# Subclinical and Incipient TB

## Lessons from history

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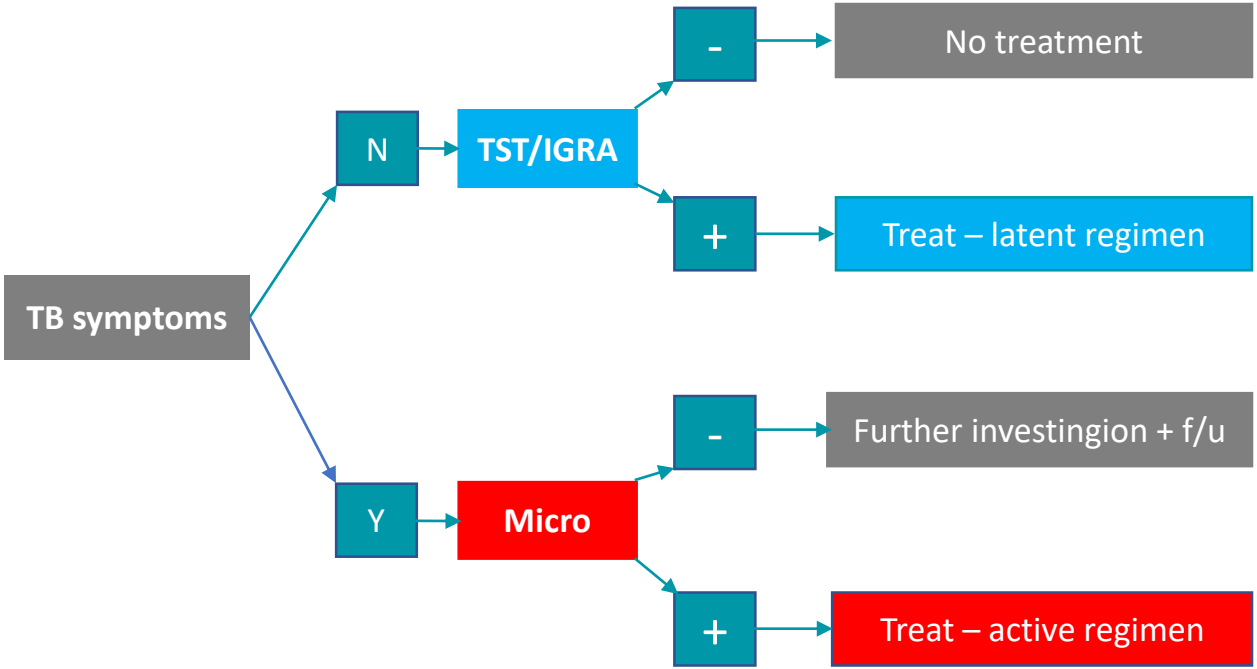
9th Sept 2019, INTER-TB, St George's

# Binary conceptualization of TB…



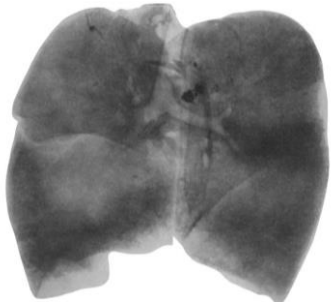

**Driven by the diagnostic and treatment paradigm...**

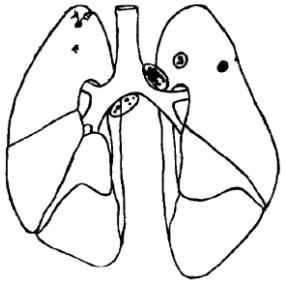
“The distinction between latent and clinical tuberculosis, which is not infrequently made, has no other basis than the limitations of diagnostic methods and the tendency of tuberculosis to proceed to recovery.”

