New biomarkers for tuberculosis infection diagnosis

Delia Goletti

Istituto Nazionale per le Malattie Infettive L. Spallanzani-IRCCS, Rome, Italy

Milano, November 28th, 2024

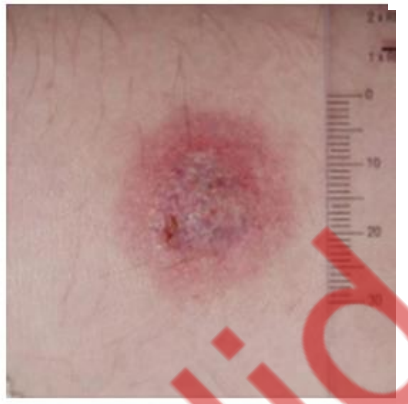
Conflicts of interest

In the last 2 years I have been a consultant or I presented talks for:

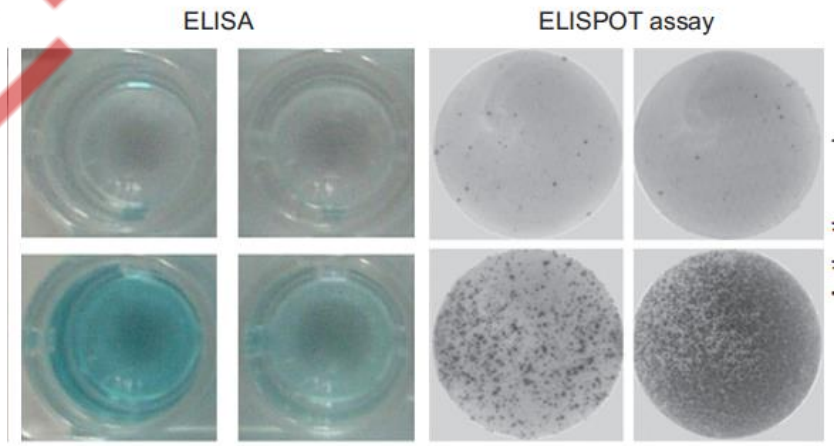
Astra Zeneca, Biomerieux, PDB Biotec

TB infection definition from a pragmatic point of view

Skin tests
TST or EC-based assays
PPD or ESAT-6 and CFP-10



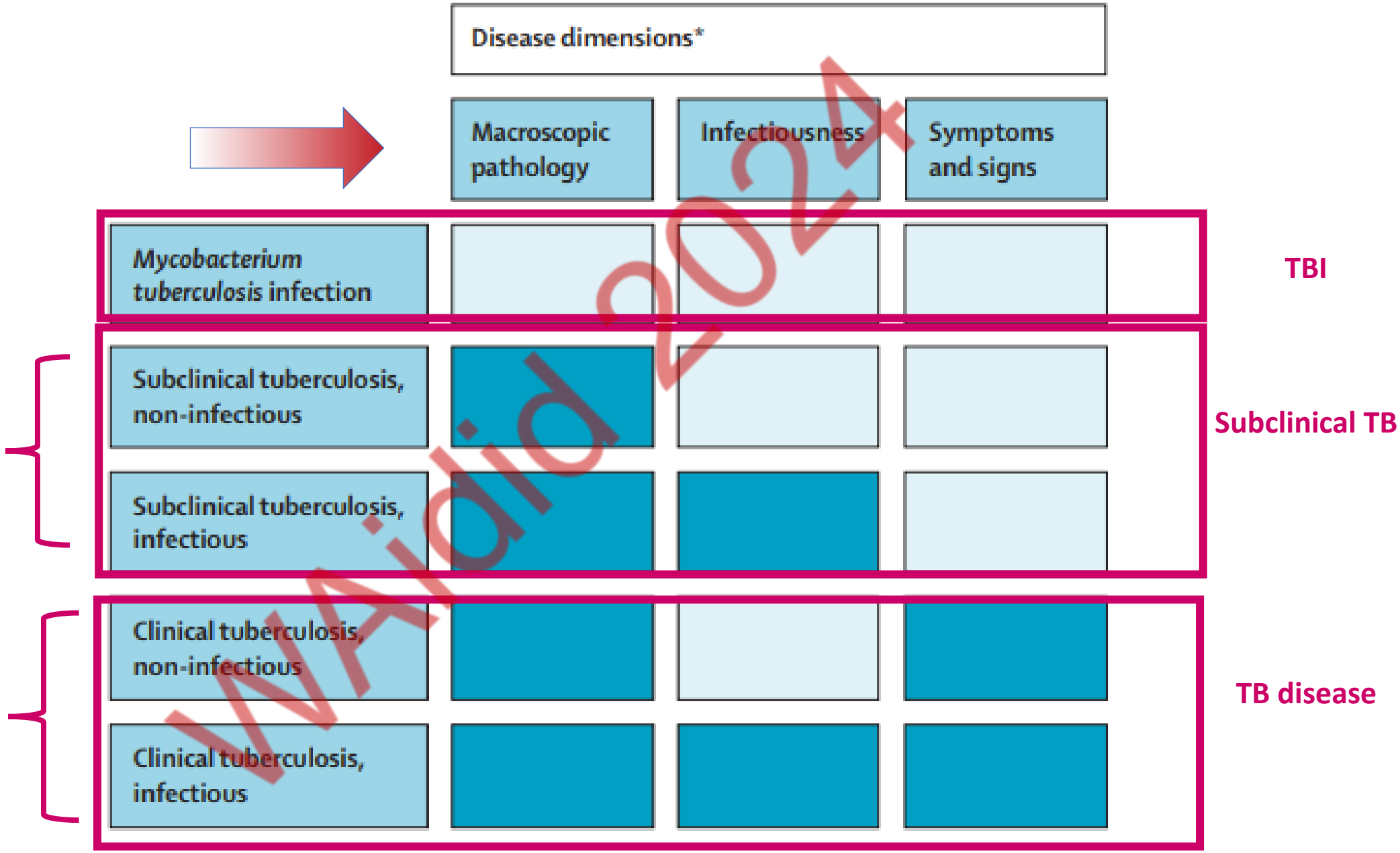
IFN-γ release assays
IGRA
ESAT-6 and CFP-10



