ROLE OF IGRA IN TB CONTROL

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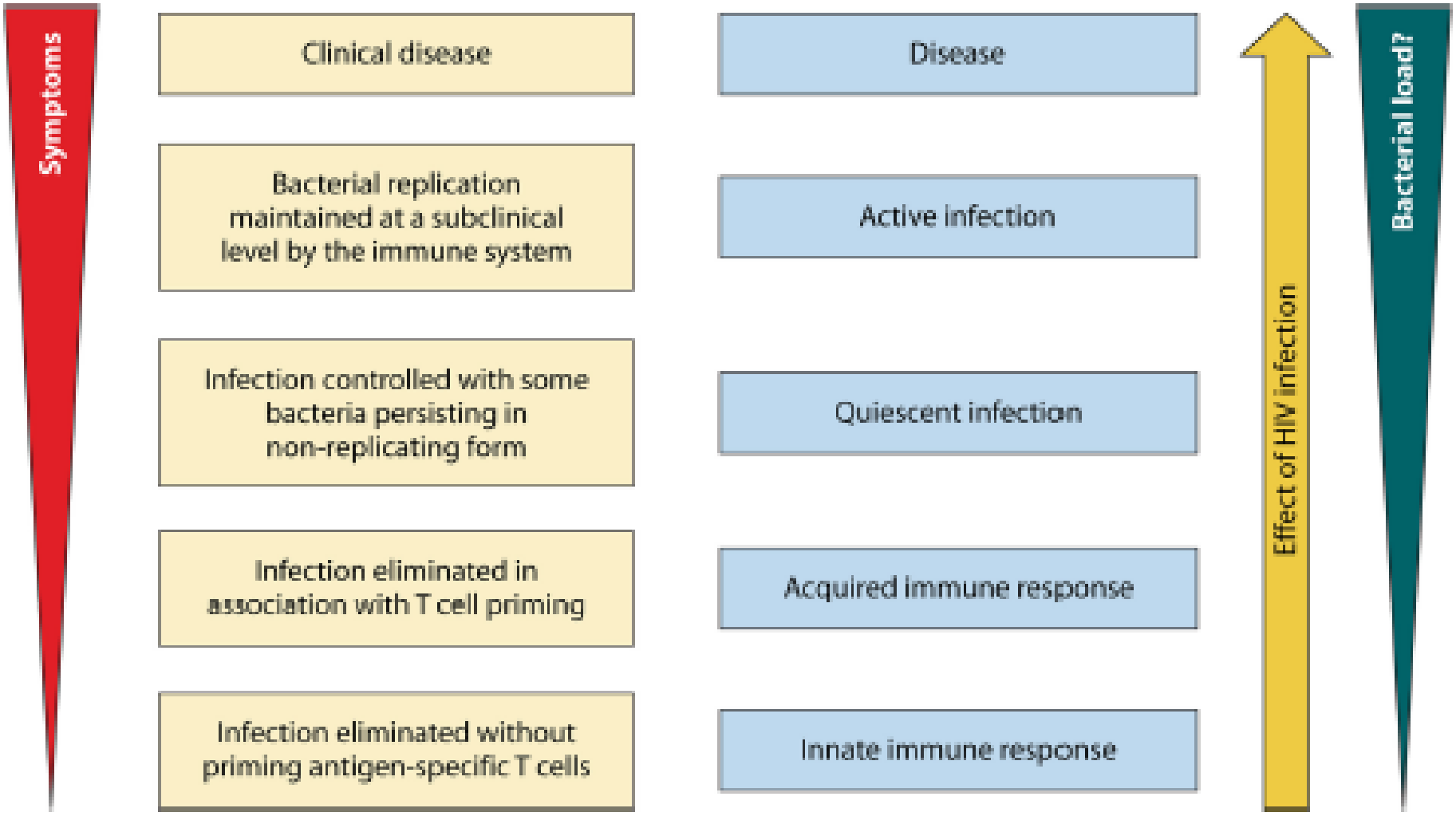
Targeted TB Testing and Treatment of Latent TB Infection

- As TB disease rates in the United States decrease, **finding and treating** persons at high risk for latent TB infection (LTBI) has become a priority.

