

The background is a dark, textured grey with numerous realistic water droplets of various sizes scattered across it. The droplets have highlights and shadows, giving them a three-dimensional appearance. The text is centered in the middle of the frame.

DISCORDANT TST & IGRA RESULTS

PETER DAVIDSON

MI TB NURSING CERTIFICATION WORKSHOP

JUNE 28, 2016

CONTENT

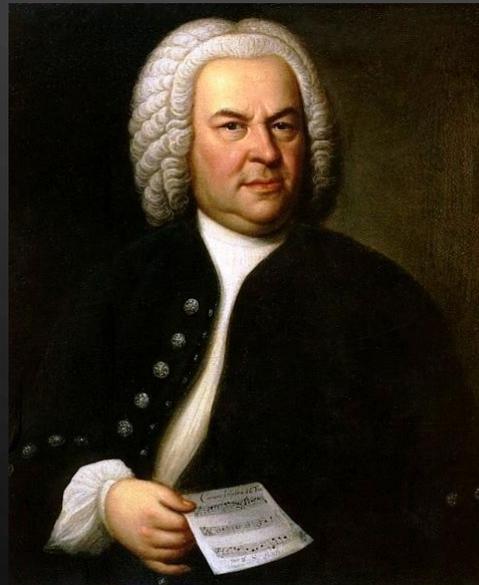
- DISCUSS SCENARIOS IN WHICH DISCORDANT TST AND IGRA RESULTS ARE LIKELY TO BE ENCOUNTERED
- DISCUSS COMMON PROBLEMS WHEN IGRA AND TST ARE USED IN THE SAME PERSON
- PROVIDE UPDATED GUIDANCE FOR INTERPRETING DISCORDANT TST AND IGRA RESULTS



AND WHAT TO DO NEXT!

A NOTE ON DISCORDANCE

- DISCORDANCE: (1) BEING AT VARIANCE; DISAGREEING; INCONGRUOUS.
(2) DISAGREEABLE TO THE EAR; DISSONANT; HARSH.
- WE WILL FOCUS ON #1 (MAY CAUSE #2 IN YOUR OFFICE)
- WHICH TEST IS DISCORDANT?
 - TST V IGRA
 - IGRA V IGRA
 - TST V TST



https://upload.wikimedia.org/wikipedia/commons/6/6a/Johann_Sebastian_Bach.jpg



http://www.celebrityrockstarguitars.com/rock/rhoads_files/randyrhoads_color.jpg

DISCORDANT RESULTS ARE LIKELY WHEN...

- PERSON(S) AT LOW RISK FOR TB INFECTION ARE TESTED FOR TB MORE THAN ONCE
- DIFFERENT TEST METHODS (TST/IGRA) ARE USED ON THE SAME PERSON (DELIBERATE OR ACCIDENTAL)
 - EXACERBATED IF PERSON IS AT LOW RISK FOR TB INFECTION
- OPERATOR ERROR
 - TECHNIQUE
 - SPECIMEN HANDLING OR PROCESSING
 - TUBE OR REAGENT STORAGE