Tuberculosis infection is defined as a state of persistent immune response to stimulation by *M. tuberculosis* antigens with no evidence of clinically manifest TB disease

(Getahun H,et al N Engl J Med. 2015)

Conceptual states of infection and disease of tuberculosis



Coussens AK et al, Lancet Respir Med, 2024

Tuberculosis as a spectrum

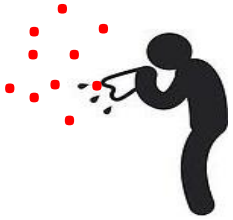
Uninfected

TB infection

"TB infection"as having evidence of TB infection and no clinical, radiological or microbiological evidence of TB disease"

Sub clinical TB

"Subclinical TB disease" is a disease that does not cause clinical TB-related symptoms but causes other abnormalities that can be detected using existing radiologic or microbiologic assays.

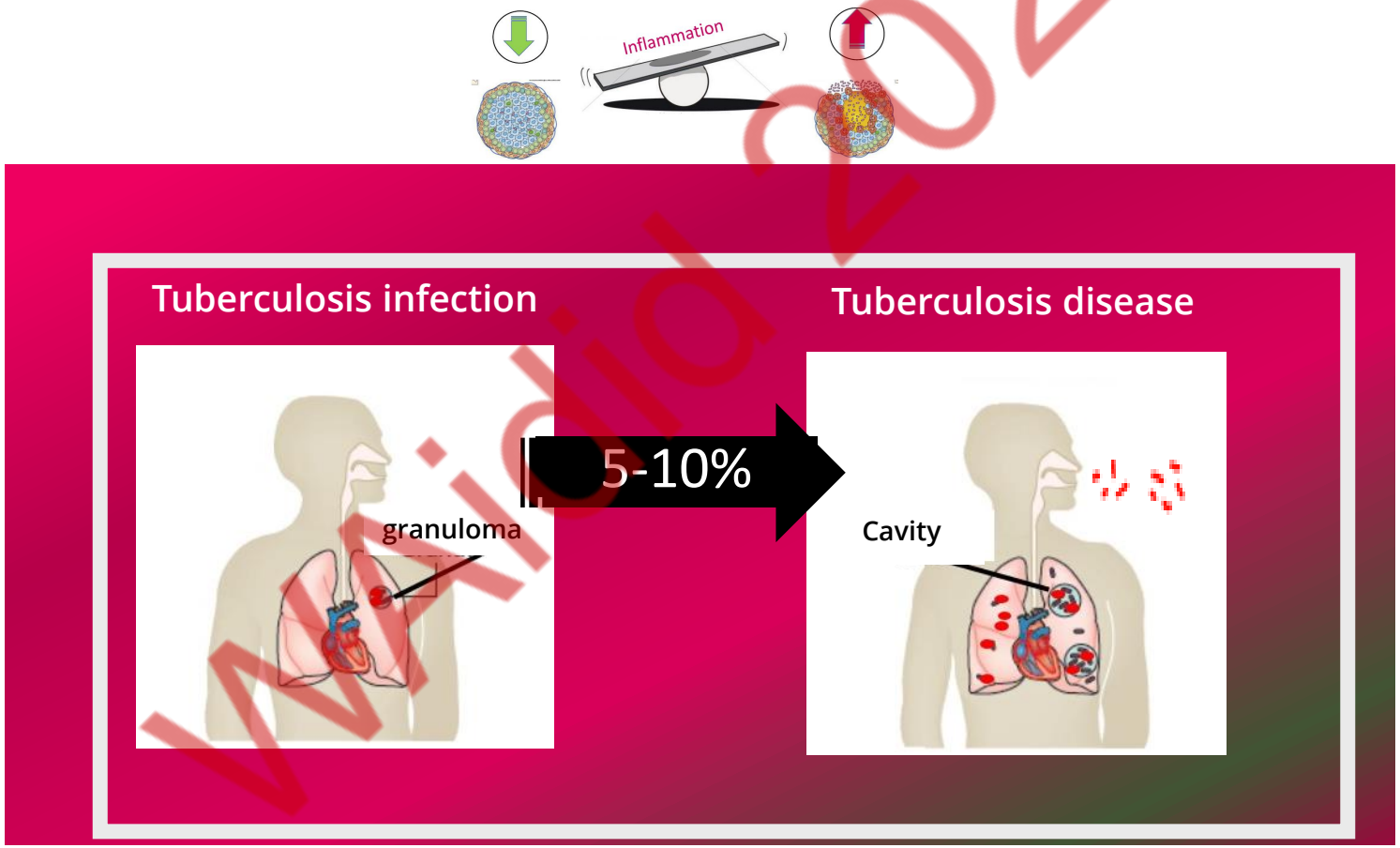


TB disease

"TB disease" as symptomatic disease with radiological or microbiological evidence of TB

Migliori et al, Breath 2021
Goletti et al, IJID 2022

Natural history of tuberculosis



Modified from Pai et al, Nature Reviews, 2016

Worldwide TBI: size of the problem

TBI

¼ of the global population

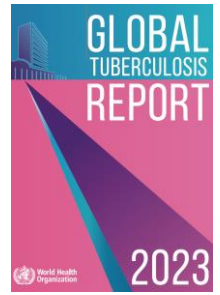
2 billion

(WHO Global TB report 2022)

TB disease
10.6 million

Around 10-20 fold difference

~100-200 million at risk to develop TB disease



IGRAs and TST accuracy during 3 years' follow-up with prespecified test thresholds in almost 10,000 participants who were at high risk for LTBI (close contacts of active TB cases or recent migrants) sequentially recruited from 54 centers in the United Kingdom