- Targeted TB testing is used to focus program activities and provider practices on groups at the highest risk for TB.

- **Treatment of LTBI substantially reduces the risk** that persons infected with *M. tuberculosis* will progress to TB disease.



Considering TB Infection As a Spectrum

Latent TB Infection (LTBI)

LTBI is the presence of *M. tuberculosis* organisms (tubercle bacilli) **without signs and symptoms or radiographic or bacteriologic evidence of TB disease**.

TB Disease – LTBI vs. Pulmonary

Latent TB Infection

- Positive TST or IGRA result
- Chest radiograph normal
- No symptoms or physical findings suggestive of TB
- If done, respiratory specimens are smear and culture negative

Pulmonary TB Disease

- TST or IGRA is usually positive
- Chest radiograph is usually abnormal
- Symptoms *may* include one or more of the following: fever, cough, night sweats, weight loss, fatigue, hemoptysis, decreased appetite
- Respiratory specimens are usually culture positive (smear positive in about 50% of patients)

Who Should Be Tested

Know

Who is considered at risk?	What countries are considered TB endemic?
Foreign born patients from TB endemic countries, where prior TB exposure is almost certain	• All of Asia except Japan • All of Central and South America • All of Africa • All of Eastern Europe **(Yes, that is practically the whole world)**

Other Groups At High Risk for TB

Groups

• Close contacts of Active TB cases
  • Usually taken care of by TB clinic
• Healthcare workers who serve high risk clients
• Residents & employees of congregate settings
• Medically underserved/low-income groups:
  • Homeless
  • Migrant workers
  • Street drug users
  • Children with parents who have risk factors

Medical Conditions that Put People at High Risk for TB

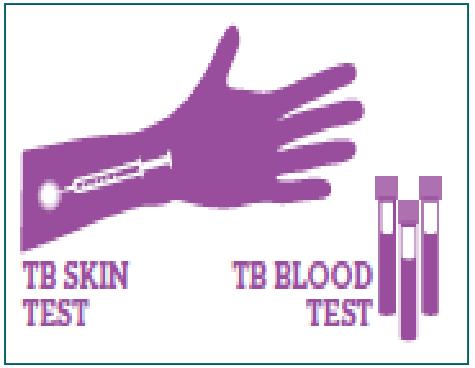
Medical Conditions
• **HIV +**
• **Renal dialysis**
• **Immunocompromised (≥15 mg prednisone qd for 1 month or more)**
• **Diabetes mellitus**
• **Silicosis**
• **Cancer of the head and neck**
• **Hematologic and reticuloendothelial diseases**
• **Intestinal bypass or gastrectomy**
• **Chronic malabsorption syndromes**
• **Low body weight**
• **Organ Transplant**

Who needs repeat LTBI testing?

1) Healthcare workers
2) Close contacts to infectious TB cases
3) Frequent travelers to abroad
   - If baseline TST is negative, consider retesting your patients that have extended travel to high risk areas.
   - Do symptom review upon return and possibly retesting 8-10 week after return.

Testing for *M. tuberculosis* Infection

- Two testing methods available for the detection of *M. tuberculosis* infection :
  - Mantoux tuberculin skin test (TST)
  - Interferon-gamma release assays (IGRA)

