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# Impact of interferon-gamma release assay for the diagnosis of pediatric tuberculosis infection

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# Rationale

- Interferon-gamma release assays (IGRAs) are intended for the diagnosis of latent TB and designed as replacements for the tuberculin skin test (TST)
  - Two commercial IGRAS are available: QuantiFERON-TB Gold In-Tube (Cellestis, Australia) and T-SPOT.*TB* (Oxford Immunotec, UK)
  - Since June 2009, the Montreal Children's Hospital (MCH) has implemented the QFT as a follow-up test to the TST, based largely on the Canadian IGRA guidelines
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# Canadian IGRA guidelines for children

- **Active TB**: the IGRA can be used in combination with the TST, in addition to microbiological tests, chest radiography and clinical history
  - **Immunocompromised children**: The IGRA can be used in children in whom there is concern about the possibility of a false-negative TST
  - **TST-positive children**: the IGRA can be used to confirm the TST result in children with low risk of LTBI and progression to active disease, including contacts
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The Montreal Children's Hospital

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## MEMORANDUM

In summary, the indications for pediatrics are as follow:

1. In support for the diagnosis of active tuberculosis in children (<18 years), in combination with other microbiological tests
2. Children in contact with a case of active infectious tuberculosis with a positive PPD
3. Immunocompromised children defined as:
  - a. Receiving Prednisone (2 mg/kg/day) for 14 days or more
  - b. Current chemotherapy or received in the past 3 months
  - c. Pre or post- bone marrow transplant
  - d. HIV positive children

In whom a clinician is still concerned about the possibility of LTBI even after a negative PPD

4. Patients with inflammatory diseases prior to starting anti-TNF medication
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Children who had TST results and who did not fall under the clinical indications were approached for a QFT under a study approved by the MCH Research Ethics Board



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# Objectives

- 1) To evaluate prospectively the performance of the QFT in children with TST results
  - 2) To determine the impact of QFT results on diagnostic and treatment decisions made by pediatric respirologists in routine clinical practice
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# Outcomes

- Concordance between TST and QFT in pre-defined subgroups
  - Proportion of changes in clinical decisions based on the QFT (e.g. LTBI → no LTBI) across these subgroups
  - Feasibility of blood draws in young children and rate of indeterminate QFT results
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# Subgroups

- Active TB suspects
  - TB contacts
  - Immunocompromised children
  - Pre-treatment patients
  - Targeted screenings: children from school-based or immigration screening programs
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# Clinical impact questionnaire

## 1) My Final Diagnosis (after work-up):

Latent TB infection (LTBI)       Active TB disease       No TB infection or disease

## 2) Did QFT test play any role in making the above DIAGNOSIS?

Yes       No       Not applicable, QFT was not requested or results were not available to me

## 3) If Yes to the above question, how was it useful?

### Latent TB

	TST	QFT	Decision
<input checked="" type="checkbox"/>	+	--	I used the negative QFT to rule out LTBI
<input type="checkbox"/>	--	+	I used the positive QFT to diagnose LTBI
<input type="checkbox"/>	+	+	I used both the positive TST and QFT to diagnose LTBI
<input type="checkbox"/>	?	+	I used the positive QFT to diagnose LTBI (regardless of TST result)
<input type="checkbox"/>			Other explanation:

### Active TB

	QFT	Decision
<input type="checkbox"/>	+	I used the positive QFT and other signs/features to diagnose active TB
<input type="checkbox"/>	--	I used the negative QFT to rule out active TB
<input type="checkbox"/>		Other explanation:

# Clinical impact questionnaire

4) If I had not ordered QFT, my diagnosis would have probably been:

Latent TB infection (LTBI)       Active TB disease       No TB infection or disease

5) My Final Treatment Decision (after work-up):

No prophylaxis for LTBI  
 LTBI prophylaxis: INH for 6 or 9 months or specify other regimen: \_\_\_\_\_  
 Active TB disease therapy

6) Did QFT test play any role in the above TREATMENT decision?

