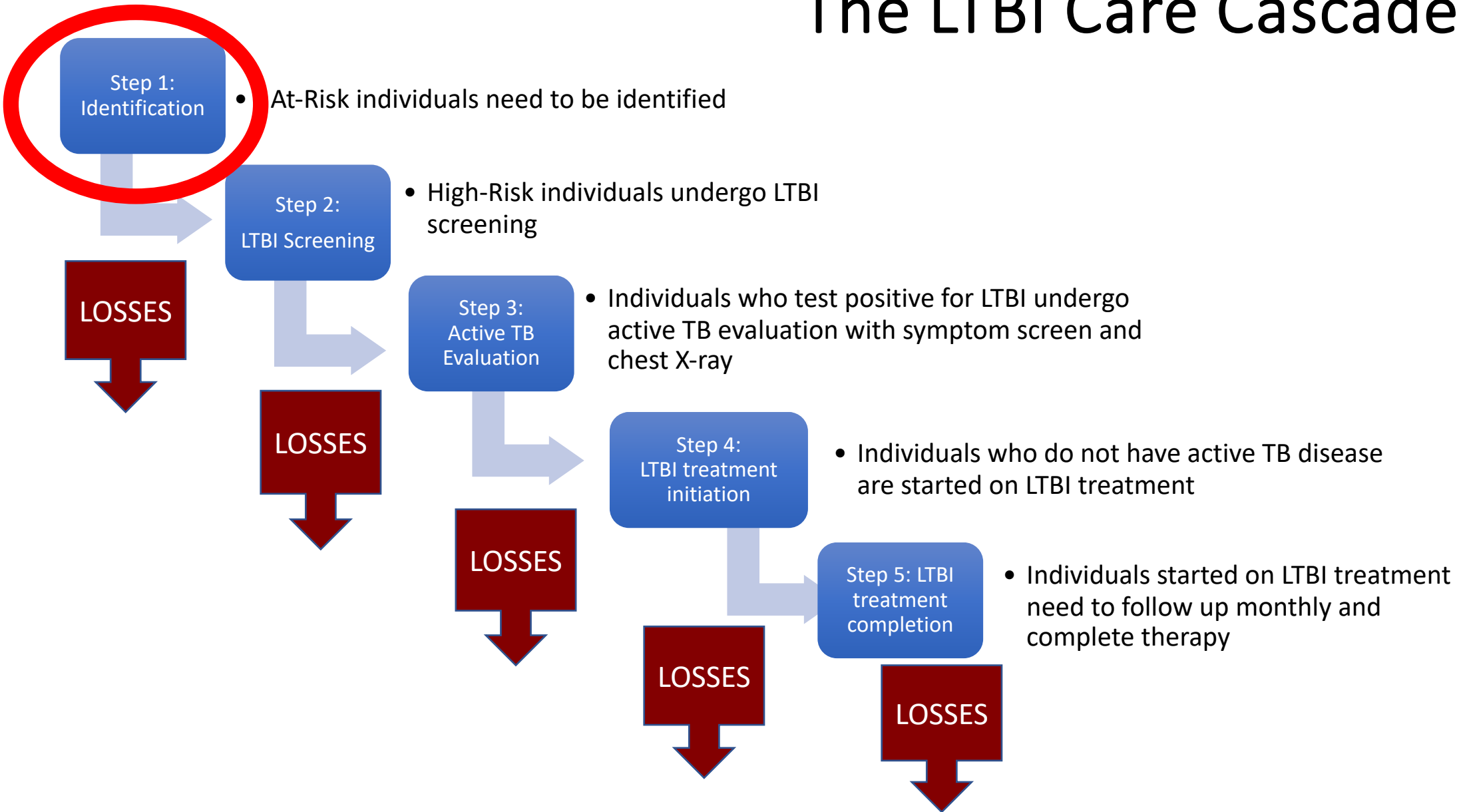
Common PCP questions along the LTBI care cascade

Daria Szkwarko, DO, MPH & Rebecca Thal, NP-C, AAHIVS

Learning Objectives

- Describe the components of the LTBI care cascade
- Consider the most common LTBI questions in primary care that come up throughout the cascade and how to address them
- Identify an individual who can help answer other LTBI questions quickly so that care can continue in primary care

The LTBI Care Cascade



Check appropriate risk factor boxes below.

Latent TB infection testing is recommended if any of the 3 boxes below is checked.

If latent TB infection test result is positive and active TB disease is ruled out, treatment of latent TB infection is recommended.

REPORT Latent TB Infection and Active or Suspected Active TB Disease

Go to www.mass.gov/tuberculosis for reporting forms

☐ **Born or lived in** a country with an elevated TB rate

- Includes any country other than the United States, Canada, Australia, New Zealand, or a country in western or northern Europe.
- If resources require prioritization within this group, prioritize patients with at least one medical risk for progression (see User Guide for list).
- Interferon Gamma Release Assay (IGRA) is preferred over Tuberculin Skin Test (TST) for foreign-born persons ≥2 years old. The TST is an acceptable test for all ages when administered and read correctly.