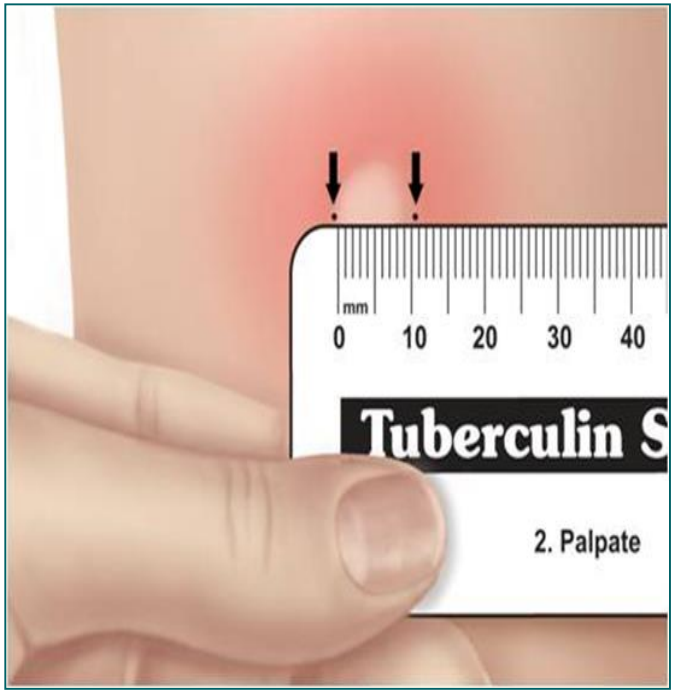


- These tests do not exclude LTBI or TB disease

- Decisions about medical and public health management should include other information, and not rely only on TST or IGRA results

Reading the TST -1

- Measure reaction in **48 to 72 hours**
- Measure **induration**, not erythema
- Record reaction in **millimeters**, not “negative” or “positive”
- Ensure **trained health care** professional measures and interprets the TST



TST Interpretation

≥ **5 mm induration** is interpreted as positive in

- HIV-infected persons
- Close contacts to an infectious TB case
- Persons with chest radiographs consistent with prior untreated TB
- Organ transplant recipients
- Other immunosuppressed patients (e.g. , those taking the equivalent of > 15 mg/d of prednisone for 1 month or those taking TNF-α antagonists)

TST Interpretation

≥ **10 mm induration** is interpreted as positive in

- Recent immigrants
- Injection drug users
- Residents or employees of congregate settings
- Mycobacteriology laboratory personnel
- Persons with clinical conditions that place them at high risk
- Children < 4 years; infants, children, and adolescents exposed to adults at high-risk

TST Interpretation

≥ 15 mm induration is interpreted as positive in

- Persons with no known risk factors for TB.
  - Although skin testing programs should be conducted only among high-risk groups, certain individuals may require TST for employment or school attendance.
  - Diagnosis and treatment of LTBI should always be tied to risk assessment.

Factors That May Cause False-Positive TST Reactions

- **Nontuberculous mycobacteria**
  - Reactions caused by nontuberculous mycobacteria are usually ≤10 mm of induration

- **BCG vaccination**
  - Reactivity in BCG vaccine recipients generally wanes over time; positive TST result is likely due to TB infection if risk factors are present

Factors That May Cause False-Negative TST Reactions

- **Anergy**
  - Inability to react to a TST because of a weakened immune system
  - Usefulness of anergy testing in TST-negative persons who are HIV infected has not been demonstrated
- **Recent TB Infection**
  - Defined as less than 10 weeks after exposure
- **Very young age**
  - Newborns (< 6 months)

Factors That May Cause False-Negative TST Reactions

- **Live virus vaccination**
  - For example, measles or smallpox
  - Can temporarily suppress TST reactivity
- **Overwhelming TB Disease**
- **Poor TST administration technique**
  - For example, TST injection too shallow or too deep, or wheal is too small

Boosting

- Some people with LTBI may have a negative skin test reaction when tested years after infection because of a waning response.
- An initial skin test may stimulate (boost) the ability to react to tuberculin.
- Positive reactions to subsequent tests may be misinterpreted as new infections rather than “boosted” reactions

Two-Step Testing

- A strategy to determine the difference between boosted reactions and reactions due to recent infection.
  - If 1st test positive, consider infected; if negative, give 2nd test 1–3 weeks later
  - If 2nd test positive, consider infected; if negative, consider uninfected