- Opie and Andersen 1920

# Human autopsy studies in those dying from non-TB causes

Post-mortem CXR

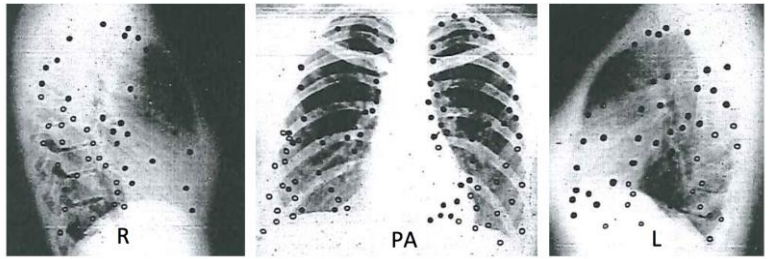




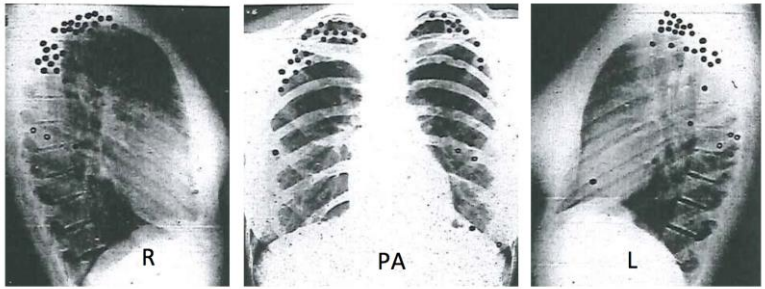
Guinea Pig inoculation to determine viable bacilli