	QFT-GIT (*IU/ml*)			T-SPOT.TB (*Spots*)			BCG-adjusted TST* (*mm*)		
	⩾0.35	⩾0.7	⩾4	⩾5	⩾8	⩾50	⩾5	⩾10	⩾15
Sensitivity									
n	50	44	19	53	50	22	62	42	25
N	82	82	82	81	81	81	89	89	89
Estimate, %	61.0	53.7	23.2	65.4	61.7	27.2	69.7	47.2	28.1
95% CI	49.6–71.6	42.3–64.7	14.6–33.8	54–75.7	50.3–72.3	17.9–38.2	59–79	36.5–58.1	19.1–38.6
Specificity									
n	6,134	6,511	7,242	5,856	6,155	6,948	5,520	6,295	6,882
N	7,755	7,755	7,755	7,363	7,363	7,363	7,445	7,445	7,445
Estimate, %	79.1	84.0	93.4	79.5	83.6	94.4	74.1	84.6	92.4
95% CI	78.2–80	83.1–84.8	92.8–93.9	78.6–80.4	82.7–84.4	93.8–94.9	73.1–75.1	83.7–85.4	91.8–93
Positive predictive value									
n	50	44	19	53	50	22	62	42	25
N	1,671	1,288	532	1,560	1,258	437	1,987	1,192	588
Estimate, %	3.0	3.4	3.6	3.4	4.0	5.0	3.1	3.5	4.3
95% CI	2.2–3.9	2.5–4.6	2.2–5.5	2.6–4.4	3–5.2	3.2–7.5	2.4–4	2.6–4.7	2.8–6.2
Negative predictive value									
n	6,134	6,511	7,242	5,856	6,155	6,948	5,520	6,295	6,882
N	6,166	6,549	7,305	5,884	6,186	7,007	5,547	6,342	6,946
Estimate, %	99.5	99.4	99.1	99.5	99.5	99.2	99.5	99.3	99.1
95% CI	99.3–99.6	99.2–99.6	98.9–99.3	99.3–99.7	99.3–99.7	98.9–99.4	99.3–99.7	99–99.5	98.8–99.3

Definition of abbreviations: BCG = bacillus Calmette-Guérin; CI = confidence interval; *n* = numerator; *N* = denominator; QFT-GIT = QuantiFERON Gold-In-Tube; TB = tuberculosis; TST = tuberculin skin test.

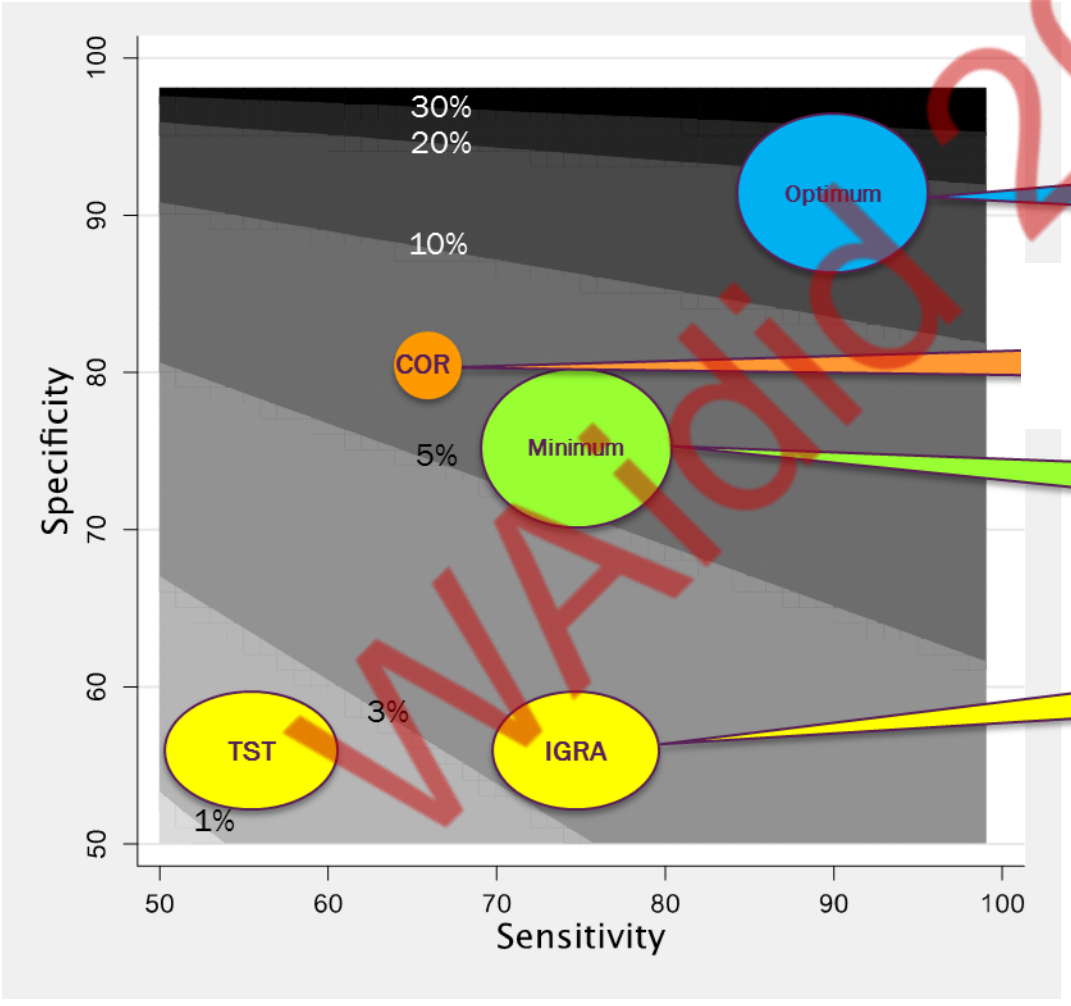
*For participants with previous BCG vaccination (defined by self-report and scar inspection), 10 mm was deducted from the quantitative TST result to adjust for the associated sensitization to BCG ("BCG-adjusted TST").