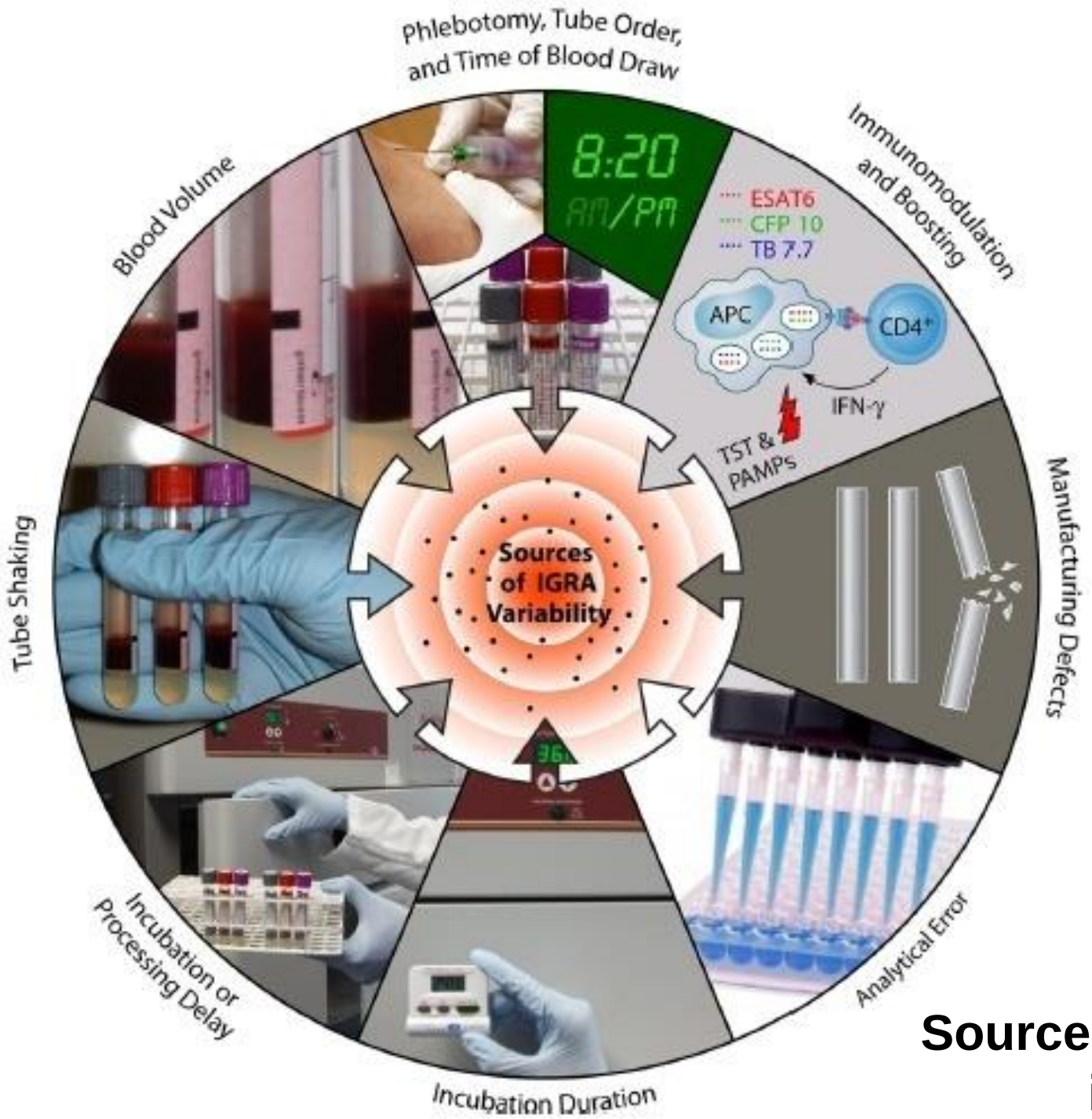
- Use two-step tests for initial baseline skin testing of adults who will be retested periodically (e.g., health care workers).