☐ **Immunosuppression**, current or planned

HIV infection, organ transplant recipient; treated with TNF-alpha antagonist (e.g., infliximab, etanercept, others), steroids (equivalent of prednisone ≥15 mg/day for ≥1 month) or other immunosuppressive medication

☐ **Close contact** to someone sick with infectious TB disease *since last TB Risk Assessment*

Just remember…Screen if patient is from a country other than…

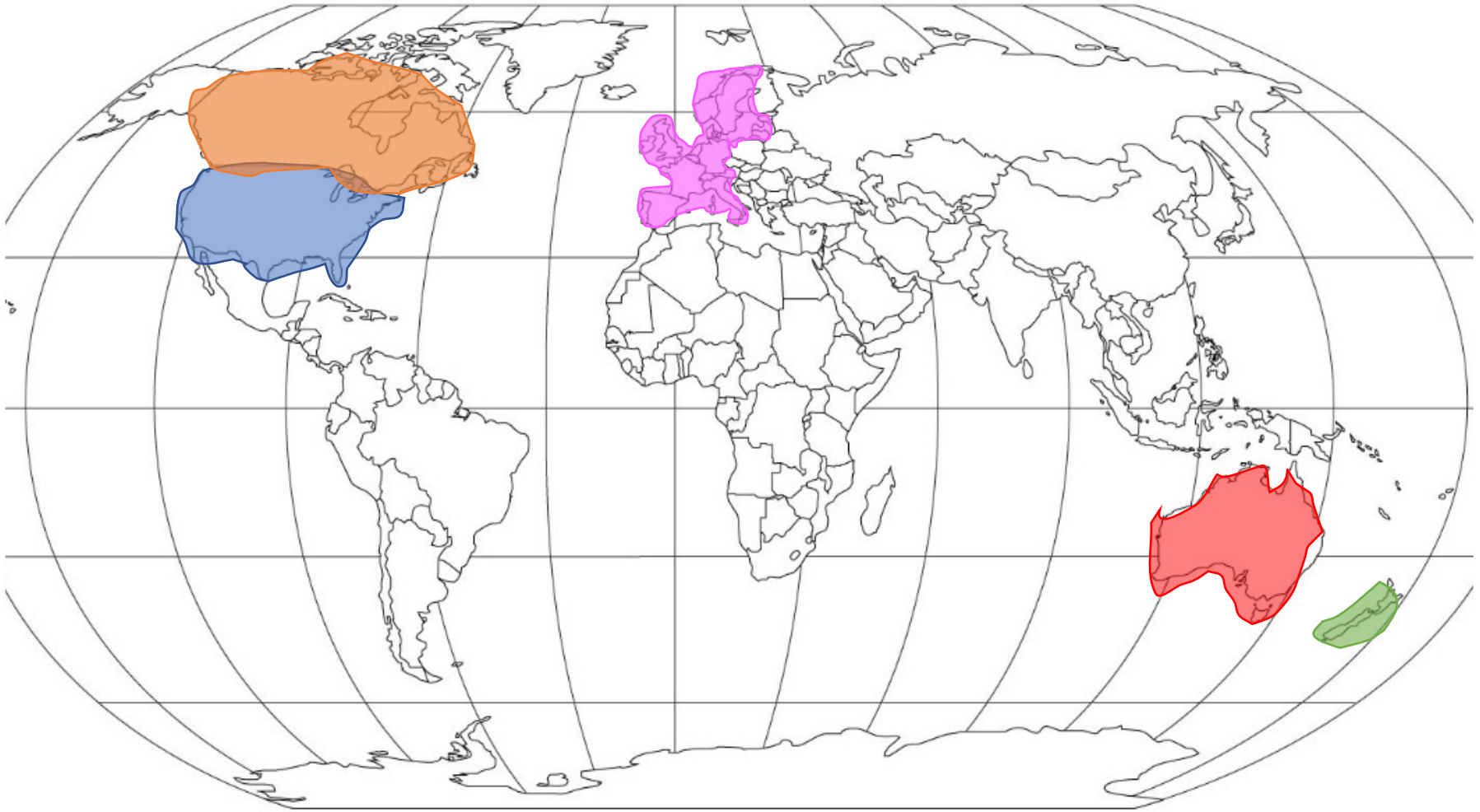
US

Canada

Australia

New Zealand

Western and Northern Europe



But what about….

- A patient who immigrated from Puerto Rico 30 years ago?
- A six month old refugee who moved to the US from Afghanistan with family 2 months ago
- A medical student who worked in a rural hospital in Kenya for a year
- A 50 year old who visits family each year in Liberia for two months

A Decision to Test is a Decision to Think….

- What is the risk of exposure to TB infection?
  - Consider risks such as family members who have had TB, where was the patient living while in a TB endemic region etc.
- What is the risk of TB disease progression?
  - Consider factors that increase risk of progression to TB disease such as immunocompromised state, age. Don’t forget the risk to others if patient progresses to TB disease (i.e medical student)
- What is the post-test probability – in other words, if the test is positive in your patient, how likely is it that they have TB infection?
  - Consider factors that may impact the specificity or sensitivity of your tests (BCG vaccination, immunosuppression)

Context matters for all scenarios below….

- A patient who immigrated from Puerto Rico 30 years ago?
- A six month old refugee who moved to the US from Afghanistan with family 2 months ago
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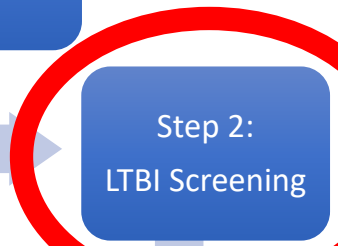
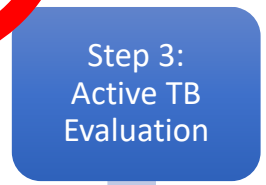
The LTBI Care Cascade