VARIANCE THAT MAY CONTRIBUTE TO DISCORDANCE

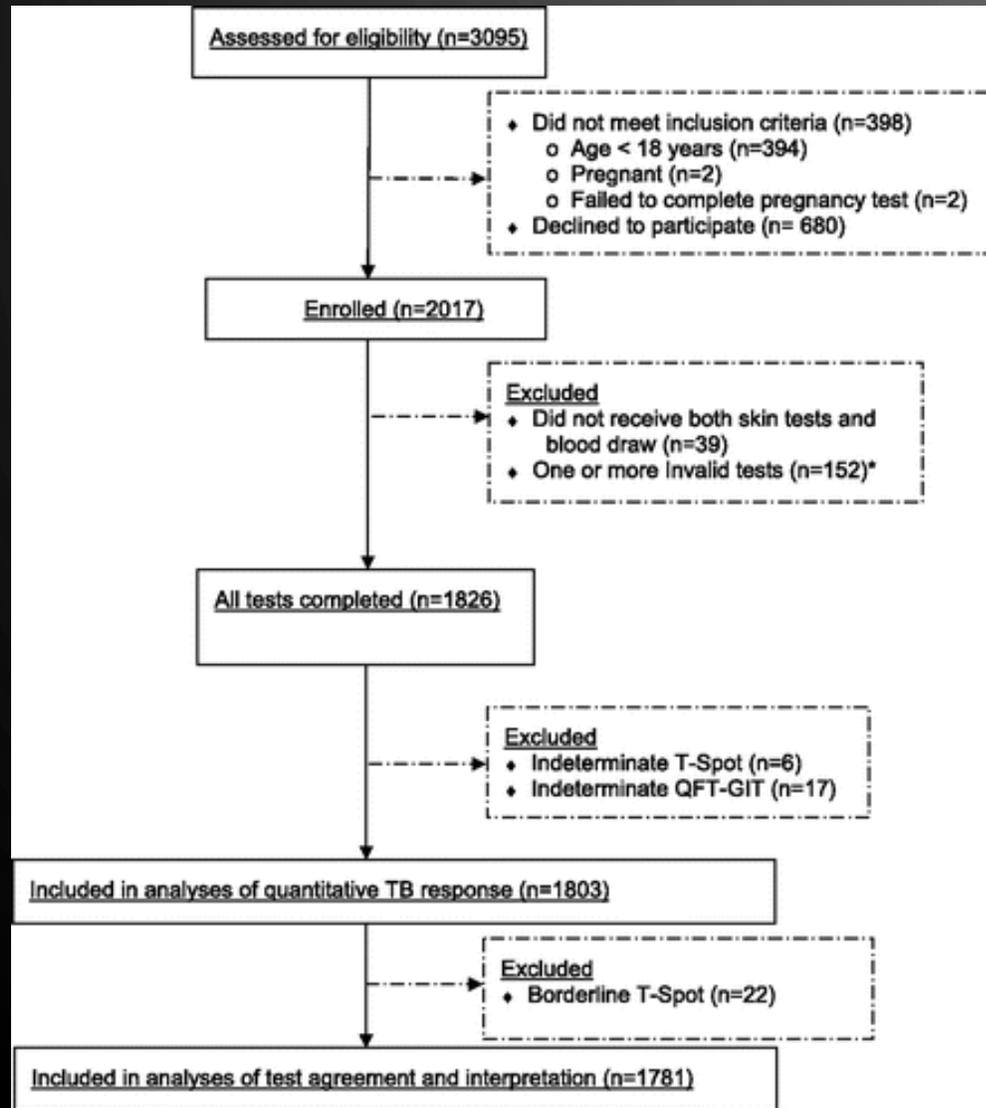
- PERSON

- TIME SINCE INFECTION IN THE ABSENCE OF FURTHER EXPOSURE TO *M. TUBERCULOSIS* ANTIGEN
- RECENT PREVIOUS TUBERCULIN SKIN TESTING (BOOSTING AN IGRA RESPONSE)
- IMMUNOSUPPRESSIVE MEDICATIONS (E.G. CORTICOSTEROIDS)
- IMMUNOSUPPRESSIVE DISEASES (E.G. HIV)
- RECENT LIVE VIRAL VACCINATION OR ILLNESS
- LYMPHOPENIA

- TEST

- MANUFACTURING ISSUES (IGRA CONTROL TUBES, ANTIGEN COATING)

MANCUSO (2012): TST VS QFT-G VS T.SPOT



- MILITARY RECRUITS, ENTRY MEDICAL SCREEN, APRIL – JUNE, 2009
- RISK FACTOR QUESTIONNAIRE PLUS:
 - TST
 - QFT-G
 - T.SPOT
- SPOILER (NECESSARY)
 - 21 HIGH-RISK
 - 409 MEDIUM-RISK
 - 1,373 LOW-RISK

MANCUSO (2012): TST VS QFT-G VS T.SPOT

| | TST Positive | TST Negative | Total |
|-----------------|--------------|-----------------|---------------|
| T.SPOT Positive | 15 (0.8%) | 19 (1.1%) | 34 (1.9%) |
| T.SPOT Negative | 33 (1.9%) | 1,714 (96.2%) † | 1,747 (98.1%) |
| Total | 48 (2.7%) | 1,733 (97.3%) | 1,781 |

LOW CONCORDANCE OF
POSITIVES

$$15/48 = 31.3\%$$

HIGH CONCORDANCE OF
NEGATIVES

$$1714/1733 = 98.9\%$$

† Includes 23 subjects with borderline TB response of five spots (11), six spots (11), or seven spots (one).

MANCUSO (2012): TST VS QFT-G VS T.SPOT

| | TST Positive | TST Negative | Total |
|----------------|--------------|---------------|-------------|
| QFT-G Positive | 11 (0.6%) | 25 (1.4%) | 36 (2%) |
| QFT-G Negative | 37 (2.1%) | 1,708 (95.9%) | 1,745 (98%) |
| Total | 48 (2.7%) | 1,733 (97.3%) | 1,781 |

LOW CONCORDANCE OF
POSITIVES

$$11/48 = 22.9\%$$



HIGH CONCORDANCE OF
NEGATIVES

$$1708/1733 = 98.6\%$$



MANCUSO (2012): TST VS QFT-G VS T.SPOT

| | QFT-G Positive | QFT-G Negative | Total |
|-----------------|----------------|----------------|---------------|
| T.SPOT Positive | 14 (0.8%) | 20 (1.1%) | 34 (1.9%) |
| T.SPOT Negative | 22 (1.2%) | 1,725 (96.9%) | 1,747 (98.1%) |
| Total | 36 (2%) | 1745 (98%) | 1,781 |