Opie, J.Exp Med - 1917
Opie and Aronson, Archives of Pathology - 1927

Localization of Primary complexes

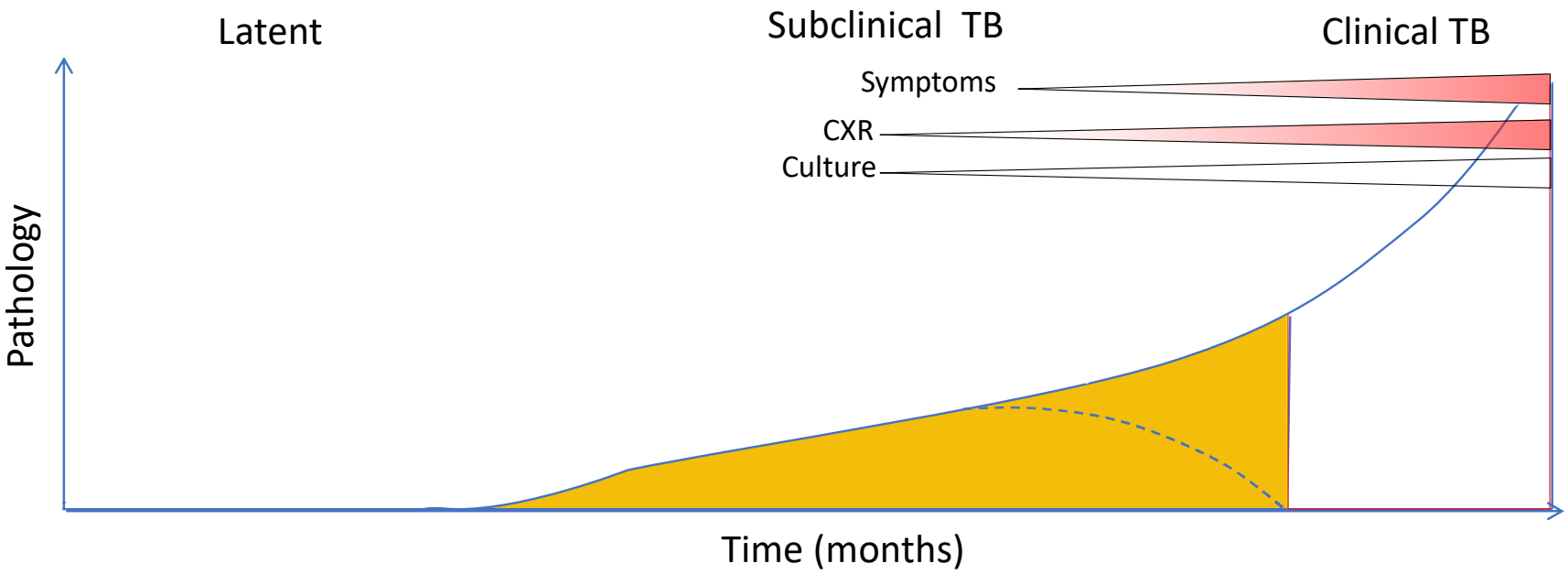



Localization of minimal TB disease lesions



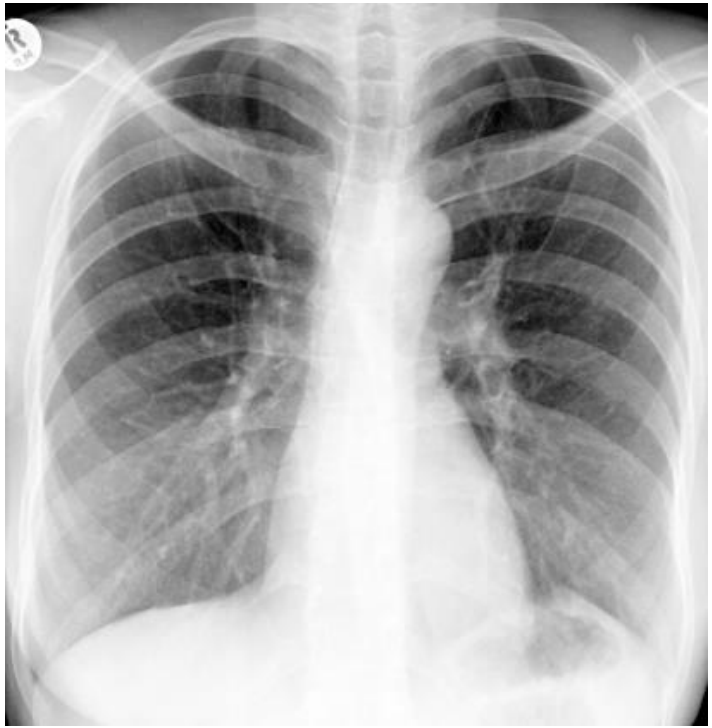

Medlar, Am. Rev Tuberc - 1948

# Subclinical TB

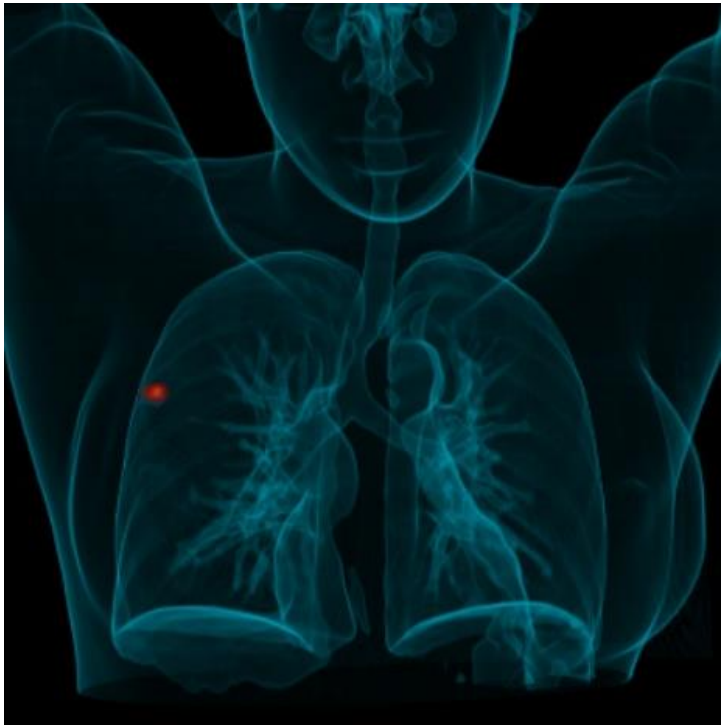



Esmail et al Phil Trans R Soc B 2014

# FDG-PET/CT for detection of Subclinical TB *in vivo*?



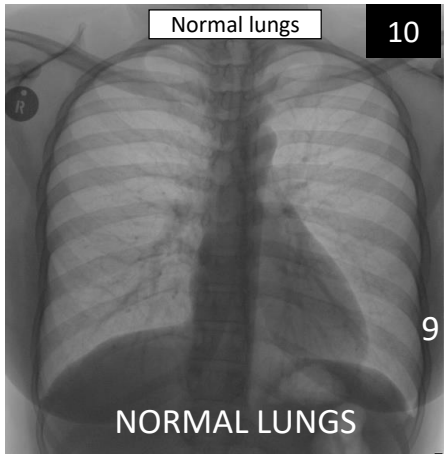
CXR

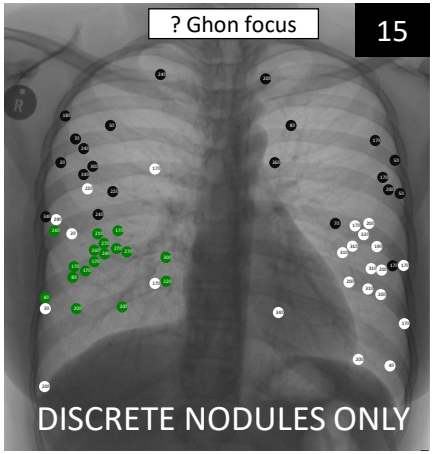


FDG-PET/CT

# FDG-PET/CT in HIV-1 infected classified as having LTBI

35 symptom -ve, QuantiFERON +ve, CXR no active TB, culture –ve, HIV-1 infected, ART naïve, CD4 > 350/mm$^3$, living in Khayelitsha township, no history of previous TB