Interferon-Gamma Release Assays (IGRAs)

- Whole-blood test used to detect *M. tuberculosis* infection
- Two U.S. Food and Drug Administration (FDA) approved IGRAs are commercially available in the U.S.:
  - **QuantiFERON® -TB Gold-in-tube test (QFT-GIT)**
  - **T.SPOT® .*TB* test (T-Spot)**

How IGRAs Work

- Blood test that measures and compares amount of interferon-gamma (IFN-γ) released by blood cells in response to antigens
- Entails mixing blood samples with antigens from *M. tuberculosis* and controls
- Cells that recognize the antigen release interferon-γ
- Amount of interferon released in response to *M. tuberculosis* antigens is compared to amount released in response to other antigens



Source of variability in QFT

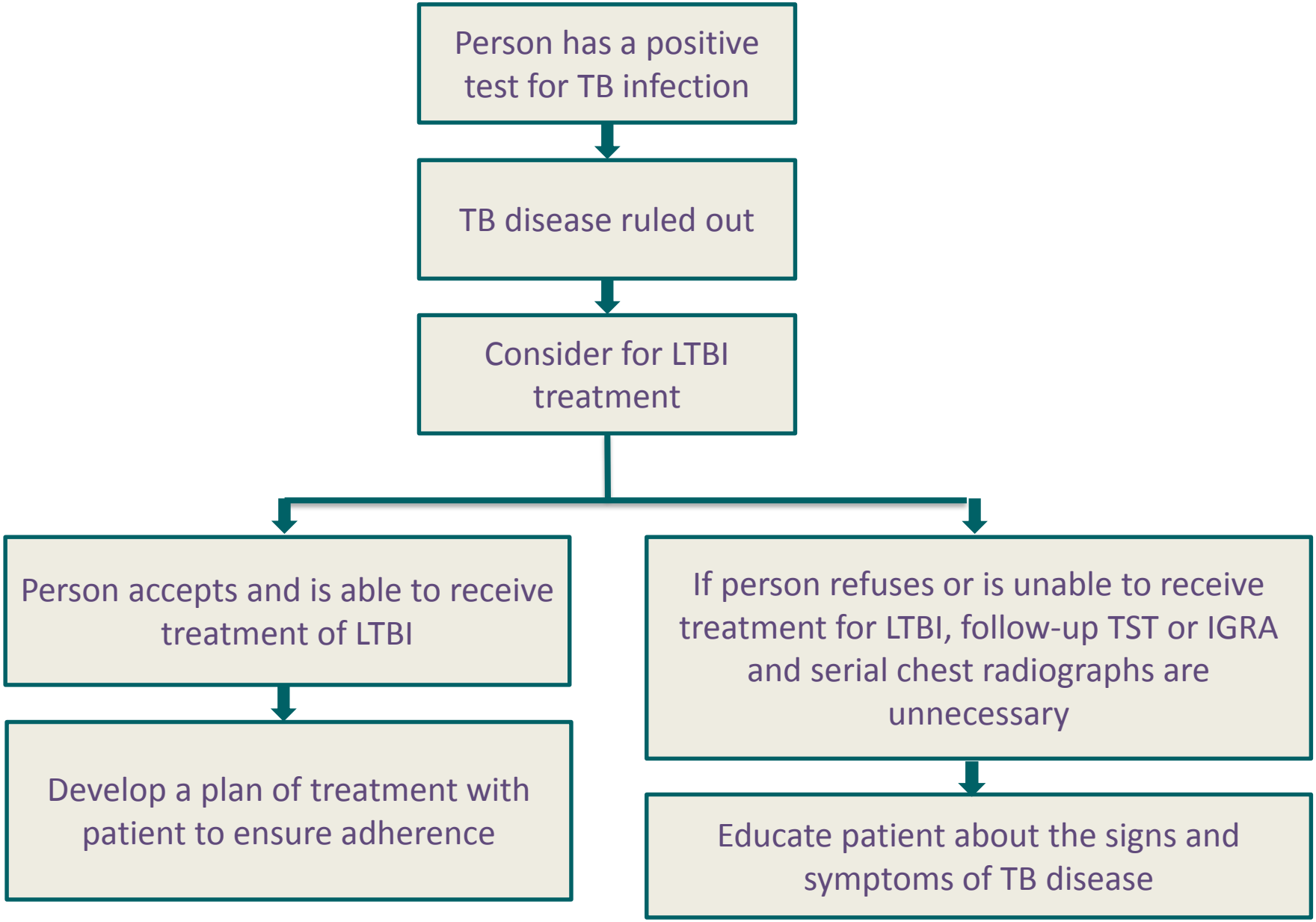
Advantages of IGRAs

- Requires a single patient visit to conduct test
- Results can be available within 24 hours
- Does not boost responses measured by subsequent tests
- Prior BCG vaccination does not cause false-positive IGRA test result

Disadvantages/Limitations of IGRAs

- Errors in **collecting and transporting blood**, or in interpreting assays can decrease accuracy of IGRAs
- Limited data on use of IGRAs to predict who will progress to TB disease in the future
- Tests may be **expensive**
- Limited data on the use of IGRAS for
  - Children < 5 years of age;
  - Persons recently exposed to *M. tuberculosis*;
  - Immunocompromised persons; and
  - Serial testing

Evaluation of Persons with Positive TB Test Results



INDIVIDUALS WITH SUSPECTED TB DISEASE