LOW CONCORDANCE OF
POSITIVES

$$14/36 = 38.9\%$$

* Although higher than
either v TST

HIGH CONCORDANCE OF
NEGATIVES

$$1725/1745 = 98.9\%$$

MANCUSO (2012): TST VS QFT-G VS T.SPOT

| | Quantitative TST Result | | | | Quantitative QFT-G Result | | | Quantitative T.SPOT Result | | |
|----------------|-------------------------|-----------------|-----------------|-----------------|---------------------------|-----------------|-----------------|----------------------------|-------------|-----------------|
| Risk Level | 0 – 4 mm | 5 – 9 mm | 10 – 14 mm | > 15 mm | < 0.35 | 0.35 – 0.99 | > 1 | < 4 spots | 5 – 7 spots | > 8 spots |
| High (5 mm) | 18 (85.7%) | 1 (4.8%) | 1 (4.8%) | 1 (4.8%) | 18 (85.7%) | 2 (9.5%) | 1 (4.8%) | 20 (95.2%) | 0 | 1 (4.8%) |
| Medium (10 mm) | 362 (88.5%) | 10 (2.4%) | 21 (5.1%) | 16 (3.9%) | 392 (95.8%) | 7 (1.7%) | 10 (2.4%) | 391 (95.6%) | 3 (0.7%) | 15 (3.7%) |
| Low (15 mm) | 1,332 (97%) | 21 (1.5%) | 10 (0.7%) | 10 (0.7%) | 1,356 (98.8%) | 13 (1%) | 4 (0.3%) | 1,336 (97.3%) | 19 (1.4%) | 18 (1.3%) |

1. Concordance is **highest** in **High-Risk** pts (3:3:1)

MANCUSO (2012): TST VS QFT-G VS T.SPOT

| Risk Level | Quantitative TST Result | | | | Quantitative QFT-G Result | | | Quantitative T.SPOT Result | | |
|----------------|-------------------------|-----------|------------|------------------|---------------------------|----------------|-----------------|----------------------------|-------------|------------------|
| | 0 – 4 mm | 5 – 9 mm | 10 – 14 mm | > 15 mm | < 0.35 | 0.35 – 0.99 | > 1 | < 4 spots | 5 – 7 spots | > 8 spots |
| High (5 mm) | 18 (85.7%) | 1 (4.8%) | 1 (4.8%) | 1 (4.8%) | 18 (85.7%) | 2 (9.5%) | 1 (4.8%) | 20 (95.2%) | 0 | 1 (4.8%) |
| Medium (10 mm) | 362 (88.5%) | 10 (2.4%) | 21 (5.1%) | 16 (3.9%) | 392 (95.8%) | 7 (1.7%) | 10 (2.4%) | 391 (95.6%) | 3 (0.7%) | 15 (3.7%) |
| Low (15 mm) | 1,332 (97%) | 21 (1.5%) | 10 (0.7%) | 10 (0.7%) | 1,356 (98.8%) | 13 (1%) | 4 (0.3%) | 1,336 (97.3%) | 19 (1.4%) | 18 (1.3%) |

2. Concordance is **weak** in **Low-Risk** pts (10:17:18)

* better between QFT & T.SPOT (17:18)

MANCUSO (2012): TST VS QFT-G VS T.SPOT

| Risk Level | Quantitative TST Result | | | | Quantitative QFT-G Result | | | Quantitative T.SPOT Result | | |
|----------------|-------------------------|-----------|------------------|------------------|---------------------------|-----------------|------------------|----------------------------|-------------|------------------|
| | 0 – 4 mm | 5 – 9 mm | 10 – 14 mm | > 15 mm | < 0.35 | 0.35 – 0.99 | > 1 | < 4 spots | 5 – 7 spots | > 8 spots |
| High (5 mm) | 18 (85.7%) | 1 (4.8%) | 1 (4.8%) | 1 (4.8%) | 18 (85.7%) | 2 (9.5%) | 1 (4.8%) | 20 (95.2%) | 0 | 1 (4.8%) |
| Medium (10 mm) | 362 (88.5%) | 10 (2.4%) | 21 (5.1%) | 16 (3.9%) | 392 (95.8%) | 7 (1.7%) | 10 (2.4%) | 391 (95.6%) | 3 (0.7%) | 15 (3.7%) |
| Low (15 mm) | 1,332 (97%) | 21 (1.5%) | 10 (0.7%) | 10 (0.7%) | 1,356 (98.8%) | 13 (1%) | 4 (0.3%) | 1,336 (97.3%) | 19 (1.4%) | 18 (1.3%) |

3. Concordance is **horrible** in **Medium-Risk** pts (37:17:15)

* better between QFT & T.SPOT (17:15)



MANCUSO (2012): OVERALL TEST AGREEMENT

| Test Results | High-Risk (5 mm) n=21 | Medium-Risk (10 mm) n=406 | Low-Risk (15 mm) n=1,354 |
|--------------------------|--------------------------|------------------------------|-----------------------------|
| All tests negative | 16 (1%) | 359 (21.2%) | 1,318 (77.9%) |
| One test positive | 4 (5.9%) | 33 (48.5%) | 31 (45.6%) |
| TST only | 2 (6.3%) | 23 (71.9%) | 7 (21.9%) |
| QFT-G only | 2 (9.5%) | 8 (38.1%) | 11 (52.4%) |
| T.SPOT only | 0 (0%) | 2 (13.3%) | 13 (86.7%) |
| Two tests positive | 0 (0%) | 7 (70%) | 3 (30%) |
| TST and QFT-G | 0 (0%) | 1 (100%) | 0 (0%) |
| TST and T.SPOT | 0 (0%) | 5 (100%) | 0 (0%) |
| QFT-G and T.SPOT | 0 (0%) | 1 (25%) | 3 (75%) |
| All three tests positive | 1 (10%) | 7 (70%) | 2 (20%) |