- At-Risk individuals need to be identified



- High-Risk individuals undergo LTBI screening



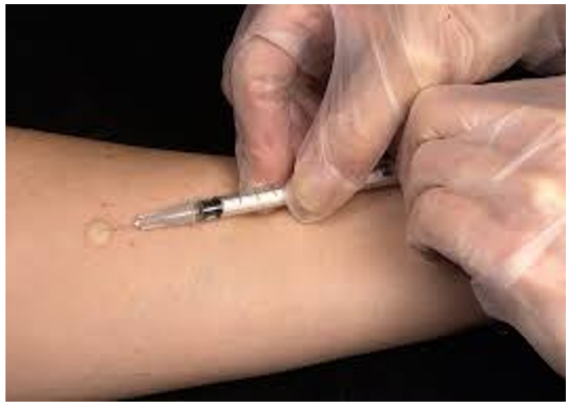
- Individuals who test positive for LTBI undergo active TB evaluation with symptom screen and chest X-ray

- Individuals who do not have active TB disease are started on LTBI treatment

- Individuals started on LTBI treatment need to follow up monthly and complete therapy

TST vs. IGRA Background

- Tuberculin Skin Test
  - Intradermal placement of purified protein derivative
  - Interpretation 48-72 hrs later
  - Reaction is measured in millimeters and interpretation varies depending on individual
  - Specificity 60-90%



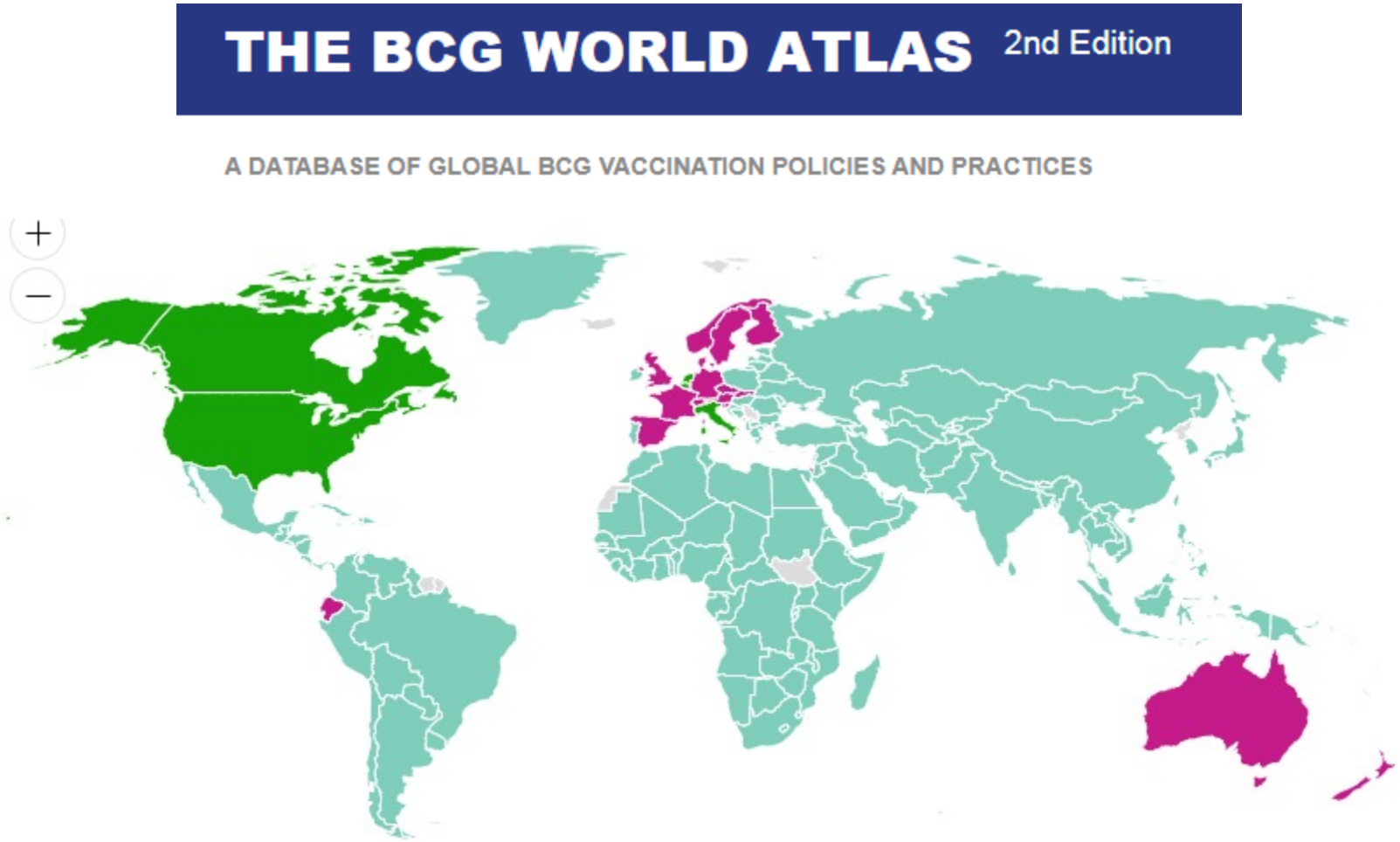
- Interferon-Gamma Release Assays
  - Two types: QuantiFERON-TB Gold In-Tube (Qiagen) and T-SPOT (Oxford Immunotec Global)
  - Single venous blood sample and lab processing within 8-30hrs after collection
  - Specificity > 95%

****USPSTF recommends IGRA as initial test for those who have had BCG vaccine or cannot return for TST!**

TB Infection Testing Interpretation

- Neither PPD or IGRAs differentiates between latent TB infection and active TB disease
- Neither is used to follow response to treatment
- After TB infection both may remain + for life

What about BCG? … https://www.bcgatlas.org



But what about…

- A low risk patient who was screened for work and has a positive TST?
- An 8 month old from Afghanistan with a 15mm TST?
- A patient who will start a biologic medication and has had two indeterminate IGRAs?