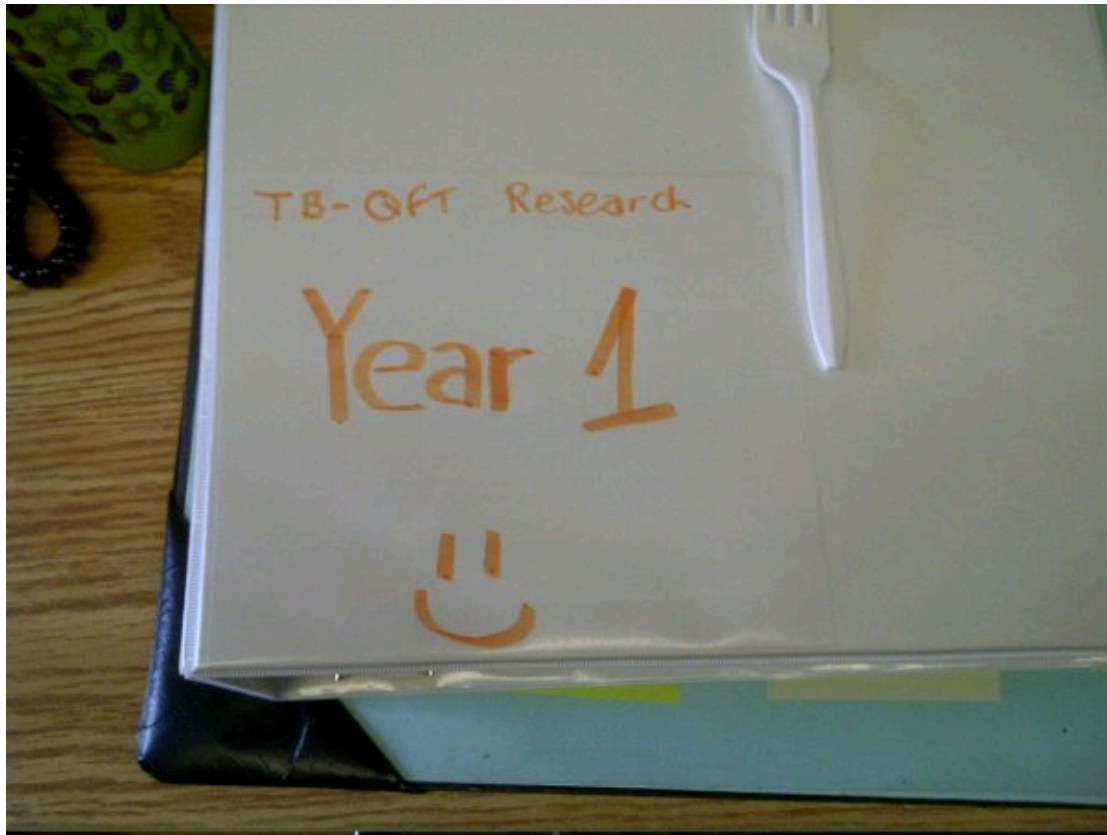
Yes       No       Not applicable, QFT was not requested or results were not available to me

7) If Yes to the above question, how was it useful?