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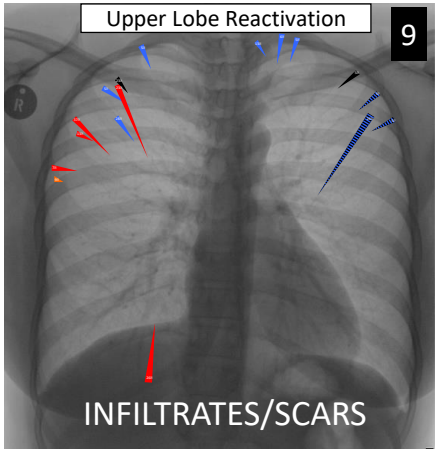
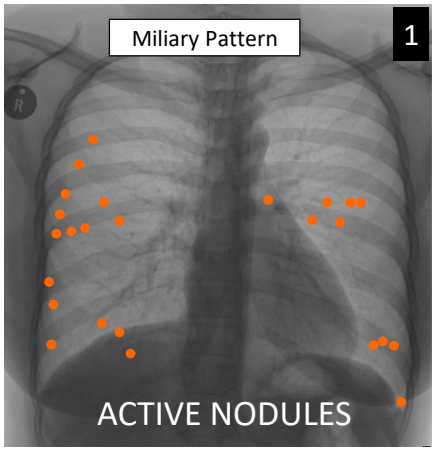
No evidence subclinical pathology

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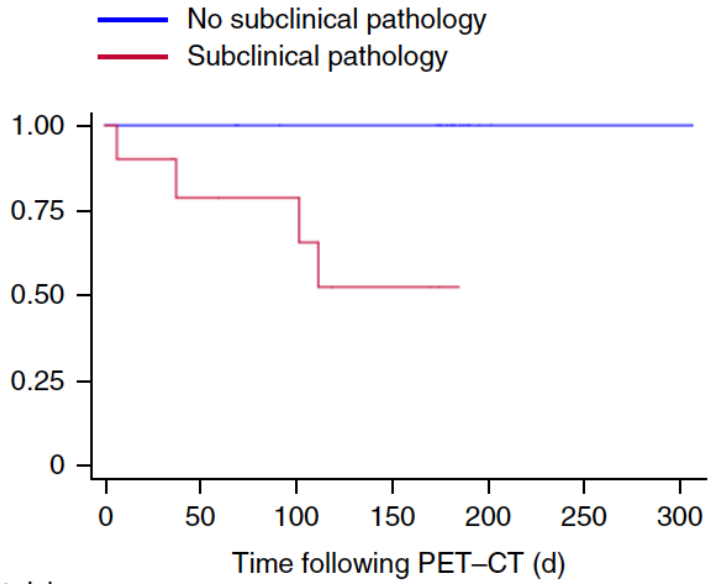
Evidence of subclinical pathology

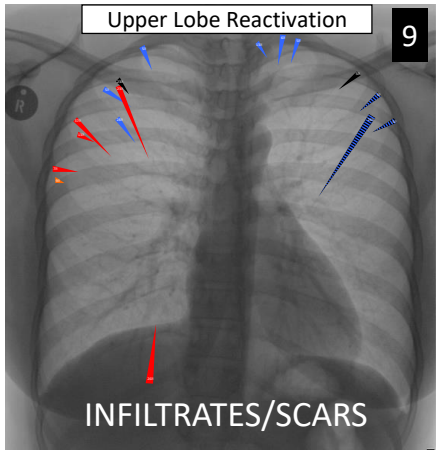
Esmail et al Nature Med 2016

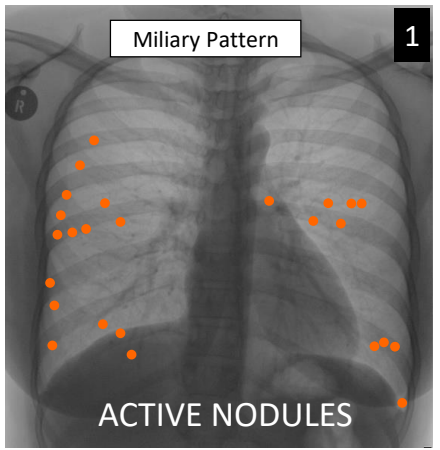
# FDG-PET/CT in HIV-1 infected classified as having LTBI

35 symptom -ve, HIV-1 infected, ART naïve, CD4 > 350/mm$^3$, QuantiFERON +ve, CXR no active TB, culture –ve, living in Khayelitsha township, no history of previous TB