Consider an alternate test?

- A decision to test is a decision to think!
  - Will it change your management? (e.g. perhaps the low risk patient works in a NICU, if the IGRA is positive in an 8 month old you may go ahead and treat, if the TST is negative in the person starting a biologic you may not treat)
- Context matters – again risk of exposure, risk of progression, risk of disease transmission to others

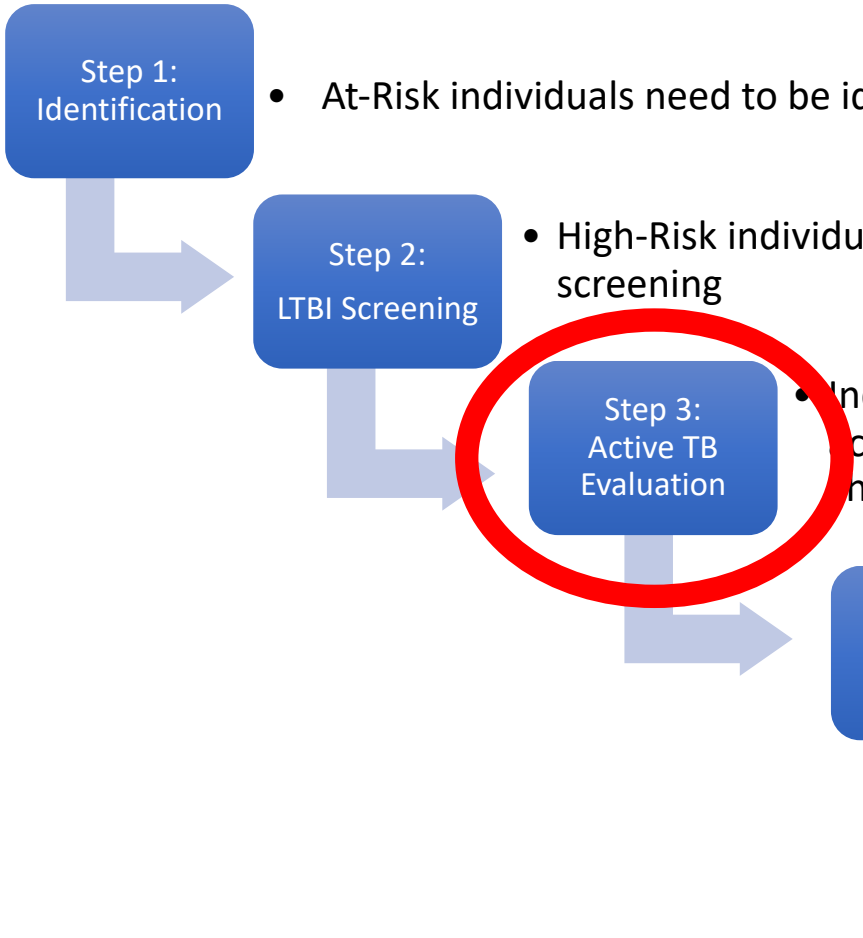
TB infection testing interpretation: Context matters!

- + PPD, - IGRA test
  - 8 yr old healthy girl from Brazil, PPD 10mm, IGRA neg
  - 60 yr old female from Brazil, uncontrolled DM and CKD, PPD 10mm, IGRA neg
  - 60 yr female from Brazil, PPD 0mm 2 yrs ago, now a contact of an active smear + case, current PPD 10mm, IGRA neg
  - 40 yr healthy male from Russia, PPD 10mm, IGRA neg, works in a neonatal ICU

Reporting LTBI

- LTBI is a reportable disease and testing provider is responsible for reporting to MA DPH
- Forms available for download at https://www.mass.gov/how-to/report-a-case-of-tuberculosis-disease-or-latent-tb-infection
- Contact DPH 617-983-6970 during business hours with questions
  - 617-983-6800 for urgent after-hours answering service

The LTBI Care Cascade



- At-Risk individuals need to be identified
- High-Risk individuals undergo LTBI screening
- Individuals who test positive for LTBI undergo active TB evaluation with symptom screen and chest X-ray
- Individuals who do not have active TB disease are started on LTBI treatment
- Individuals started on LTBI treatment need to follow up monthly and complete therapy