Gupta et al, AJRCCM, 2020

Positive Predictive Value according to Sens/Spec for risk of progression

E. Petruccioli L. Petrone

cumulative incidence: 2%
IPT effectiveness: 50%



Optimum TPP
- PPV: ~16%

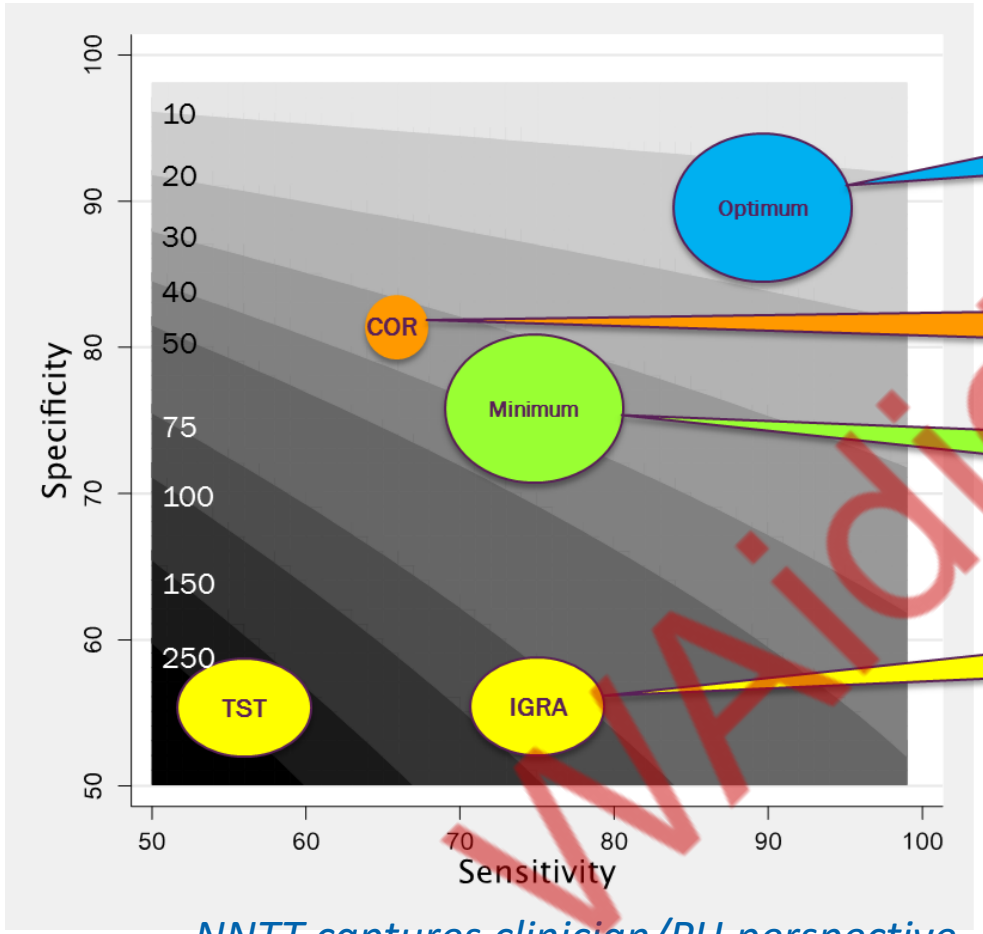
Minimum TPP
- PPV: ~6%

TST / IGRA
- PPV: ~2% / ~3%

Petruccioli et al, ERJ 2016

Number Needed to Test & Treat according to Sens/Spec for risk of progression

E. Petruccioli L. Petrone



Optimum TPP
- NNT: ~13

Minimum TPP
- NNT: ~40

TST / IGRA
- NNT: ~250 / ~85

cumulative incidence: 2%
IPT effectiveness: 50%

NNTT captures clinician/PH perspective (If treating all test+, how many do I need to test and treat to prevent one case?)