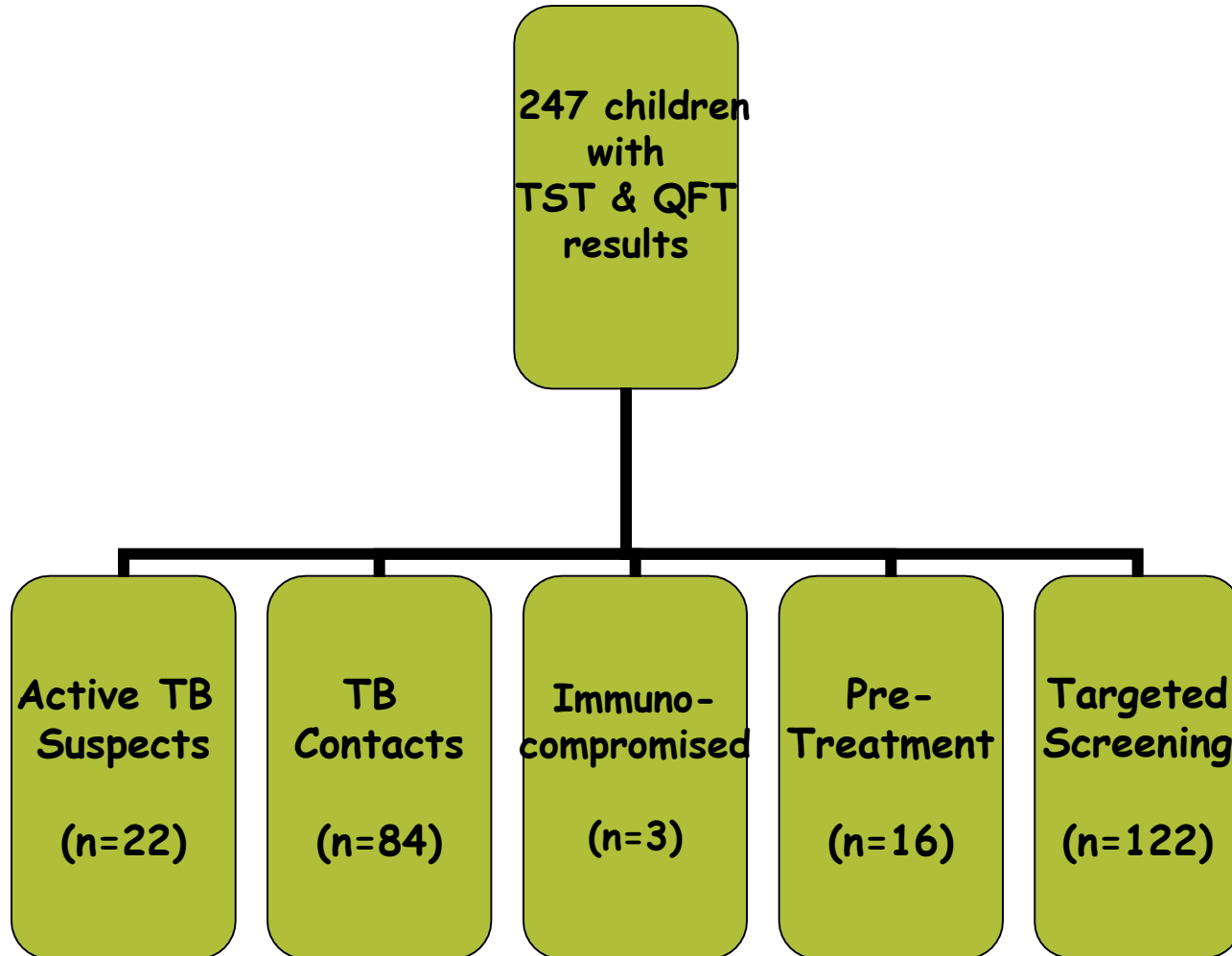
	TST	QFT	Decision
<input checked="" type="checkbox"/>	+	--	I used the negative QFT to withhold LTBI prophylaxis
<input type="checkbox"/>	--	+	I used the positive QFT to initiate LTBI prophylaxis
<input type="checkbox"/>	+	+	I used both the positive TST and QFT to initiate LTBI prophylaxis
<input type="checkbox"/>	?	+	I used the positive QFT to initiate LTBI prophylaxis (regardless of TST result)
<input type="checkbox"/>	Active TB	+	I used the positive QFT & other signs/features to initiate anti-TB therapy
<input type="checkbox"/>			Other explanation:

Signature \_\_\_\_\_ Date \_\_\_\_\_ Chart # \_\_\_\_\_

# Year 1 Results



# Subgroups



# Concordance

TB contacts (n=84)		
	TST +	TST -
QFT +	20	0
QFT -	25	37
QFT indeterminate	1	1

Concordance:  $57/84 = 68\%$

\* 4 contacts had conversion post-exposure on the TST, all were QFT-

# Screening

Targeted screenings (n=122)		
	TST +	TST -
QFT +	16	1
QFT -	96	8
QFT indeterminate	1	0

Concordance:  $24/122 = 20\%$

# The 2x2 Table

Total sample (n=247)		
	TST +	TST -
QFT +	42	1
QFT -	130	69
QFT indeterminate	2	3

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# The TST-/QFT+ case

- 2 sisters from Mexico had a TST done as part of the school-based screening
    - 1 is positive (16mm) and 1 is “negative” (7mm)
    - The TST+ child comes to the MCH for evaluation and gets a QFT automatically (positive); her sister comes along
  - Dad is a scientist and is happy to consent to a research QFT for the other daughter, which turns out to be positive
  - At the next visit, her 2<sup>nd</sup> TST is 20mm; her 2<sup>nd</sup> QFT is now negative
  - Both sisters start 9 months of INH together
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# Clinical changes

- TB contacts: In 24 TST+/QFT- contacts, the QFT was not used to change clinical decisions in all but 2 cases (92%). INH was prescribed regardless of the QFT result. The 2 cases were casual contact.
  - Targeted screening: In 96 TST+/QFT- children, the QFT changed the initial diagnosis from LTBI → no LTBI in 72 (75%) children. INH was withheld.
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# Other findings

- The rate of indeterminate results was 2%
  - The refusal rate among children who did not need a clinical QFT was ~25%
  - Unsuccessful blood draws occurred in ~5% of children, but creativity was involved!
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# Another question

When the TST and QFT results are concordant, it's said that this makes the physicians "feel better" ...

But how much better?

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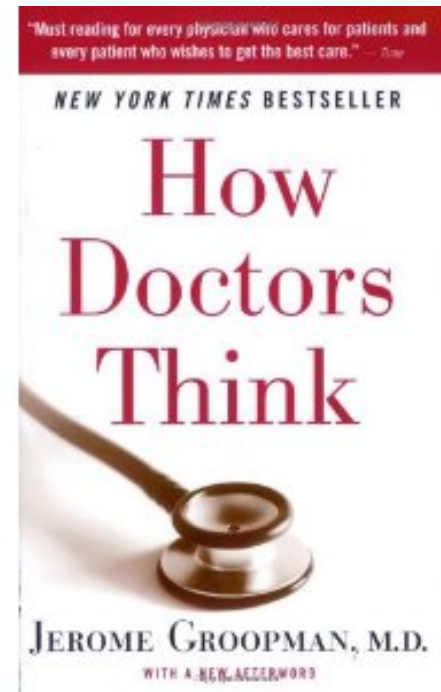
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# Surveys

- We created 10 hypothetical cases with TST results that are based on a representative study sample
  - We asked the physicians:
    - What is the probability that this patient has TB?
    - Would you treat this patient?
  - On the back of each page, we give them the QFT result and ask the same 2 questions
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# Overview

1. Active TB (TST+/QFT+)
2. Active TB (TST+/QFT-)
3. Contact (TST+/QFT+)
- 4. Contact (TST-/QFT-)**
5. Contact (TST+/QFT-)
6. HIV infected (TST-/QFT-)
7. Pre-treatment (TST-/QFT-)
8. <5 years (TST+/QFT-)
- 9. Screening (TST+/QFT+)**
10. Screening (TST+/QFT-)



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# Screening

11 year old female who was born in Haiti and arrived in Canada at age 9. She was BCG vaccinated 5 months after birth. She was referred from the multicultural clinic for a positive TST result of 13mm. She has no known history of contact. Her CXR is normal. She appears healthy and is asymptomatic.