Interpreting in Rows

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| TST and T.SPOT | 0 (0%) | 5 (100%) | 0 (0%) |
| QFT-G and T.SPOT | 0 (0%) | 1 (25%) | 3 (75%) |
| All three tests positive | 1 (10%) | 7 (70%) | 2 (20%) |

1. Majority of 'all negatives' are in Low-Risk pts

* Expected

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| TST and T.SPOT | 0 (0%) | 5 (100%) | 0 (0%) |
| QFT-G and T.SPOT | 0 (0%) | 1 (25%) | 3 (75%) |
| All three tests positive | 1 (10%) | 7 (70%) | 2 (20%) |

2. 'One positives' are roughly even between Med- and Low-Risk; individual positives mostly in Low-Risk, except for TST

* Not Expected

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| QFT-G and T.SPOT | 0 (0%) | 1 (25%) | 3 (75%) |
| All three tests positive | 1 (10%) | 7 (70%) | 2 (20%) |

3. 'Two positives' most common in Medium-Risk, and most likely between TST and T.SPOT

* Expected? Why? Who knows?

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| All three tests positive | 1 (10%) | 7 (70%) | 2 (20%) |

4. 'All three positive' generally unlikely, and most often in Medium-Risk

* What the heck?

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5. No test, alone or in combination, was often positive among High-Risk

*ARRGHGH!!!

ARE WE
DISCORDANT
YET?



http://l.yimg.com/os/publish-images/sports/2014-05-01/3fa90770-d139-11e3-ba0e-6fe11e85ac34_133606027.jpg

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| QFT-G only | 2 (50%) | 8 (24.2%) | 11 (35.5%) |
| T.SPOT only | 0 (0%) | 2 (6.1%) | 13 (41.9%) |
| Two tests positive | 0 (0%) | 7 (1.7%) | 3 (0.2%) |
| TST and QFT-G | 0 (0%) | 1 (14.3%) | 0 (0%) |
| TST and T.SPOT | 0 (0%) | 5 (71.4%) | 0 (0%) |
| QFT-G and T.SPOT | 0 (0%) | 1 (14.3%) | 3 (100%) |
| All three tests positive | 1 (4.8%) | 7 (1.7%) | 2 (0.1%) |

Interpreting in Columns... Things look a little different

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1. Proportion of 'all negative' increases as Risk level decreases

* Expected

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| All three tests positive | 1 (4.8%) | 7 (1.7%) | 2 (0.1%) |

2. Proportion of 'one positive' decreases as Risk level decreases

* Expected (but odd distribution in Medium- and Low-Risk)

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| All three tests positive | 1 (4.8%) | 7 (1.7%) | 2 (0.1%) |

3. No 'two positives' in High-Risk

* Unexpected

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4. Highest proportion of 'all positive' in High-Risk, and proportion decreases as Risk level decreases

* Expected...Yes!

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Could pts have been misclassified in Risk level? Pt recall or response?

Weakness or gaps in questionnaire?

WHAT DOES MANCUSO'S PAPER TELL US?

- IN GENERAL, DO NOT EXPECT CONCORDANT TB TEST RESULTS
 - MORE LIKELY IN HIGH-RISK PATIENTS, BUT RARE EVEN THEN
- REMEMBER THAT TST AND IGRAS ARE VERY DIFFERENT TESTS
 - THEY ARE MEASURING DIFFERENT PARTS OF THE IMMUNE SYSTEM
 - AS DR. KISSNER SHOWED, THE QUANTITATIVE VALUES FOR IGRAS ARE CRUCIAL TO UNDERSTAND THE RESULT

CASE EXAMPLE

- 19 YR F, US-BORN
- PARENTS BORN IN INDIA
- TRIPS TO INDIA, LASTING ~ 1 MONTH/TRIP AT AGES:
 - 6 MONTHS OLD
 - 11 MONTHS OLD
 - 3 YEARS OLD

CASE EXAMPLE

- MULTIPLE TB TESTS

- TST 5/19/2000 (4 YRS): **20 MM**

- QFT-G 1/31/2015 (18-19 YRS): **NEG**

- QFT-G 2/2/2015: **POS**

- T.SPOT 4/6/2015: **BORDERLINE**

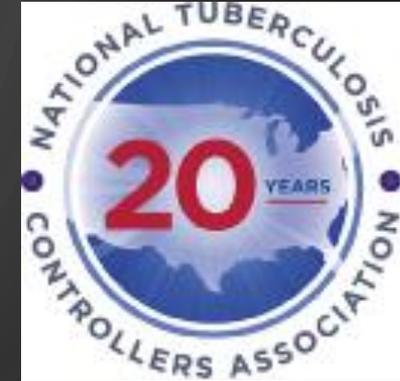
- 2015 (18-19 YRS) PATIENT HAD EYE IRRITATION/INFECTION, TESTED DUE TO SUSPECT OCULAR TB