PROPORTION NOT ON STANDARD TB THERAPY

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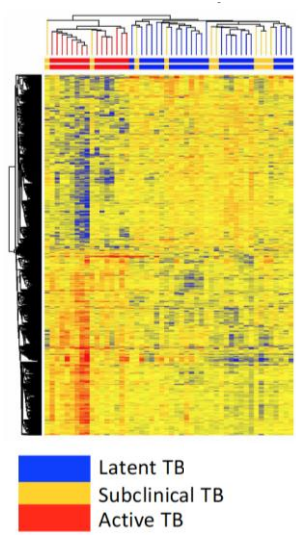
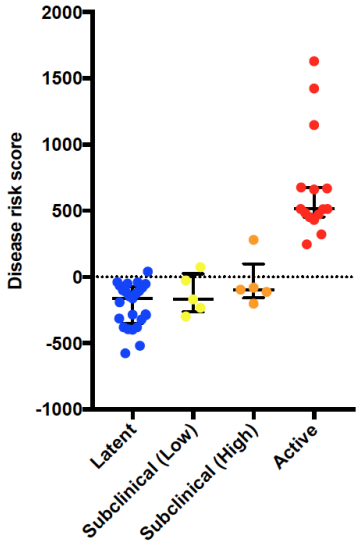
Evidence of subclinical pathology

Esmail et al Nature Med 2016

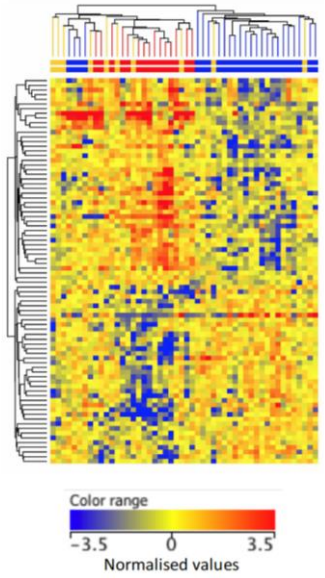
# Subset of active TB transcripts identify subclinical disease