- What is the probability that this patient has latent TB (0-100)?  
\_\_\_\_\_ %
  - Would you treat with 9 months of INH (y/n)? \_\_\_\_\_
-

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# Screening

11 year old female who was born in Haiti and arrived in Canada at age 9. She was BCG vaccinated 5 months after birth. She was referred from the multicultural clinic for a positive TST result of 13mm. She has no known history of contact. Her CXR is normal. She appears healthy and is asymptomatic.

- What is the probability that this patient has latent TB (0-100)?

80 %

- Would you treat with 9 months of INH (y/n)? **YES**
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# Screening

If the QFT result is **Positive**,

- What is the probability that this patient has latent TB (0-100)? \_\_\_\_\_ %
  - Would you treat with 9 months of INH (y/n)? \_\_\_\_\_
-



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# Screening

If the QFT result is **Positive**,

- What is the probability that this patient has latent TB (0-100)?      **100%**
  
  - Would you treat with 9 months of INH (y/n)?  
                  **YES**
-

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# Contact

8 year old male who was born in Canada. He has been in contact with his uncle, who is on full anti-TB meds and is smear-negative. The patient visits his uncle on the weekends. His pre and post-exposure (8 weeks later) TST results are both 0mm. He appears healthy and is asymptomatic.

- What is the probability that this patient has latent TB (0-100)?  
\_\_\_\_\_ %
  - Would you treat with 9 months of INH (y/n)? \_\_\_\_\_
-

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# Contact

8 year old male who was born in Canada. He has been in contact with his uncle, who is on full anti-TB meds and is smear-negative. The patient visits his uncle on the weekends. His pre and post-exposure (8 weeks later) TST results are both 0mm. He appears healthy and is asymptomatic.

- What is the probability that this patient has latent TB (0-100)?  
0 %
  - Would you treat with 9 months of INH (y/n)? NO
-

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# Contact

If the QFT result is **Negative**,

- What is the probability that this patient has latent TB (0-100)? \_\_\_\_\_ %
  - Would you treat with 9 months of INH (y/n)? \_\_\_\_\_
-