- ALSO HAD AN UNSPECIFIED IMMUNE SYSTEM DISORDER (BELIEVED TO BE IMMUNOSUPPRESSED)

- DIAGNOSIS OF OCULAR TB AND TREATED FOR 6 MO

GUIDANCE FOR INTERPRETING DISCORDANT TST AND IGRA RESULTS

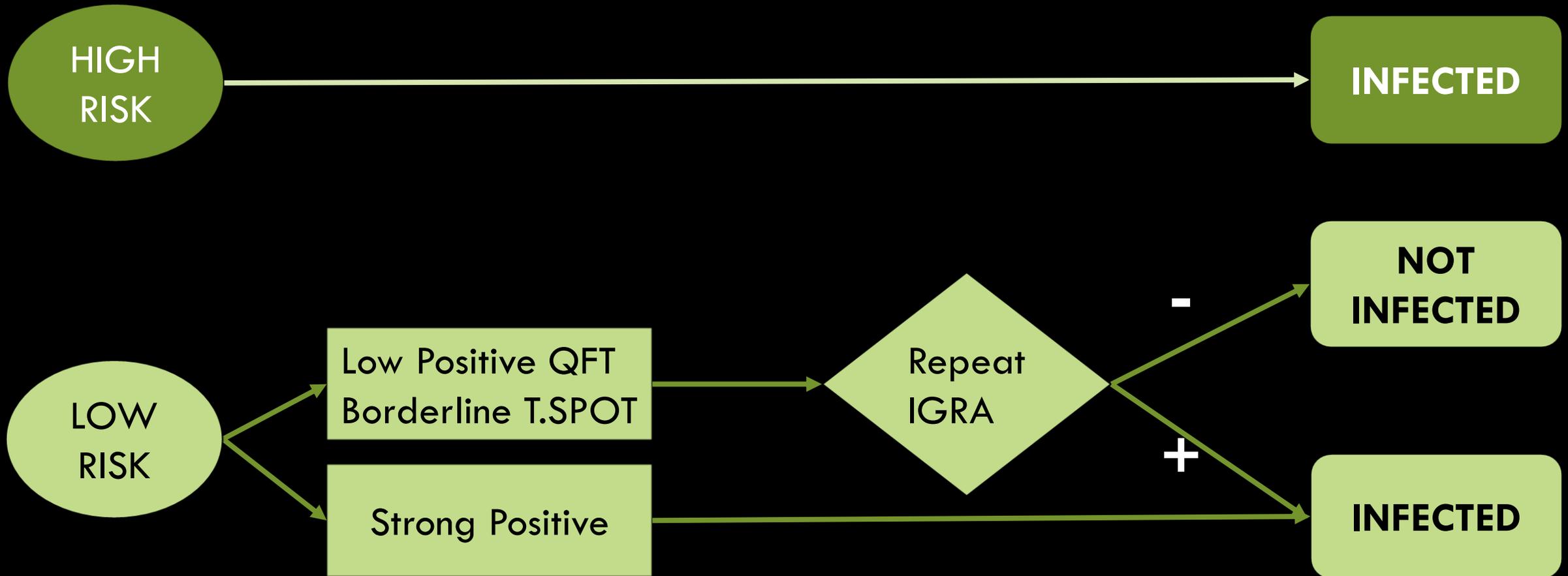
- THINK VERY CAREFULLY ABOUT HOW YOU WILL PROCEED
- NEVER RETEST A PATIENT TO REFUTE A PRIOR RESULT
- THOROUGHLY ASSESS AND DOCUMENT ALL RISK FACTORS
 - RISK FOR INFECTION HELPS DETERMINE WHICH RESULT TO BELIEVE
 - RISK FOR PROGRESSION HELPS DETERMINE WHETHER TO ORDER ANOTHER TEST
- CLINICAL DECISION IS NECESSARY, AND MUST ACCOUNT FOR PATIENT'S RISK FACTORS