Petruccioli et al, ERJ 2016

1st screening

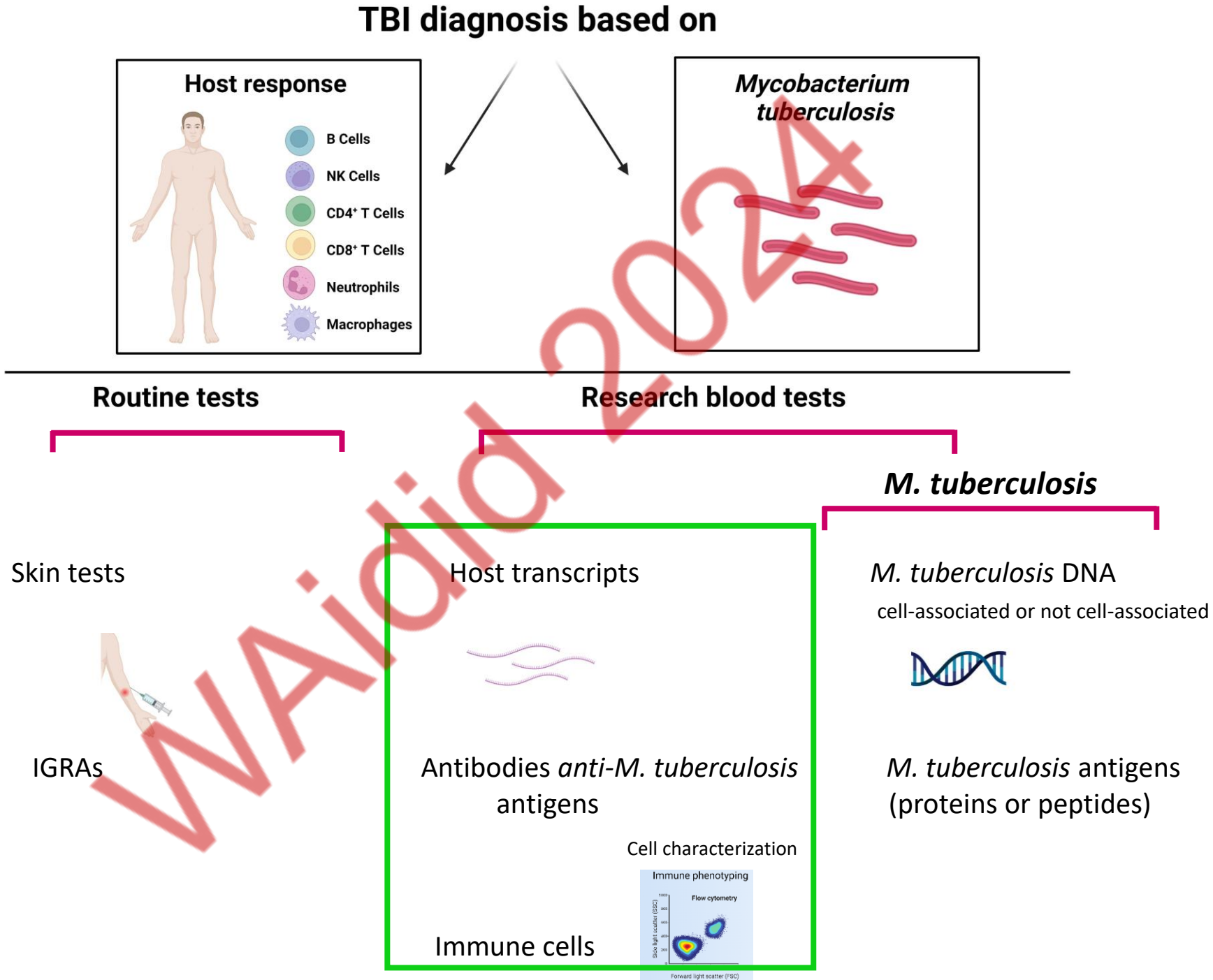
Skin test+ or IGRA+

Based on the guidelines,
we offer TB preventive therapy to
all individuals skin test+ or IGRA+

Research tests for the diagnosis of tuberculosis infection

Alonzi T, Repele F, Goletti D. Expert Review of Molecular Diagnostics, 2023

Figure made by F. Repele by Biorender



Top 30 gene signatures of each of incipient, subclinical, and clinical TB

Tabone et al, J Exp Med 2021

Table 1. **Top 30 gene signatures of each of incipient, subclinical, and clinical TB**

Incipient versus control	Subclinical versus control	Clinical versus control
MTRNR2L10[a]	*MSLN*	*MTRNR2L10*[a]
C1QC[b]	*CCDC144A*	*C1QC*[b]
C1QB[a]	*SPACA3*	*MTRNR2L1*
CCL2	*HIST1H4A*	*C1QB*[a]
HESX1	*HIST1H1B*	*ANKRD22*[a]
PCGF2	*HIST1H4F*	*SEPT4*
SERPING1[b]	*NXPH3*	*SERPING1*[b]
LCN8	*HIST1H4B*	*BATF2*[b]
SEMA6B	*ZBED6*	*FAM20A*
SIGLEC1	*HSPA12B*	*ETV7*[b]
C1QA[a]	*TRAJ4*	*EXOC3L4*
ISG15	*ETV7*[b]	*PDCD1LG2*
AHRR	*TAS2R3*	*METTL7B*
NEIL3	*HTRA1*	*APOL4*
FBXO39	*BATF2*[b]	*CFB*
AXL	*SERPING1*[b]	*C1QA*[a]
C2[a]	*GALNT4*	*VWA3B*
IFI6	*HIST2H2AB*	*SLC8A2*
LGALS2	*HIST1H1D*	*GBP6*[a]
IFITM3	*HIST1H1E*	*FCGR1A*
RUFY4	*GBP6*[a]	*C2*[a]
ETV7[b]	*HIST1H3C*	*CARD17*
TCN2	*SLC2A14*	*EXOC3L1*[a]
LGALS3BP	*TICAM2*	*RHOV*
EXOC3L1[a]	*GBP5*	*AOC1*
COL23A1	*C1QC*[b]	*KCNMA1*
MT2A	*TAS2R60*	*FAM26F*
BATF2[b]	*ANKRD22*[a]	*KCNJ10*
CXCL10	*CH17-296N19.1*	*CD274*
SCT	*HIST1H4C*	*SDC3*

Blood signature of gene expression changes in incipient, subclinical, and clinical TB.

Tabone et al, J Exp Med 2021

Pathway: Incipient TB vs control	p(adj)	Ratio
Immune response_IFN-γ in macrophages activation	6.590e-5	5/50
Immune response_Classical complement pathway	6.590e-5	5/53
Immune response_IFN-α/β signaling via JAK/STAT	8.645e-5	5/62
Putative pathways of activation of classical complement system in major depressive disorder	8.645e-5	4/28
Immune response_Lectin induced complement pathway	7.395e-4	4/50
Immune response_IFN-α/β signaling via MAPKs	2.762e-3	4/73
Inhibition of Ephrin receptors in colorectal cancer	2.831e-3	3/30
Alternative complement cascade disruption in age-related macular degeneration	2.831e-3	3/31
NETosis in SLE	2.831e-3	3/31
Immune response_Alternative complement pathway	1.265e-2	3/53
Coronavirus disease-19	1.545e-2	4/134
Signal transduction_PDGF signaling via JAK-STAT and reactive oxygen species	2.000e-2	3/66
T cell generation in COPD	4.055e-2	2/25
Defective macrophage-mediated bacterial phagocytosis in COPD	4.055e-2	2/25
Role of fibroblasts and keratinocytes in the elicitation phase of allergic contact dermatitis	4.092e-2	2/26
Release of pro-inflammatory mediators and elastolytic enzymes by alveolar macrophages in COPD	4.182e-2	2/28