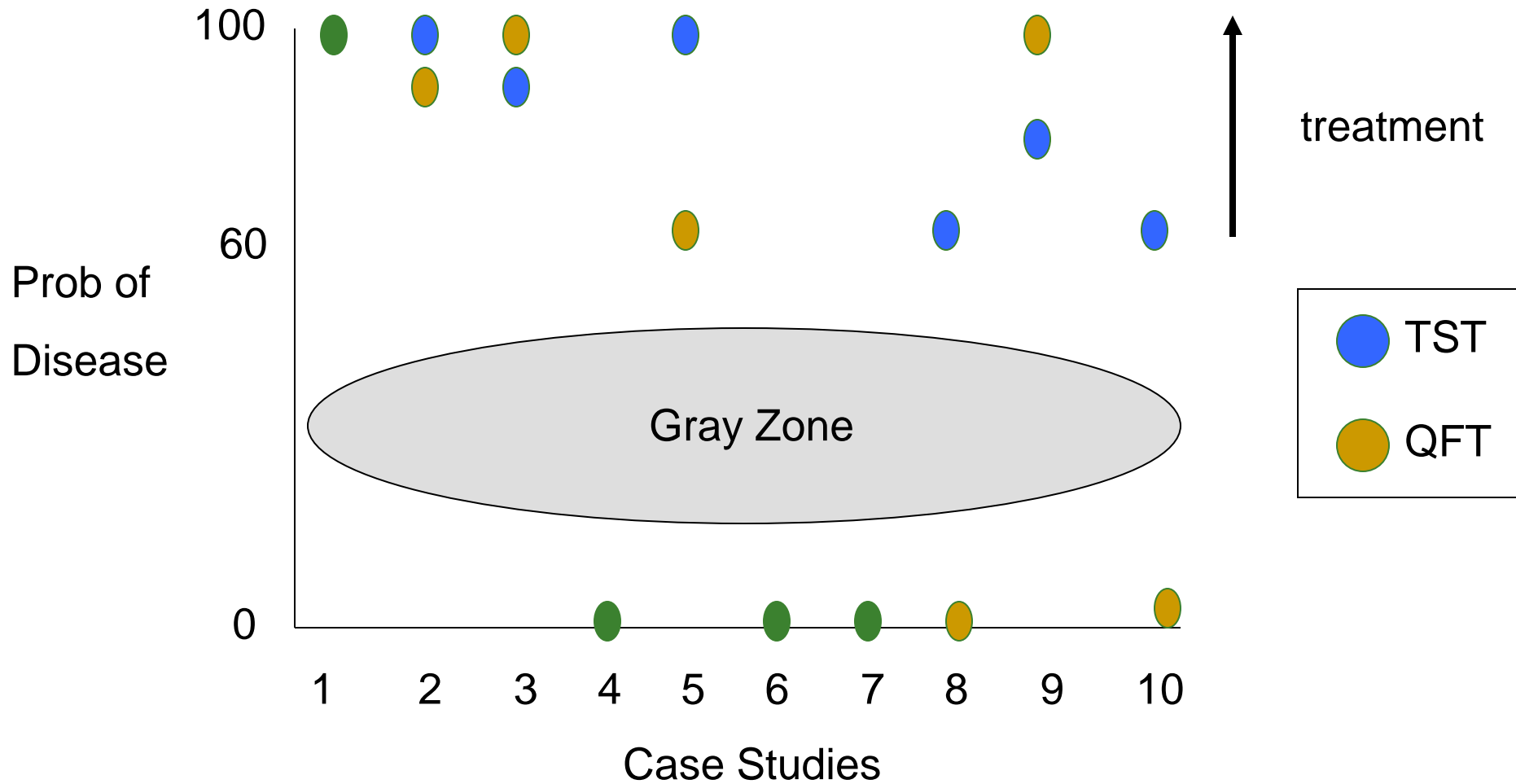
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# Contact

If the QFT result is **Negative**,

- What is the probability that this patient has latent TB (0-100)?     0%
  
  - Would you treat with 9 months of INH (y/n)?  
      NO
-

# Probabilities



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# Provider preferences

- Logistic regression analysis with outcome as clinical change=1, no change=0
  - Determine which factors are associated with a clinical change, including
    - Age <5 years
    - BCG vaccination
    - TST size
    - History of contact
  - Cluster by physician to account for provider preferences, which will give more conservative estimates
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# Pragmatic study

## Strength

- Gives a sense of when the QFT is actually useful and should be done (feedback loop to ultimately save resources)
- Goes beyond the test accuracy paradigm
- Takes a first step in developing meaningful thresholds / probabilities for TB, which would be useful for modeling designs

## Weakness

- Descriptive in nature, hard to quantify phenomena
  - Subject to biases
    - Selection bias
    - Verification bias
    - Time bias
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**Hawthorne Effect**

***Self-fulfilling prophecy***

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**Intention to test = Intention to treat**

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# Limitation

- Does the change in clinical decision necessarily lead to an improved outcome?
  - If a child does not receive INH due to a negative QFT and subsequently develops active TB, the clinical change actually led to a worse outcome
  - For children not prescribed INH, a nurse follows up with a phone call 1 year later to see if they have developed symptoms
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# Phone follow-up

- We have created risk assessment forms in English and French that ask about:
    - Travel to endemic countries
    - Contact with TB cases
    - Presence of symptoms
    - Reasons for doctor or ER visits in the past year
  - So far, 64 calls have been made
    - 38 (59%) reached
    - 18 (28%) no answer/machine
    - 8 (13%) moved
  - At least 1 year after final diagnosis, no parent has reported signs of progression to active TB for their children
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# A big THANKS

- Montreal Chest Institute
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*Bo Kaap, Cape Town*