Evaluation Recap

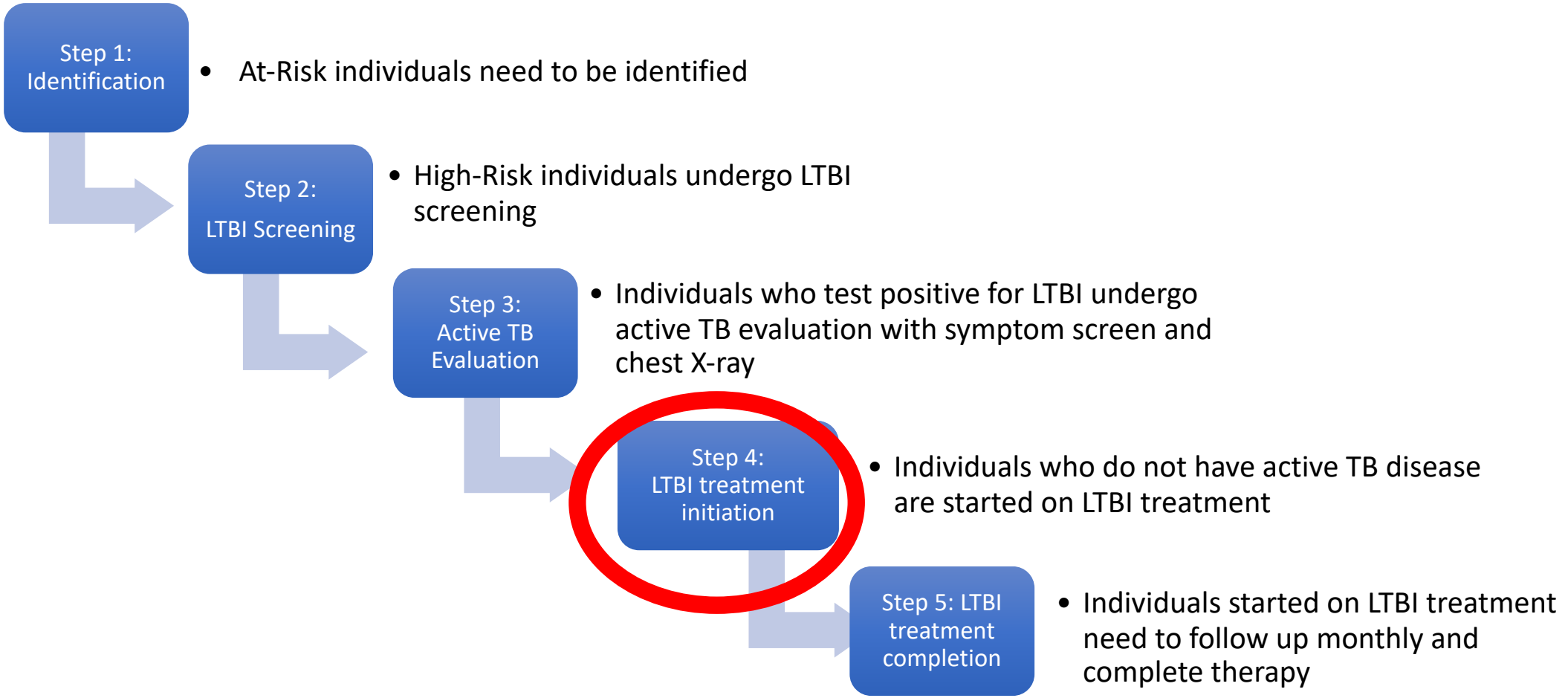
- History and physical examination are key
  - Don’t forget to ask questions and perform physical exam to look for extrapulmonary disease!

- X-ray recap
  - In adults, one single PA view is sufficient
  - In children, two views needed!
  - Need chest x-ray within 2 months of starting treatment

But what about….

- An abnormal X-ray with evidence of ? Old TB disease or hilar lymphadenopathy
  - Remember, our specialists are always there for us. An abnormal X-ray warrants a discussion with a specialist!
- A 6 month old X-ray
  - Repeat it!
- History and PE suggestive of an abnormality that may or may not be TB (e.g. persistent unilateral adenopathy, fatigue, chronic cough without other symptoms)
  - TB infection treatment is not an emergency! As PCPs we are experts in working up non-specific complaints. Take the time to feel good about finding another diagnosis prior to initiating LTBI treatment