Pathway: Subclinical TB vs control	p(adj)	Ratio
Immune response_IFN-α/β signaling via JAK/STAT	4.751e-13	14/62
Immune response_IFN-γ actions on blood cells	1.910e-6	7/28
Immune response_IFN-α/β signaling via MAPKs	6.626e-6	9/73
Cell cycle_Initiation of mitosis	1.832e-5	6/26
Immune response_Antimicrobial actions of IFN-γ	1.832e-5	7/43
NETosis in SLE	3.956e-5	6/31
Cell cycle_Chromosome condensation in prometaphase	1.035e-4	5/21
Cell cycle_Start of DNA replication in early S phase	8.193e-4	5/32
Immune response_IFN-γ in macrophages activation	6.618e-3	5/50
Putative pathways of activation of classical complement system in major depressive disorder	6.967e-3	4/28
Immune response_Classical complement pathway	7.158e-3	5/53
Development_YAP/TAZ-mediated co-regulation of transcription	8.524e-3	5/56
Immune response_IFN-α/β signaling via PI3K and NF-κBpathways	1.197e-2	6/94
DNA damage_ATM/ATR regulation of G2/M checkpoint: nuclear signaling	3.169e-2	4/45
HCV-dependent regulation of RNA polymerases leading to HCC	3.205e-2	3/21
Immune response_Induction of apoptosis and inhibition of proliferation mediated by IFN-γ	3.267e-2	4/47

Pathway: Clincal TB vs control	p(adj)	Ratio
Immune response_IFN-α/β signaling via JAK/STAT	2.444e-14	16/62
Immune response_IFN-γ actions on extracellular matrix and cell differentiation	6.171e-6	9/54
Immune response_IFN-α/β signaling via MAPKs	6.171e-6	10/73
Immune response_Antiviral actions of Interferons	4.829e-5	8/52
Immune response_Antimicrobial actions of IFN-γ	1.496e-4	7/43
Immune response_Induction of apoptosis and inhibition of proliferation mediated by IFN-γ	2.263e-4	7/47
NETosis in SLE	2.263e-4	6/31
Immune response_IFN-γ in macrophages activation	2.692e-4	7/50
Immune response_IFN-γ actions on blood cells	1.969e-3	5/28
Attenuation of IFN type I signaling in melanoma cells	7.170e-3	5/37
Putative pathways of activation of classical complement system in major depressive disorder	2.544e-2	4/28
PDE4 regulation of cyto/chemokine expression in inflammatory skin diseases	2.544e-2	5/50
Immune response_IFN-γ signaling via MAPK	2.578e-2	5/51
Immune response_Classical complement pathway	2.865e-2	5/53
Immune response_Sialic-acid receptors (Siglecs) signaling	3.263e-2	3/14
Signal transduction_Activin A signaling regulation	3.554e-2	4/33

Cross-validation performance of the tuberculosis risk 16-gene signature in the ACS training set by days before tuberculosis diagnosis

	ROC AUC (95% CI)	Sensitivity (95% CI)	Threshold
By 6 month period			
1–180	0·79 (0·76–0·82)	71·2% (66·6–75·2)	61%
181–360	0·771 (0·75–0·79)	62·9% (59·0–66·4)	61%
361–540	0·726 (0·70–0·76)	47·7% (42·9–52·5)	61%
541–720	0·540 (0·49–0·59)	29·1% (23·1–35·9)	61%
>720	0·496 (0·43–0·56)	5·4% (2·4–13·0)	61%
By 12 month period			
1–360	0·779 (0·76–0·80)	66·1% (63·2–68·9)	61%
360–720	0·647 (0·62–0·673)	37·5% (33·9–41·2)	61%
Total time period	0·743 (0·73–0·76)	58·4% (56·1–60·7)	61%

Sensitivity values are reported at a specificity of 80·0% (95% CI 78·6–81·4). ROC AUC=area under receiver operating characteristic curve. ACS=adolescent cohort study.