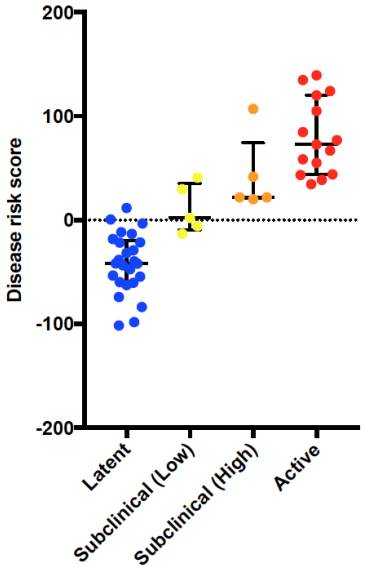
## ACTIVE SIGNATURE – 893 transcripts




## SUBCLIN SUBSET – 82 transcripts

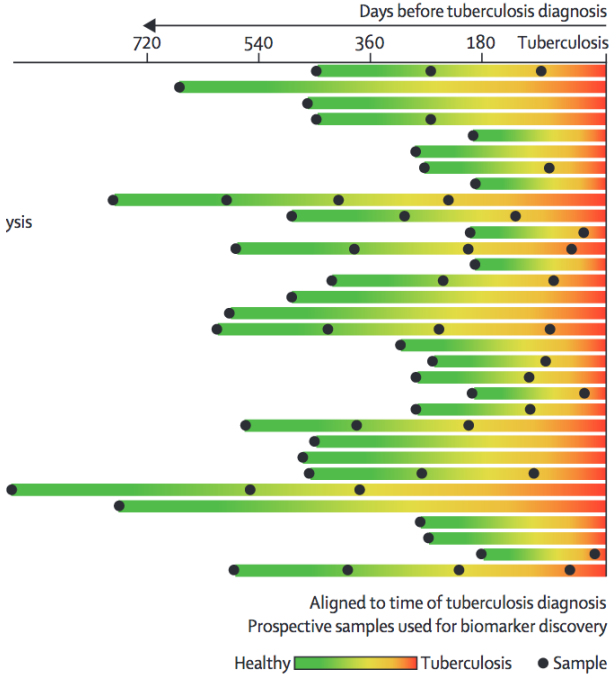


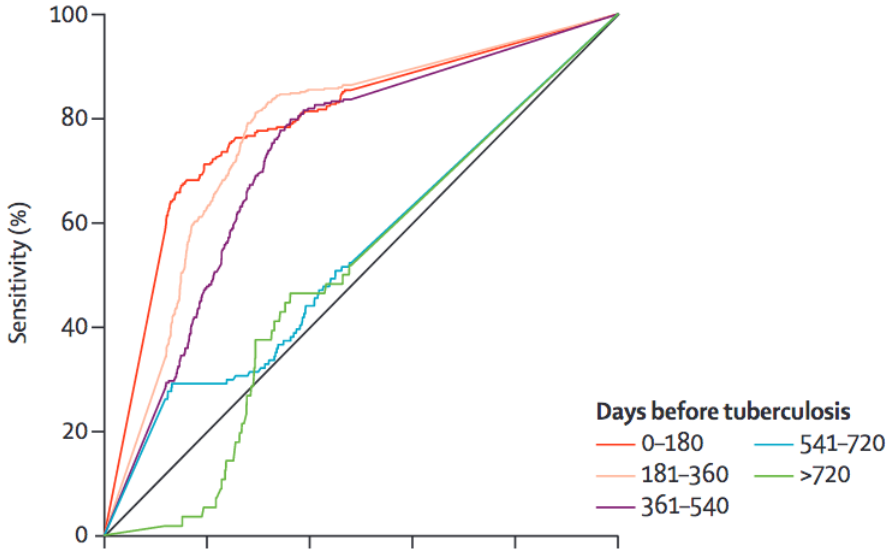

Esmail et al – PNAS 2018

# Incipient TB – Transcript signatures predict TB progression

- 6363 SA HIV-uninfected adolescents followed for 2 years with 6 months blood
- 53% QuantiFERON +ve, 1.3% developed disease over 2 years
- Transcripts of 46 progressors compared to 107 controls