The LTBI Care Cascade



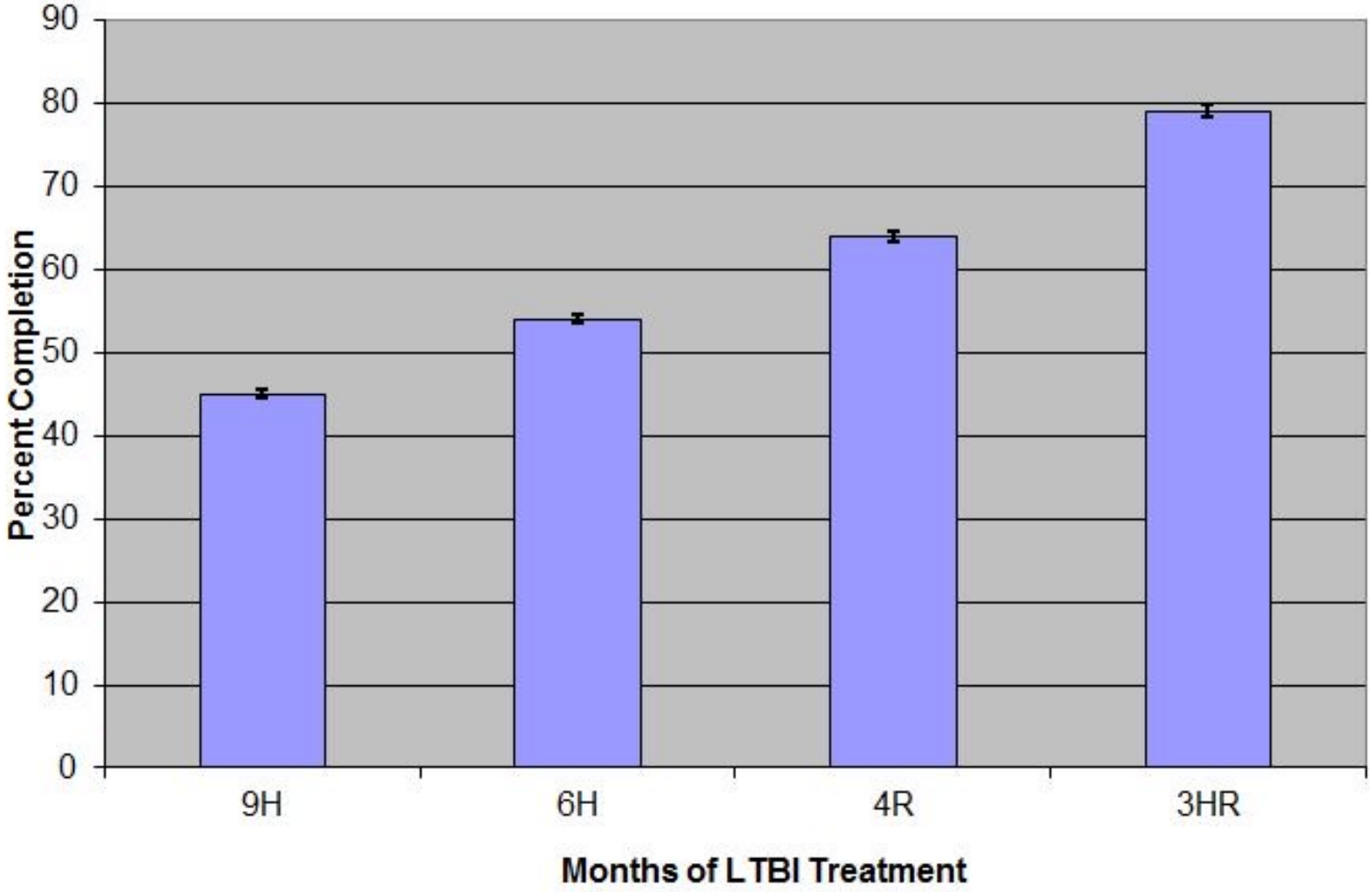
Initiate treatment at the “right” time

- Treatment of LTBI is NOT an emergency (except in very advanced HIV and in the very young, exposed or infected, non BCG-vaccinated children)
- Emphasis must be on shared decision making
- Patient centered care includes a discussion with the patient about life circumstances and willingness to be treated
  - Example:
    - Patient found to have LTBI but she was 6 months away form completing her hormonal therapy for breast cancer
    - Patient found to have LTBI but in the midst of a work up for a colon mass that is going to require surgical resection
    - Patient with LTBI who had a miscarriage at 12 weeks and is in the midst of grieving her pregnancy loss
    - In all of these patients, we together decided to delay treatment. In Patient #1, she returned and completed 4 months of R. In Patient #2, he has recovered from his surgery and started R 4 weeks post op. In patient #3, she returned 2 months later ready to engage in treatment.

Treatment Regimens for LTBI

Drugs, dose	Dosing frequency	Duration
Rifampin 600 mg (4R)	**Daily**	**4 months**
Isoniazid 300 mg (6-9H)	**Daily**	**6-9 months **9 months preferred**
Isoniazid 900 mg + Rifapentine 900 mg (3HP)	**Once weekly**	**3 months**

Completion of LTBI Treatment by Regimen



Chest 2010;137:401

Treatment overview: rifampin

- **4 months, 120 doses (must take within 6mo).** Well tolerated, convenient.
- **Recommended use:** Adults and children without clinically significant medication interactions who are able to take a daily medication. Used in pregnancy only if INH cannot be used. Approved in breastfeeding.
- **Adverse effects:** **Orange-red discoloration of body fluids** (urine, sweat, tears) is normal and benign. Other potential side effects include rash, hepatitis, fever, thrombocytopenia, flu-like symptoms.
- **Drug interactions:** Many, via CYP3A4 induction pathway. Decreases levels of many drugs including methadone, ART, hormonal contraceptives, coumadin, glucocorticoids, oral hypoglycemic agents, anticonvulsants. Use a medication interaction checker prior to prescribing.

Treatment overview: isoniazid

- **9 months, 270 doses (must take within 1y).** Fewest drug interactions, but longest regimen.
- **Recommended use:** Adults and children unable to take rifamycin-based regimens. Preferred regimen in pregnancy. Approved in breastfeeding.
- **Adverse effects:** Rash, hepatotoxicity, peripheral neuropathy, mild central nervous system effects.
  - Coadminister with pyridoxine (vitamin B6) 25-50mg/day if at elevated risk of peripheral neuropathy (diabetes, HIV, renal failure, alcoholism, or in pregnant or breastfeeding women).
- **Drug interactions:** Few. May increase levels of phenytoin, disulfiram.

Treatment overview: 3HP

- **12 weeks, 12 doses.** Shortest regimen! Must commit to weekly DOT.
- **Recommended use:** In adults and children >2yo who do not have clinically significant drug interactions with rifamycins, who desire the shortest possible regimen, and who are able to adhere to weekly directly observed therapy (DOT). Not recommended in pregnancy (has not been studied). Approved in breastfeeding.
- **Adverse effects:** See INH and RIF. 3HP is associated with a flu-like reaction seen in ~4% of patients, most commonly seen after the third or fourth dose of treatment. This should prompt discontinuation of 3HP, but patients can likely tolerate daily RIF.
- **Drug interactions:** Many (RPT has same CYP induction mechanism as other rifamycins). Use an interaction checker prior to prescribing.

Rifamycin Drug-Drug Interactions

A Guide for Primary Care Providers Treating Latent Tuberculosis Infection

Concomitant Drug or Drug Class	Rifamycin	Interaction	Recommendations and Clinical Comments	More information	References and Pubmed ID
Bupropion	Rifampin	↓ bupropion concentration or efficacy expected	**Co-administer with extreme caution if benefits outweigh risks.** Input from a clinical pharmacist or subspecialist recommended. Bupropion dose may need to be increased but maximum dose should not be exceeded due to risk of seizures.	The AUC of bupropion was decreased by 67.2% with steady state rifampin (600 mg daily) while the AUC of the active metabolite hydroxybupropion was decreased by 42.9%. Half-life of the parent drug and metabolite both decreased 2-fold. Cmax of bupropion decreased by 62.3% while hydroxybupropion increased by 38.7%.	Package insert 16815319 20876786
	Rifapentine (once weekly dosing)	No interaction expected	**Co-administer without modifications**, no clinically significant interaction likely.	No drug-specific data available; no expected interaction based on metabolic pathway and lack of CYP2B6 activity with rifapentine.	
	Rifabutin	No interaction expected	**Co-administer without modifications**, no clinically significant interaction likely.	No drug-specific data available; no expected interaction based on metabolic pathway and lack of CYP2B6 activity with rifabutin.	

https://www.currytbcenter.ucsf.edu/sites/default/files/2022-12/Rifamycin_2022.pdf

But what about…

- Those nitrosamines!