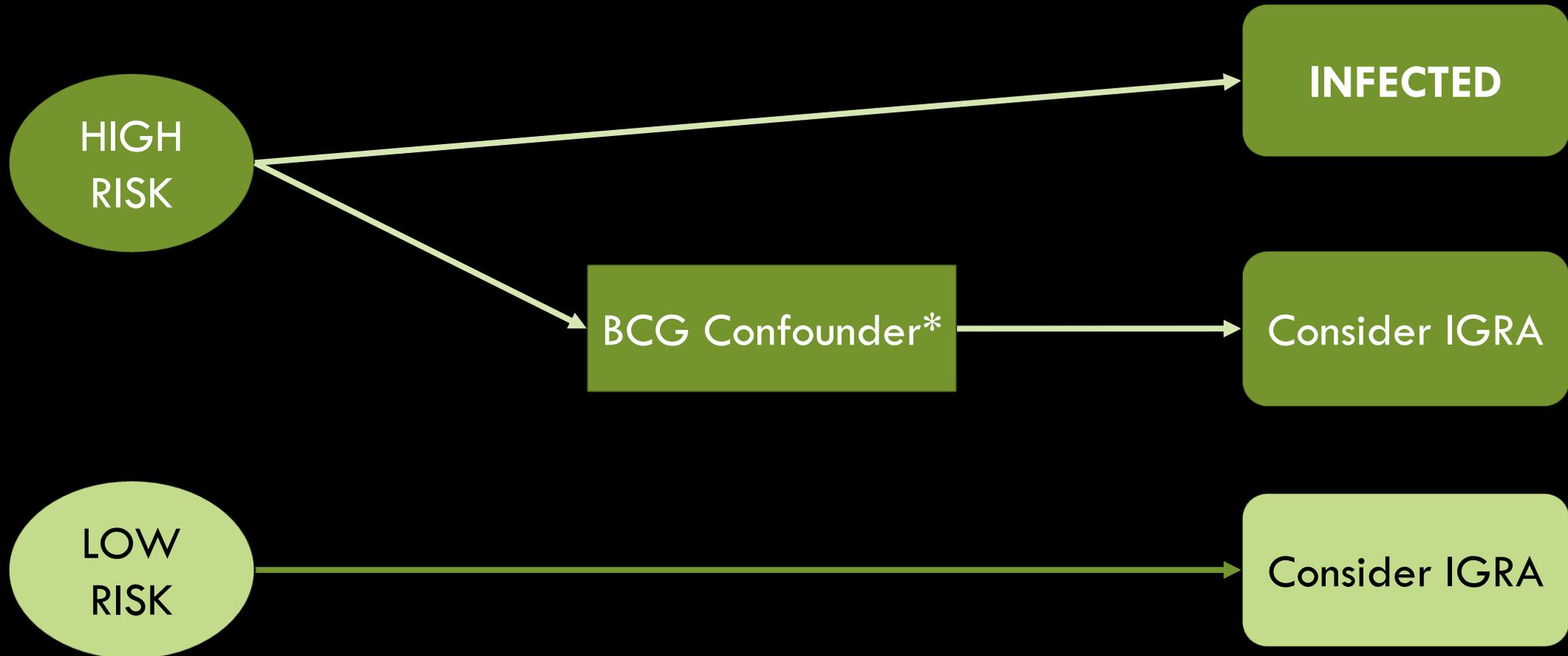
KNOW THE RISK – HIGH VS LOW

- NTCA GUIDELINES EMPHASIZE RISK OF PROGRESSION FROM INFECTION TO DISEASE
- ONLY TWO RISK LEVELS: HIGH & LOW
 - HIGH RISK:
 - HIV/AIDS
 - PERSONS BEING CONSIDERED FOR IMMUNOSUPPRESSIVE THERAPY
 - PRE-TRANSPLANTATION
 - SILICOSIS
 - END STAGE RENAL DISEASE
 - POORLY-CONTROLLED DIABETES MELLITUS

WHAT TO DO IF...
IGRA: POSITIVE/BORDERLINE
TST: UNKNOWN/NOT DONE/NEGATIVE



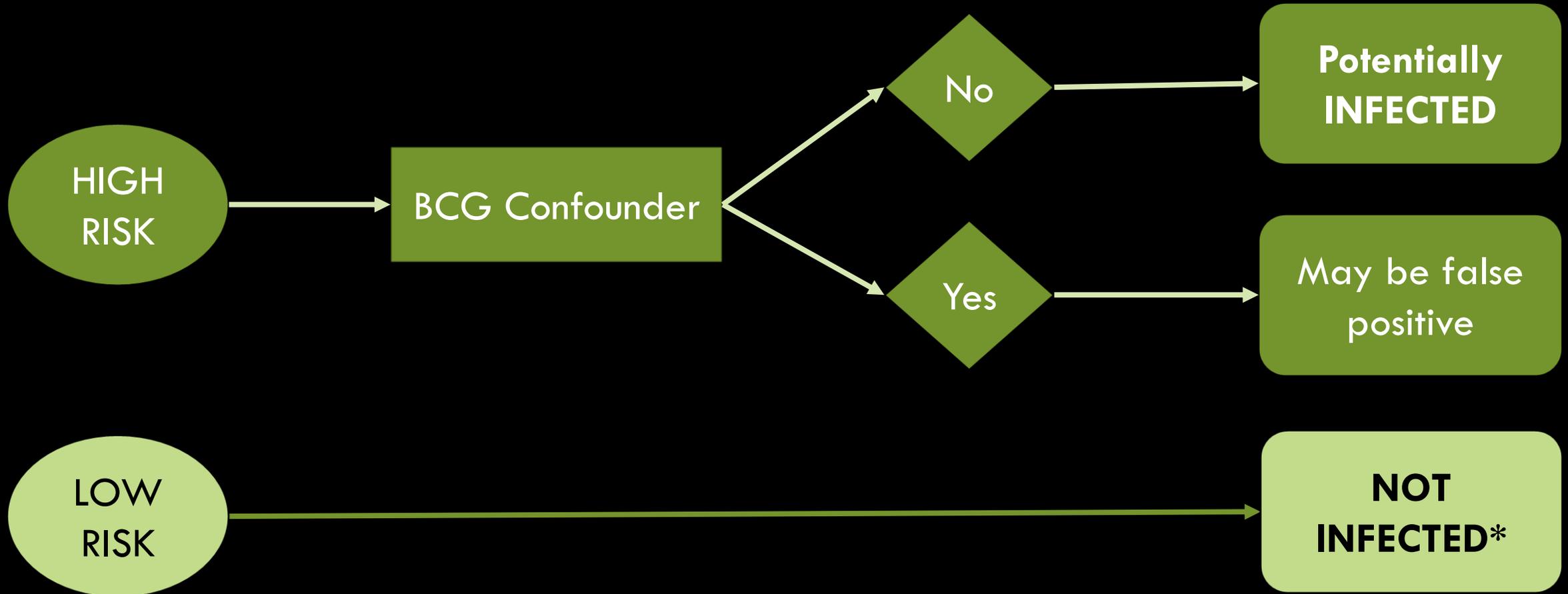
WHAT TO DO IF...
IGRA: UNKNOWN/NOT DONE
TST: POSITIVE