- BOTH IGRAs AND TST HAD POOR SPECIFICITY IN DISTUINGUISHING EXTRAPULMONARY TB FROM LTBI ESPECIALLY IN LOW-INCOME COUNTRIES
- CONSIDERED IN LIGHT OF CONVENTIONAL RISK FACTORS, INCLUDING SIGNS, SYMPTOMS, AND CHEST RADIOGRAPH – THERE IS LIMITED ADDED VALUE FOR ADULTS IN SETTINGS WITH EITHER LOW OR HIGH TB INCIDENCE
- CURRENT GUIDELINES **DISCOURAGE USE OF IGRAs AS STAND-ALONE TESTS TO DIAGNOSE ACTIVE TB**

HIV-INFECTED PERSONS

- IGRAs PERFORM SIMILARLY TO THE TST IN IDENTIFYING HIV-INFECTED INDIVIDUALS WITH PRESUMED LTBI
- BOTH TST AND IGRAs HAVE SUBOPTIMAL SENSITIVITY FOR ACTIVE TB – **POTENTIAL ROLE FOR USING BOTH TESTS** ESPECIALLY IN IMMUNOCOMPROMISED INVIDUALS

IMIDs

(Immune-mediated Inflammatory Diseases

- SCREENING WITH QFT IS SUFFICIENT PRIOR TO TREATMENT WITH TNF-ANTAGONIST IN REGIONS MODERATE OR HIGH TB PREVALENCE
- **DUAL TESTING STRATEGY OF TST AND IGRA IMPROVES SENSITIVITY**
- IN THIS POPULATION, **A PATIENT WHO IS POSITIVE BY EITHER TEST SHOULD BE CONSIDERED TO HAVE LTBI**

PATIENTS RECEIVING DIALYSIS FOR END-STAGE RENAL DISEASE

- IN HEMODIALYSIS PATIENTS QFT IS MORE SENSITIVE THAN TST, AND CONSIDERATION SHOULD BE GIVEN **TO USING IT AMONG PATIENTS RECEIVING HEMODIALYSIS**

OTHER IMMUNOCOMPROMISED POPULATIONS, INCLUDING CANCER AND TRANSPLANT

- IT IS DIFFICULT TO MAKE ANY DEFINITE RECOMMENDATIONS REGARDING THE USE OF IGRAs TO DIAGNOSE LTBI IN THESE POPULATIONS
- TST REMAINS THE BEST STUDIED TEST IN THESE POPULATIONS – SUGGEST THAT **TST IS THE TEST OF CHOICE** PENDING FURTHER DATA