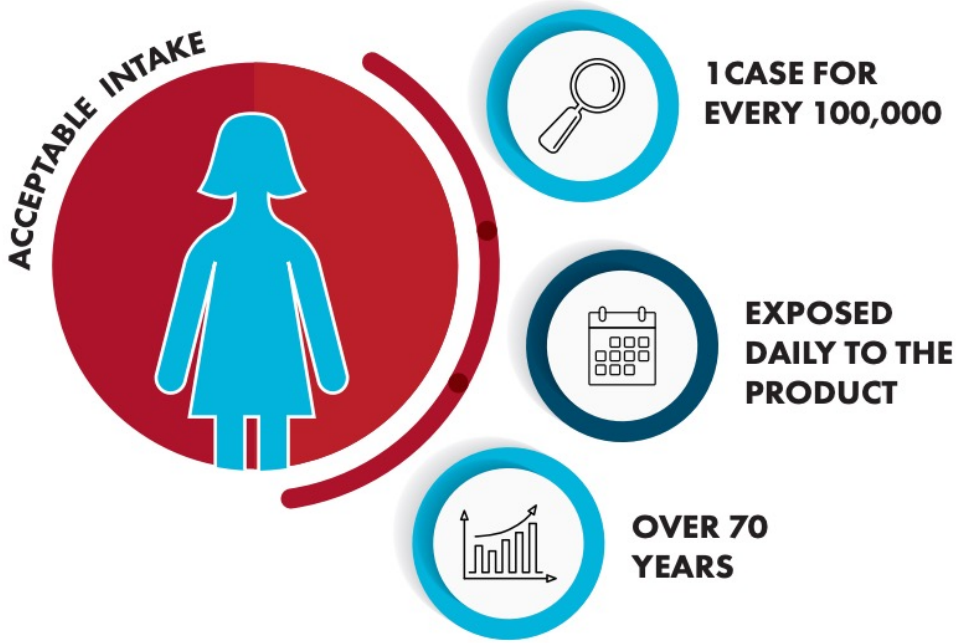
- those kids who just won’t swallow the medication??

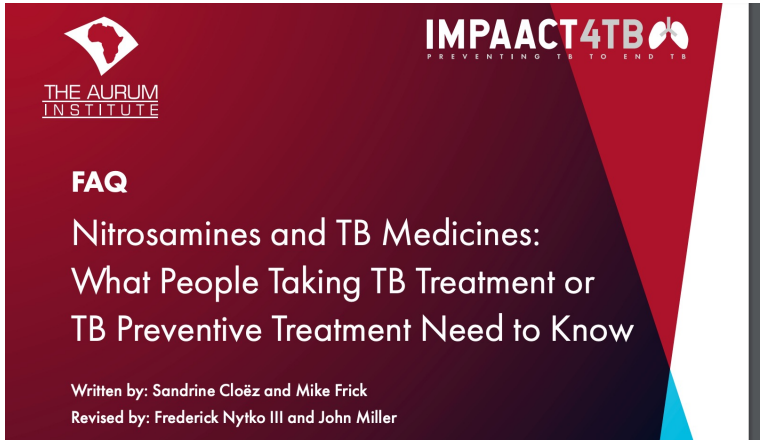
N-nitrosamines, Cancer Risk and TB Medications

- Everyone is exposed to N-nitrosamines in every day life
  - Drinking water, foods (grilled or cured meats, dairy products, and veggies), tobacco exposure and some latex and rubber products
  - There are multiple N-n with varying mutagenic potential
  - In 2018, health authorities starting looking at medications for N-n contamination
    - API, drug synthesis products, cross contamination, recovery processes for solvents or drug degradation
- Acceptable Intake (AI) = daily exposure approximates a cancer risk of 1:100,000 after 70 years of exposure; regulatory bodies have set minimum daily intake limits to remain under this break point
- Present levels of N-n in 4R would be between 1 and 12 months of exposure
- Pharmaceutical companies are working to continue to reduce N-n in all Rifampin compounds and must monitor all batches for specific contamination levels

Nitrosamines and Rifamycins: Some Considerations

- **Treatment of latent TB infection:**
  - **Adults and children:** Mention the risk. Do not discourage individuals from starting a rifamycin based regimen.
  - **Pregnant individuals and breastfeeding individuals:** Mention the risk and consider treating with isoniazid