* IF TST WAS PLACED W/IN 10 YRS OF BCG

WHAT TO DO IF...

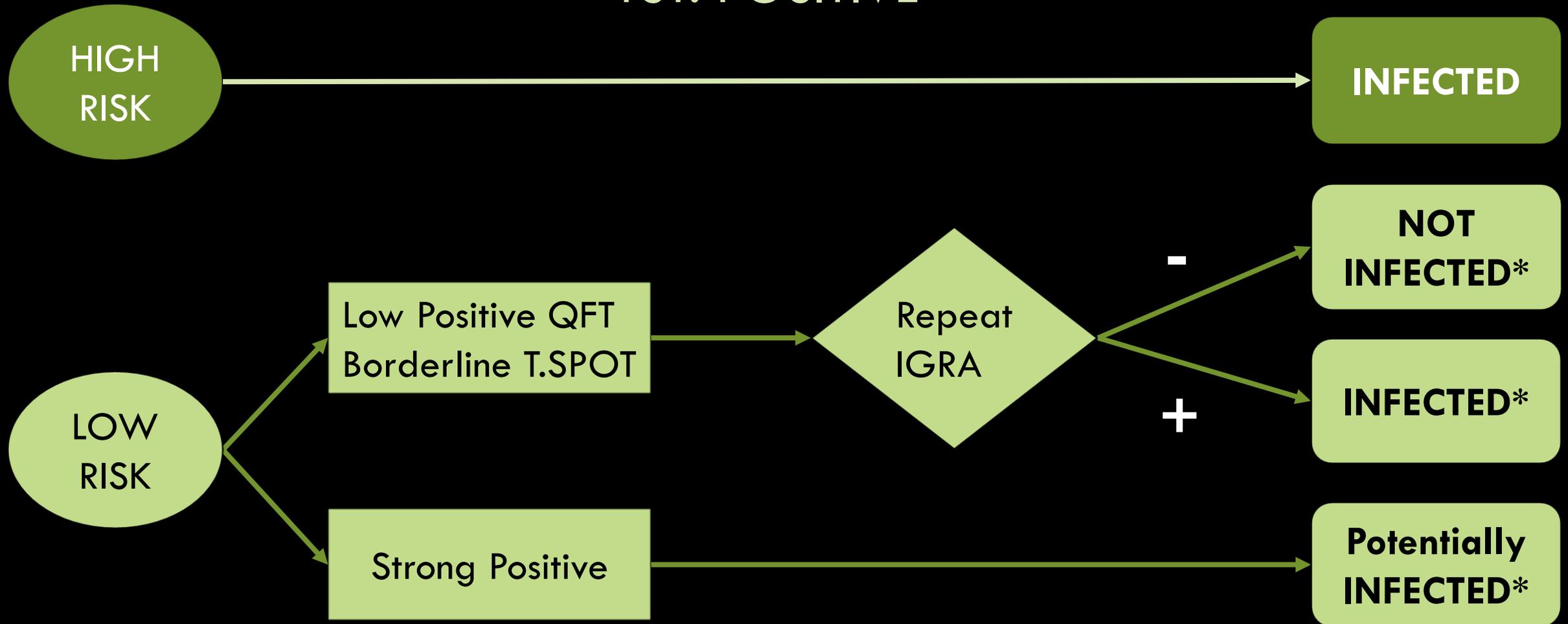
IGRA: NEGATIVE
TST: POSITIVE



* TST likely false positive, recommend IGRA for future testing

WHAT TO DO IF...