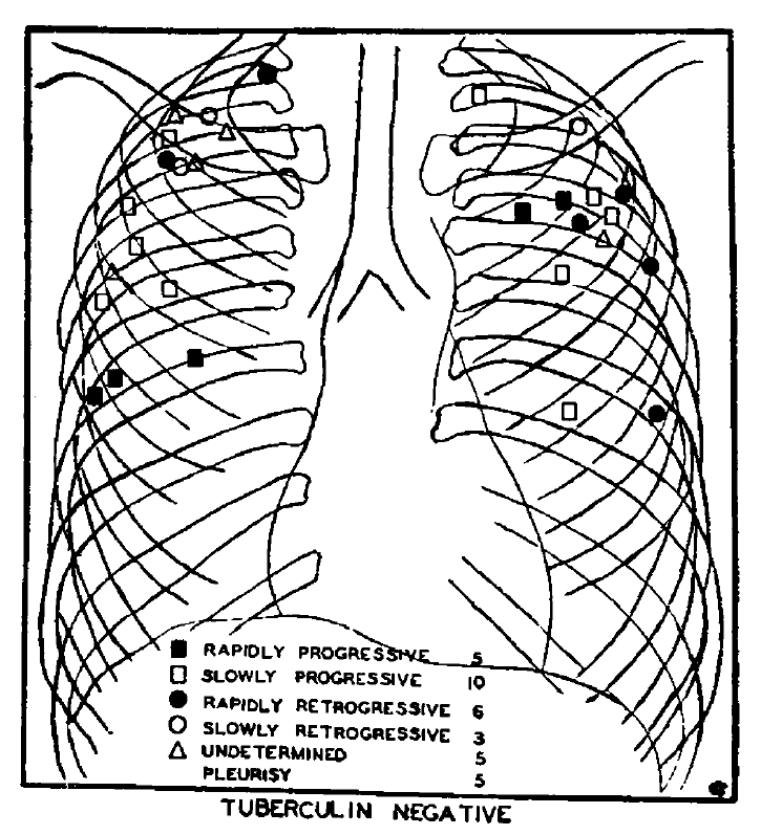



ROC curve showing predictive potential of 16 transcript signature




Zak et al – Lancet 2016

# Kinetics of Subclinical TB



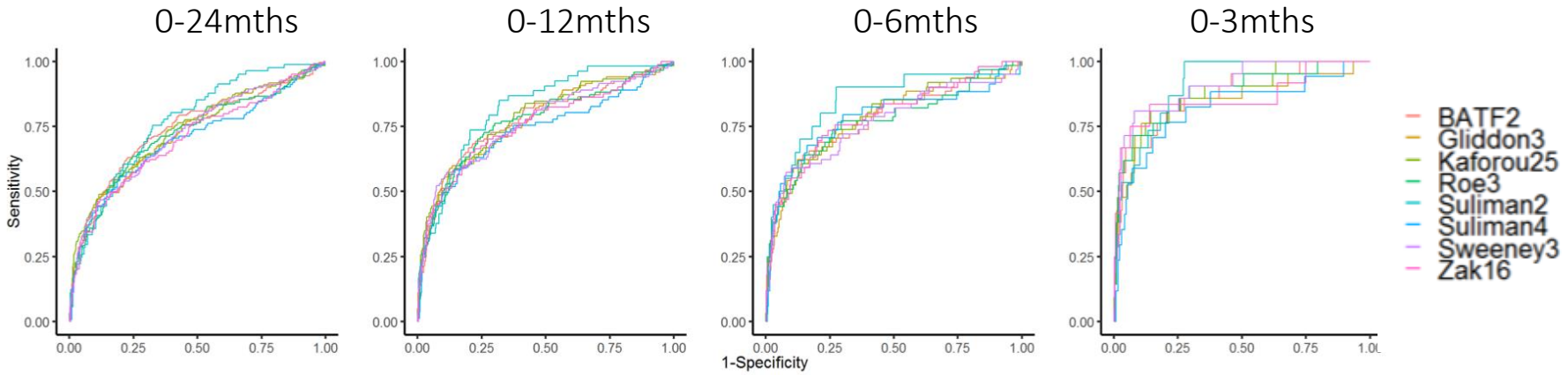

- 277 TST-ve Nursing students USA 1935-9
- All became TST positive (tested 4mthly)
- CXR (4mthly) – over > 3 years
- 29 (10.4%) developed pulmonary lesions
  - Rapid progression 5/29 (17%)
  - Slow progression 10/29 (34%)
  - Rapid Regression 6/29 (21%)
  - Slow Regression 3/29 (10%)
  - Undetermined 5/29 (17%)

Israel et al JAMA 1941

# Kinetics of Subclinical TB: Impact on diagnostic performance

- Meta-analysis of performance of validated TB transcriptional signatures to predict TB
- 17 validated diagnostic signatures; 4 datasets - 127 cases of incipient TB
- 8 signatures had similar performance

Time before disease presentation (months)