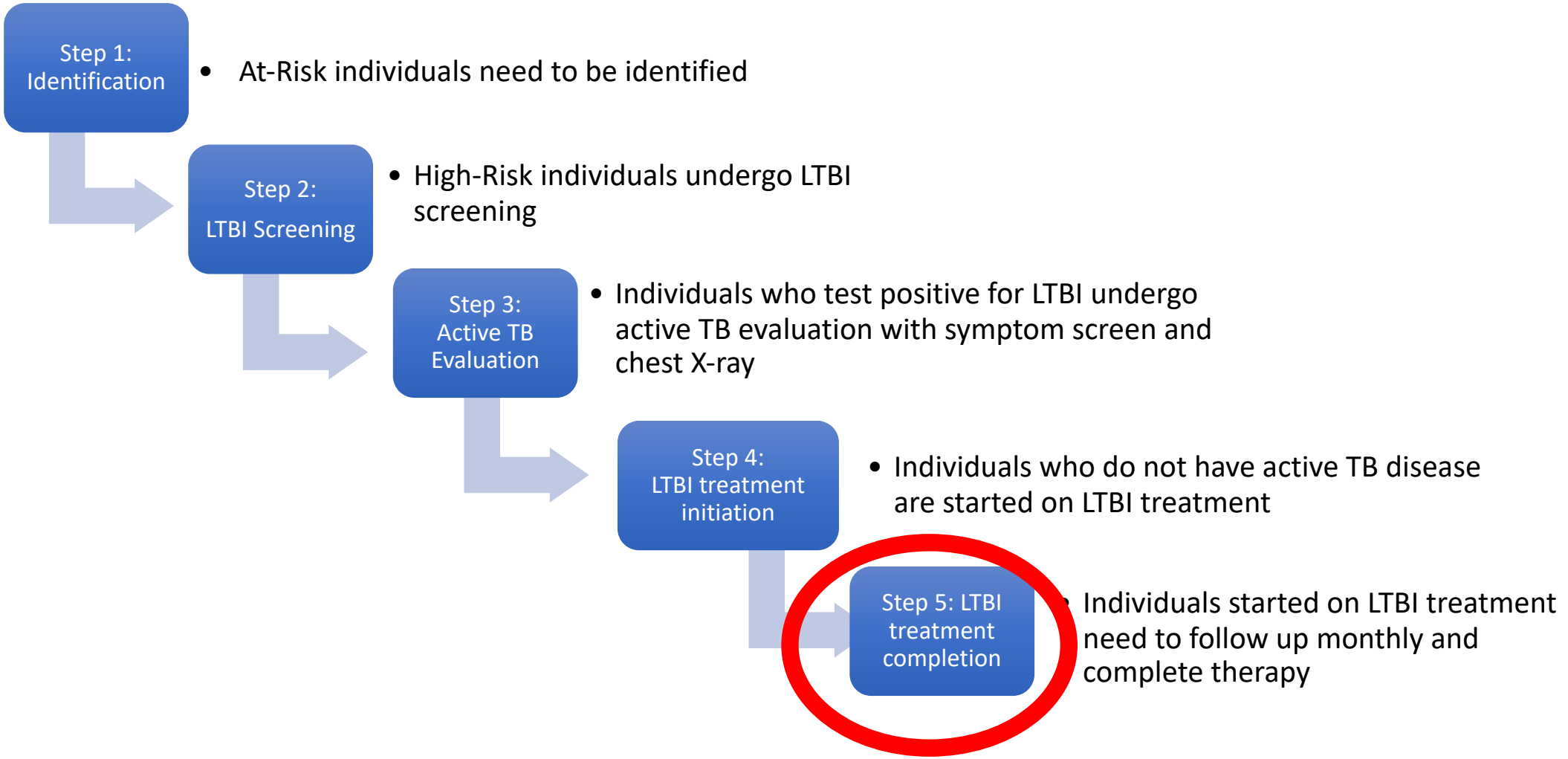


https://www.treatmentactiongroup.org/wp-content/uploads/2023/04/04_23_nitrosamine_FAQs_final.pdf

Medication administration

- RIF capsules can be broken and powder sprinkled and mixed with foods
- RIF syrup (preferred) or INH syrup for exclusively breastfed infants
- Crushed pills can be mixed with food (don’t let the kid see)
  - Pudding
  - Chocolate syrup
  - Nutella
  - Applesauce
  - Yogurt
  - Double-Stuffed Oreo

The LTBI Care Cascade



Monitoring of patients on treatment for LTBI

- **Baseline laboratory testing *not needed* except for:**
  - HIV infection
  - Pregnancy
  - History of liver disease/heavy alcohol use
  - Patient on chemotherapy

- **Evaluate monthly for:**
  - Adherence
  - Signs/symptoms of adverse reactions
  - Laboratory studies in persons at-risk (LFT, CBC)
    - If following LFTs: stop treatment if LFTs >3 times upper limit + symptoms OR if LFTs >5 times upper limit + no symptoms

But what about….

- My patient had baseline LFTs done by another provider and I felt obligated to continue checking monthly. Now they are elevated 3 times at month 3! When do I repeat?
  - If asymptomatic, could repeat in 2 weeks to see if stable. Likely would repeat one additional time and then ensure that patient knows to stop medication if any symptoms develop
  - If LFTs are continuing to increase, can call specialist for further guidance

Stop - Start Rules
(How much LFT abnormality can I tolerate?)

- Remember the risk of hepatotoxicity increases with age and with dosing above the recommended weight based guidelines
- The “Stop and Start” rules for monitoring for hepatotoxicity were all developed around both **AST(SGOT) and symptom screens**
- Approximately 1/3 of patients in the first two months of treatment with INH will have mild elevations in their transaminases so intensive blood screening will find this. Not clear how much this happens with Rifampin
- Any elevation in association with symptoms of hepatoxicity should cause the LTBI medications to be stopped (nausea, vomiting, abdominal pain)
- Treatment is halted for > 5x baseline even if asymptomatic
- When transaminases are elevated, a query regarding other hepatotoxins is indicated (Tylenol, ETOH, other viral infections - Hep A?)
- CDC and Massachusetts DPH recommend no blood monitoring but rather symptom screening unless the patient has concomitant risk for hepatotoxicity