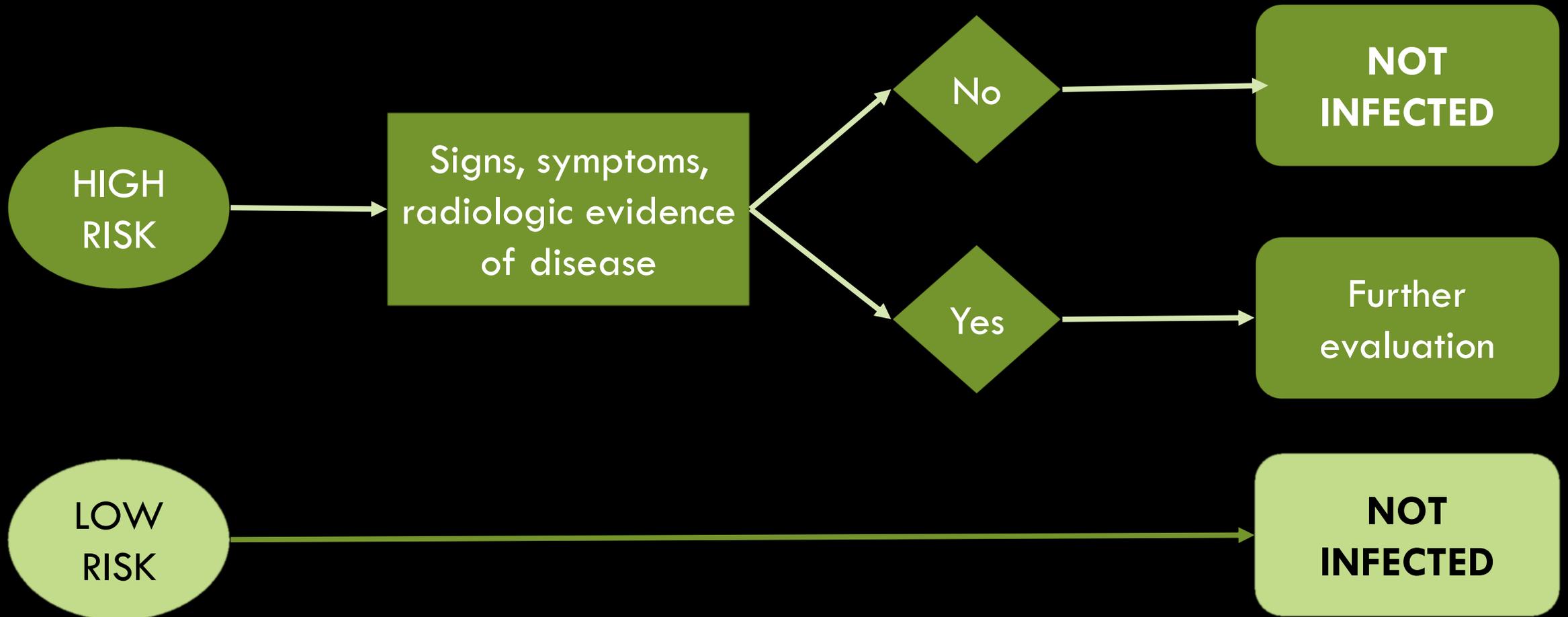
IGRA: POSITIVE
TST: POSITIVE



* Consider risks/benefits of treatment vs evaluation

WHAT TO DO IF...

IGRA: NEGATIVE
TST: NEGATIVE



SUMMARY

- MANY SCENARIOS CAN GIVE RISE TO DISCORDANT TB TEST RESULTS
- VARIANCES IN PERSON BEING TESTED, AND COMPONENTS OF THE TESTS THEMSELVES, CONTRIBUTE TO DISCORDANT RESULTS
- THE TST AND IGRAS ARE FUNDAMENTALLY DIFFERENT TESTS, WHICH MEASURE DIFFERENT PARTS OF THE IMMUNE SYSTEM
- UNDERSTANDING AND INTERPRETING TB TEST RESULTS REQUIRES:
 - COMPLETE KNOWLEDGE OF PERSON'S RISK FOR INFECTION AND PROGRESSION
 - QUANTITATIVE DATA FROM THE IGRA REPORT

CONCLUSIONS

- DISCORDANT TB TEST RESULTS SHOULD BE EXPECTED AND PLANNED FOR
 - FAR MORE LIKELY IN LOW-RISK PERSONS
- A DECISION TO **TEST** MUST BE A DECISION TO **THINK**
 - PERSON'S RISK FACTORS
 - STRATEGY IN ADVANCE FOR WHEN TO REPEAT TB TEST, AND HOW TO INTERPRET
- IGRAS CAN REQUIRE AS MUCH INTERPRETATION AS TST
- NO TB TEST IS PERFECT, AND NO SINGLE TEST SHOULD BE USED TO REFUTE PRIOR RESULTS

THANK YOU!

QUESTIONS?



REFERENCES

- [MANCUSO \(2012\) HTTP://WWW.ATSJOURNALS.ORG/DOI/FULL/10.1164/RCCM.201107-1244OC#.V18SFBVR_IU](http://www.atsjournals.org/doi/full/10.1164/RCCM.201107-1244OC#.V18SFBVR_IU)
- [POLLOCK \(2008\) HTTP://WWW.NCBI.NLM.NIH.GOV/PUBMED/18713053](http://www.ncbi.nlm.nih.gov/pubmed/18713053)
- NTCA (2016, PENDING) RECOMMENDATIONS & BEST PRACTICES FOR THE USE AND INTERPRETATION OF IGRAS