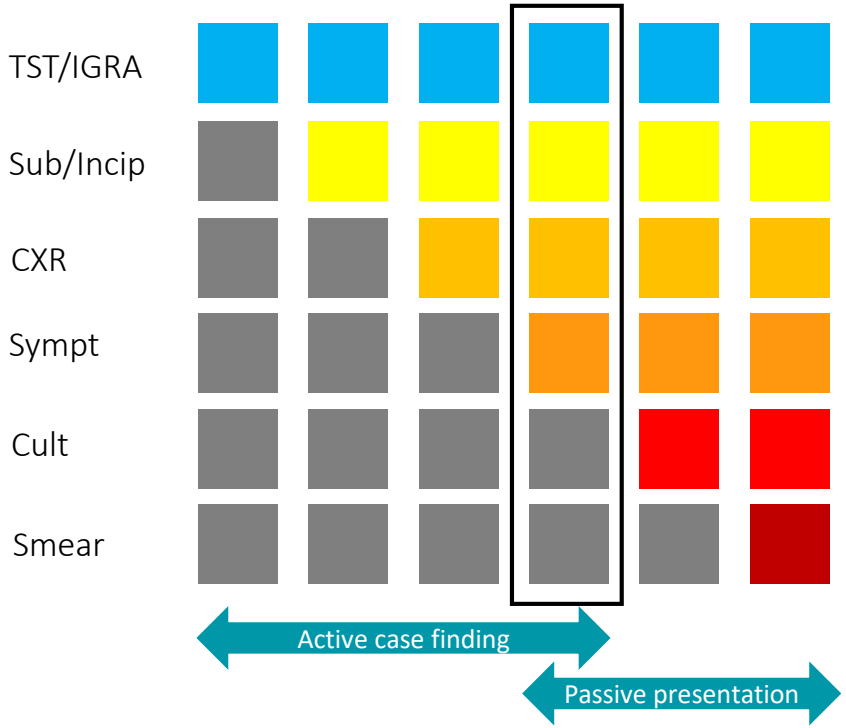


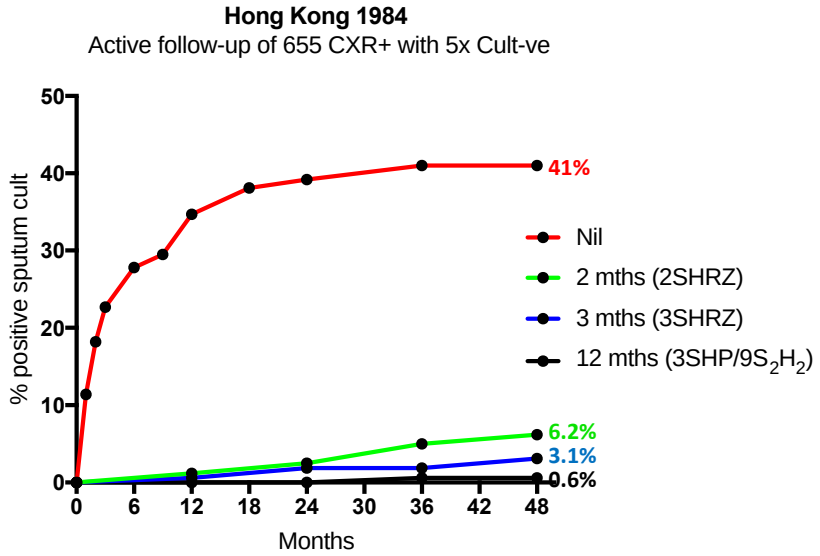

| 0-24mths | 0-12mths | 0-6mths | 0-3mths |
|---|---|---|---|
| PPV = 6.8-9.4 % | PPV = 8.3-10.3 % | PPV = 9.5-11.7 % | PPV = 11.1-14.3 % |
| Sens = 25-40 % | Sens = 33-52 % | Sens = 43-57 % | Sens = 47-81 % |
| Spec = 92-95 % | Spec = 92-95 % | Spec = 91-95 % | Spec = 91-95 % |

Gupta et al – Lancet Resp Med *in press*

# What is the optimal Tx for different parts of disease spectrum?

Number of imperfect tests that loosely relate to pathological spectrum of disease…

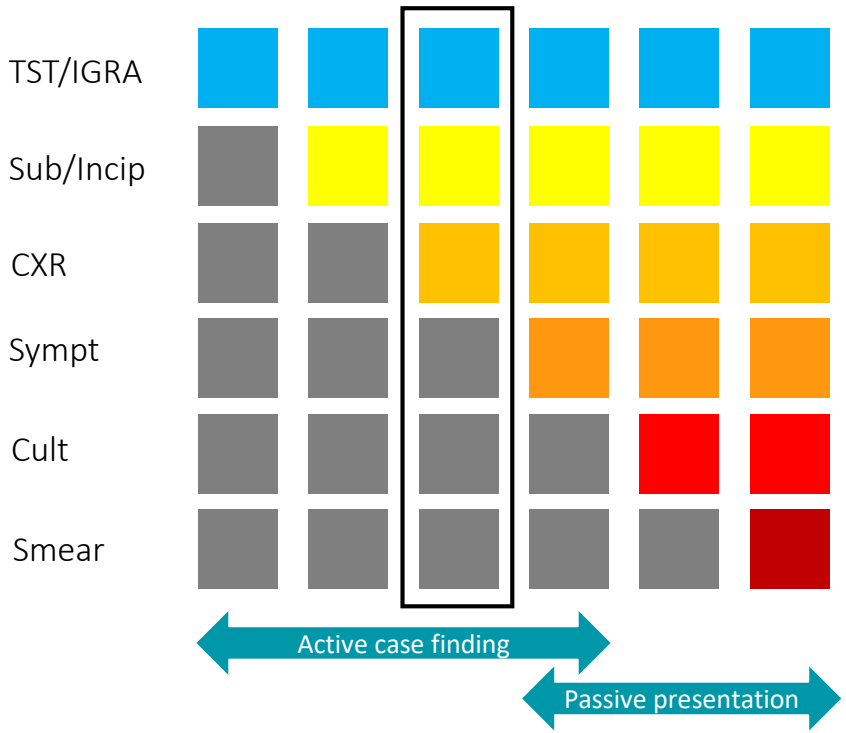



- CXR suggestive of active TB and 5x culture –ve
- 68% had symptoms (60% cough)
- 173 not treated – intensive f/u

# What is the optimal Tx for different parts of disease spectrum?

Number of imperfect tests that loosely relate to pathological spectrum of disease…




*Tubercle, Lond.*, (1958), **39**, 129

ORIGINAL ARTICLES

## A Controlled Trial of Chemotherapy in Pulmonary Tuberculosis of Doubtful Activity

Report from the Research Committee of the Tuberculosis Society of Scotland*

- 191 CXR suggestive of active TB and culture –ve
- No symptoms or other signs of disease
- Randomized to $6H_{200}PAS_{10}$ or observation
- 24 month f/u

- 17.8% bact/radiographic deterioration (control)
- 8.5% bact/radiographic deterioration (6HPAS)

TB Scotland, Tubercle 1958

# Conclusions

- Binary approach to TB reflects the diagnostic and treatment paradigm
- Disease pathology may precede disease presentation by months - years
- Likely that novel tests for incipient TB detect those with early disease
- Most early disease will be identified by active case finding
- Optimal treatment is unclear

# Acknowledgements


## Imaging

- Robert J Wilkinson
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- Friedrich Thienemann
- Jerry Ellner

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- Rein Houben
- Alex Richards
- Bianca Sossen
- Katharina Kranzer
- Torben Heinsohn
- Friedrich Thienemann
- Frank Cobelens




TB Modelling and Analysis Consortium

Increasing the effectiveness of TB care and prevention