HCWs AND SERIAL TESTS

- IGRAs ARE INHERENTLY DYNAMIC IN A SERIAL TESTING – SHOWS HIGH RATES OF BOTH CONVERSIONS AND REVERSIONS
- THE MANUFACTURER'S DICHOTOMOUS CUTOFFS ARE USED FOR CONVERSIONS – LIKELY RESULT IN **CONVERSION RATES THAT INCOMPATIBLE WITH WHAT EPIDEMIOLOGICALLY EXPECTED**

MONITORING OF ANTITUBERCULOSIS THERAPY

- THERAPY – BACILLARY BURDEN/LOAD DECREASED – IGRA RESPONSE +

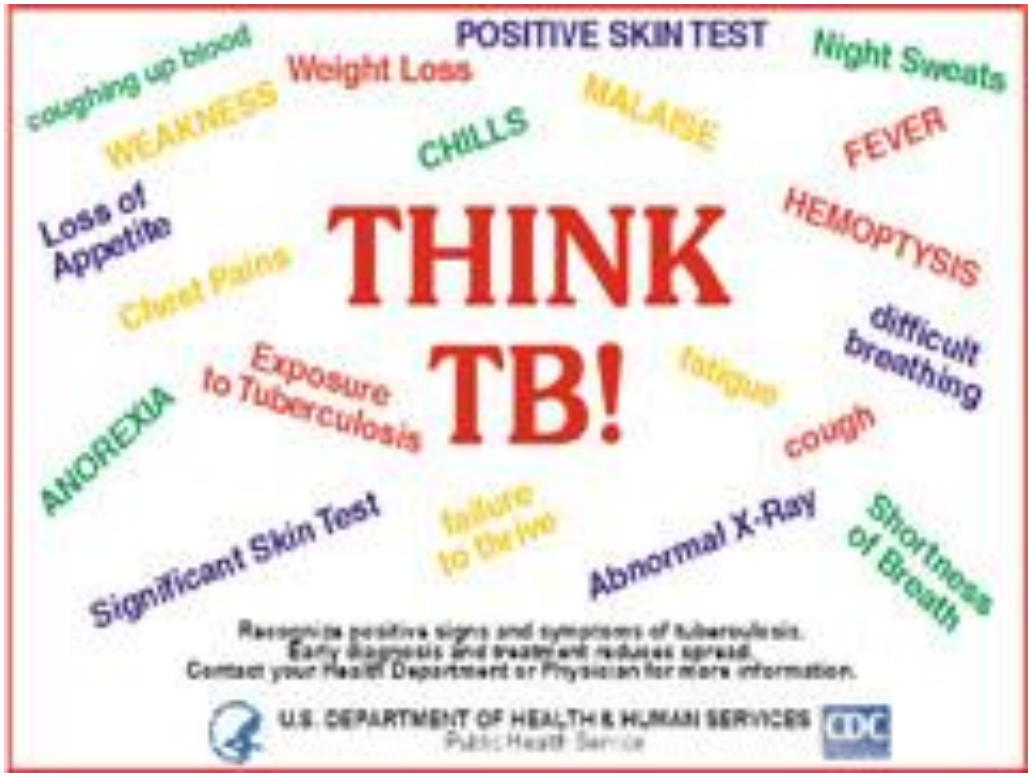
- RESULT : **INCONSISTENT**

PROGRESSION TO TB DISEASE

- TST AND IGRAs ARE LIKELY TO BE POSITIVE IN ALL STAGES OF TB SPECTRUM
- **TST AND IGRAs ARE GENERALLY UNABLE TO SELECT OUT THE PHENOTYPES THAT ARE MOST LIKELY TO BENEFIT FROM TB TREATMENT**
- LOW RATE OF PROGRESSION TO DISEASE EVEN IN IGRA AND TST POSITIVE

Physicians Caring for At Risk Populations

THANK YOU



- Always include TB in the DDx
- “THINK TB” and “TB RISK”