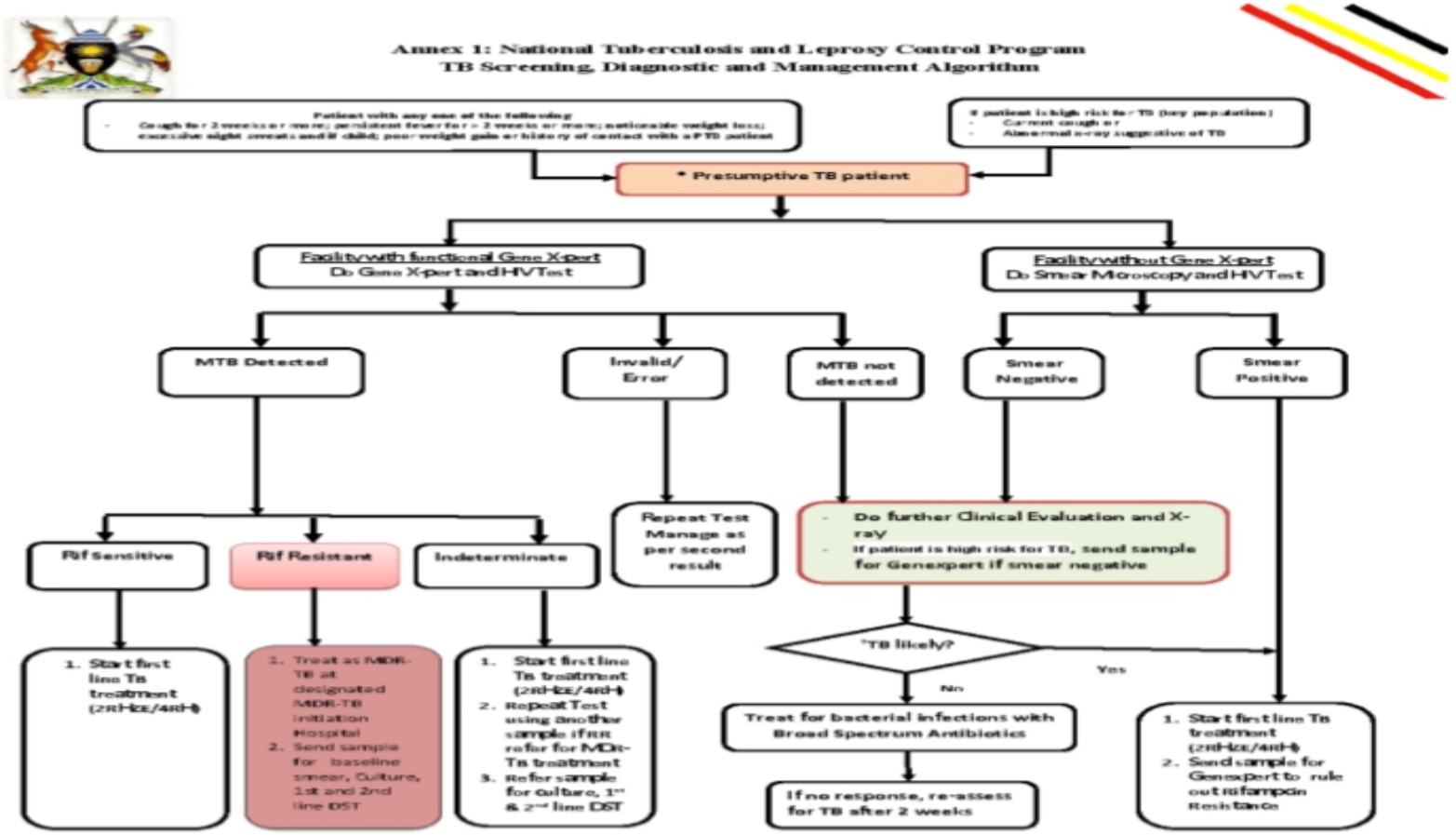
Example of the Uganda TB diagnostic algorithm

Appendix 1: GeneXpert diagnostic algorithm



1. ***Presumptive TB** is presence of any or a combination of the following symptoms; cough≥ 2weeks or current cough if high risk patient, fever, night sweats, history of contact with a TB case, weight loss or poor weight gain for children. Also consider abnormal chest x-ray in a high risk patient as presumptive TB
2. **"High risk patients"** include PLHIV, previously treated TB patients, prisoners, contacts of TB patients, diabetic patients, health workers, miners and refugee populations
3. **Smear positive** (AFB positive): is defined as at least one positive smear
4. **Smear negative**: defined as two negative smears. If patient is from high risk category, send a sample for GeneXpert test
5. **"TB likely:** Abnormal Chest X-ray findings suggestive of TB e.g. cavitation, pleural effusion, miliary picture , hilar lymph nodes
6. **HIV positive patients:** Presumptive or diagnosed TB patients who are HIV positive should be offered comprehensive HIV care services. Chest x-ray should be used to screen for active TB for all PLHIV enrolling in care. Those in whom TB has been excluded should be offered IPT as per IPT guidelines. HIV positive adults in whom TB is not picked by microscopy or GeneXpert and are very sick (CD4 less than 100) should be tested for TB using Urine TB LAM test
7. **Treatment monitoring:** Follow up sputum smear microscopy should be done at the end of 2, 5 & 6 months for susceptible TB and monthly smear and culture for DR-TB.
8. **Recording & Reporting:** All diagnosed TB patients (resistant, sensitive, and indeterminate) record in the Unit TB register and included in facility quarterly(HMIS 106a) notification report and all rifampicin resistant(RR) TB patients should be notified in the weekly (HMIS 033b)report by the facility that refer the sample for Gene Xpert test. In addition record RR TB patients in the district line list and the Drug resistant TB register at the treatment initiation facility.

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Summary

- The lab has 3 objectives and 12 indicators under the end TB strategy
- A country may adopt any of the WHO recommended algorithm depending on the policies, finances and other factors
- Genotypic DST techniques have a shorter TAT compared to the phenotypic methods hence ensuring rapid initiation of patient on treatment

Assessment

1. Menion the 3 Lab targets in the End TB Strategy?

2. Explain how a specimen referal system can contribute in achieving the targets mentioned above?

3. Which factors would one consider when selecting an algorithm for their country from the available WHO recommended models of TB diagnositic alogarithm?

References

- GLI TB training package http://www.stoptb.org/wg/gli/trainingpackages.asp
- Global tuberculosis report 2019, https://apps.who.int/iris/bitstream/handle/10665/329368/9789241565714-eng.pdf?ua=1
- GLI guide to TB specimen referral systems and integrated network http://www.stoptb.org/wg/gli/assets/documents/GLI_Guide_specimens_web_ready.pdf
- Guidelines for the Uganda national health laboratory hub and sample transport network http://cphl.go.ug/sites/default/files/2019-06/Hub%20Guidlines.pdf

Acknowledgments

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gli
global laboratory initiative
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