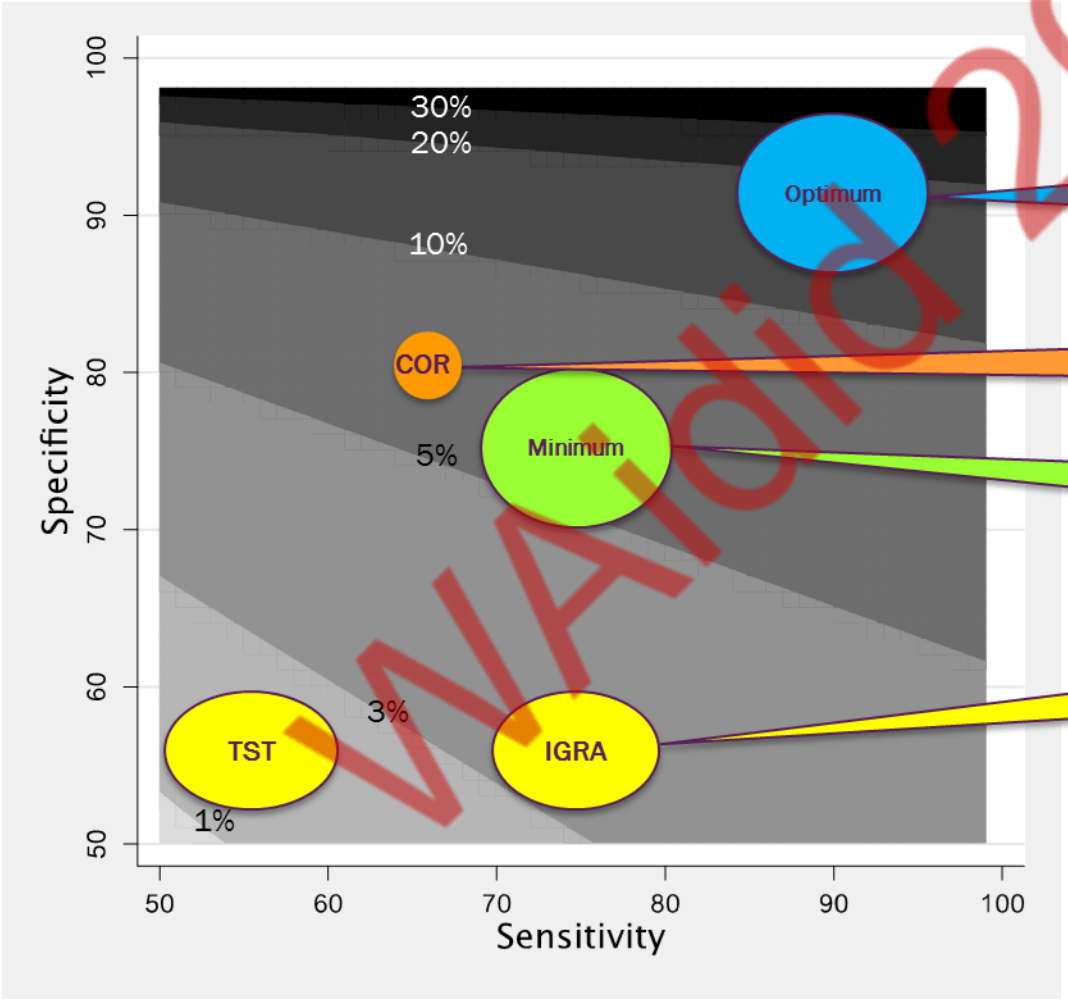
***Table 1*: Cross-validation performance of the tuberculosis risk signature in the ACS training set by days before tuberculosis diagnosis**

Zak at al, Lancet, 2016

Positive Predictive Value according to Sens/Spec for risk of progression

E. Petruccioli L. Petrone

cumulative incidence: 2%
IPT effectiveness: 50%



Optimum TPP
- PPV: ~16%

16-gene transcriptomic
COR - PPV: ~7%

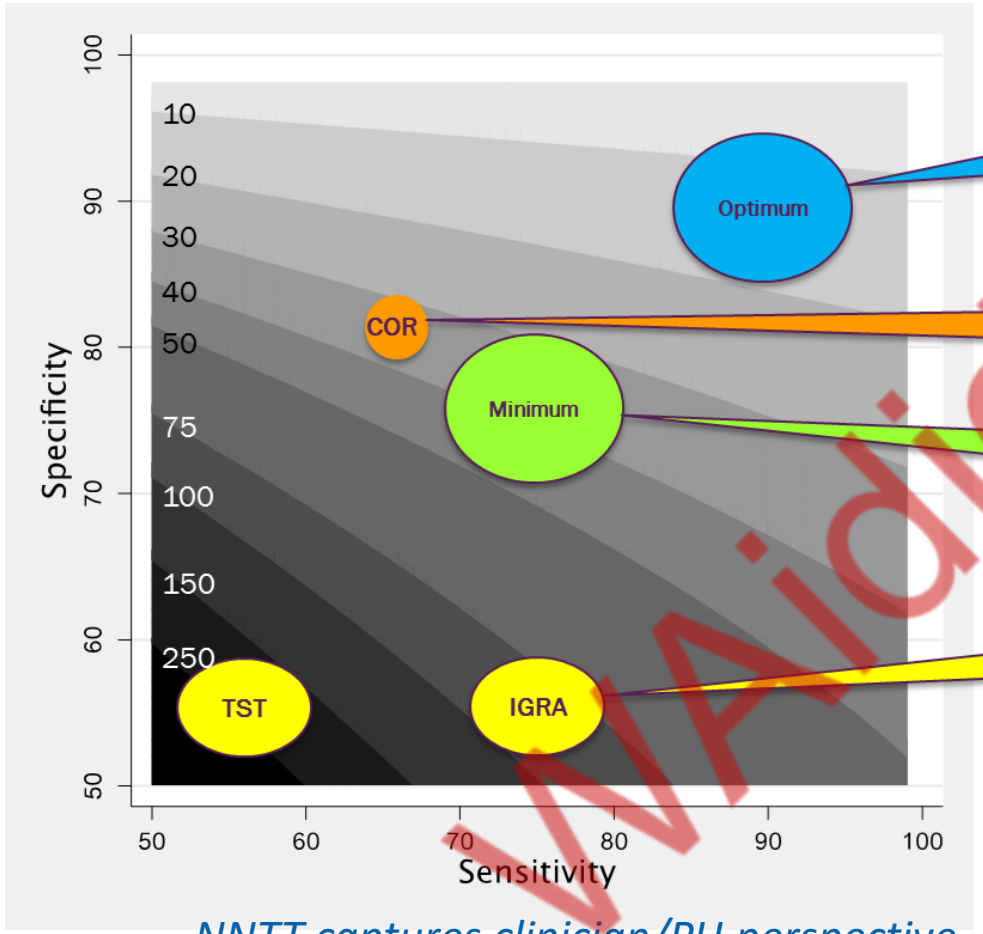
Minimum TPP
- PPV: ~6%

TST / IGRA
- PPV: ~2% / ~3%

Petruccioli et al, ERJ 2016

Number Needed to Test & Treat according to Sens/Spec for risk of progression

E. Petruccioli L. Petrone



Optimum TPP
- NNT: ~13

16-gene transcriptomic
COR - NNT: ~37

Minimum TPP
- NNT: ~40

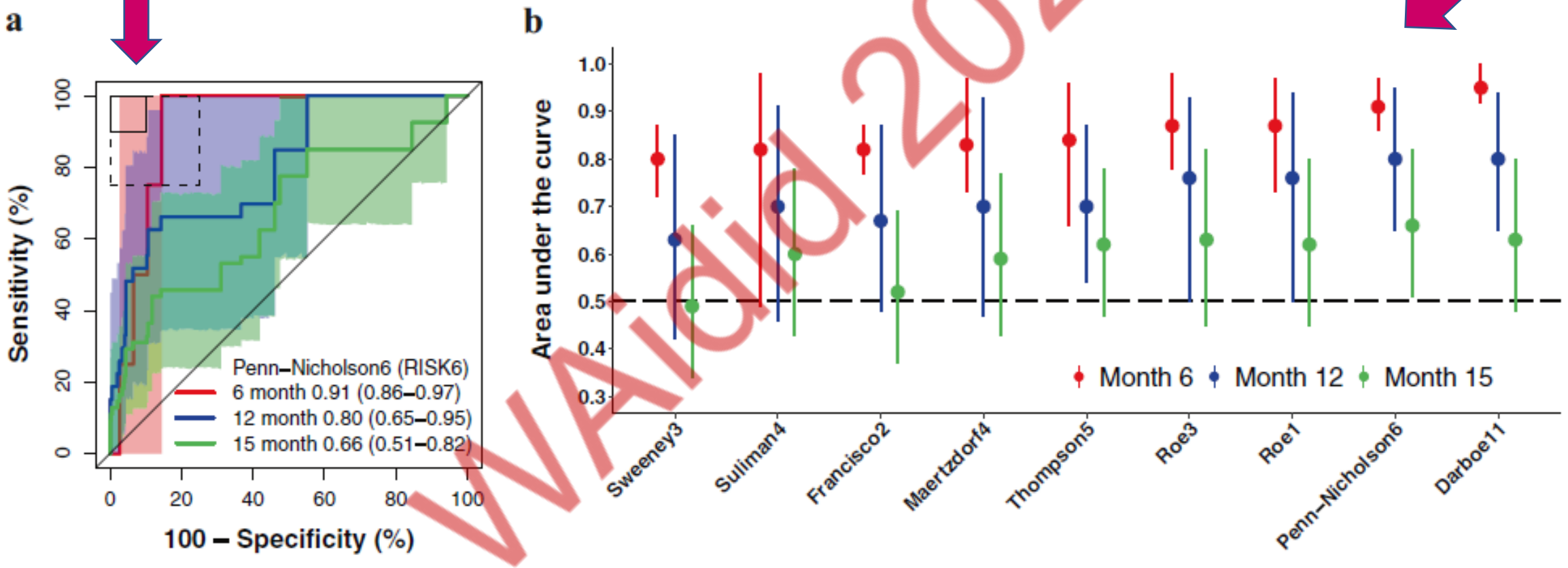
TST / IGRA
- NNT: ~250 / ~85

cumulative incidence: 2%
IPT effectiveness: 50%

NNTT captures clinician/PH perspective (If treating all test+, how many do I need to test and treat to prevent one case?)

Petruccioli et al, ERJ 2016

Parsimonious signature prognostic performance for incident TB in people without HIV infection



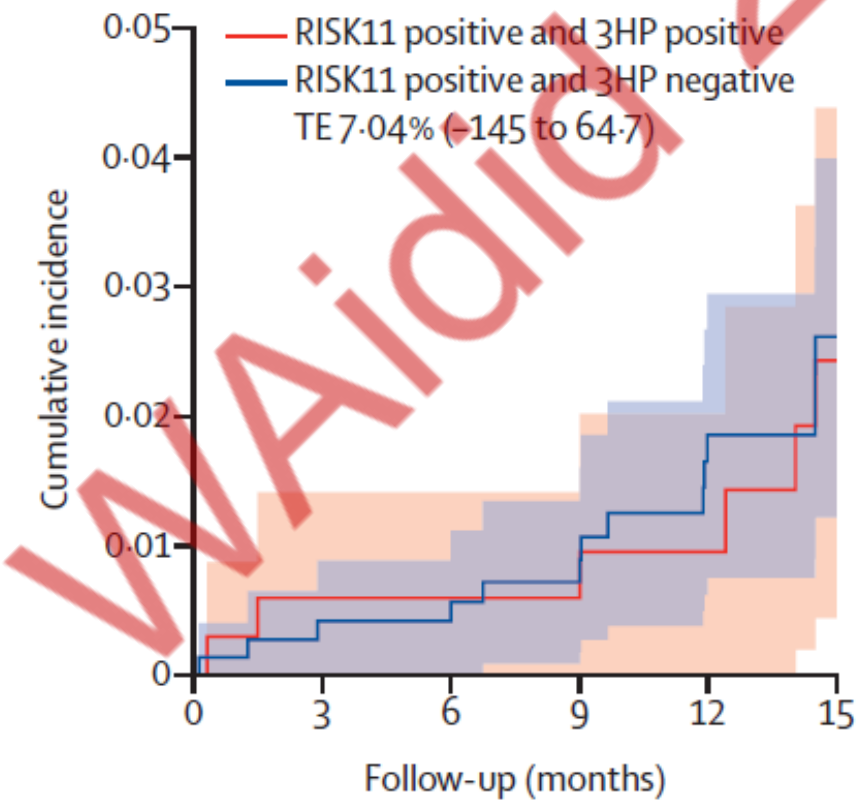
The solid box depicts the optimal WHO criteria (90% sensitivity and 90% specificity) and the dashed box depicts the minimal criteria (75% sensitivity and 75% specificity) set out in the WHO Target Product Profile for an incipient test.

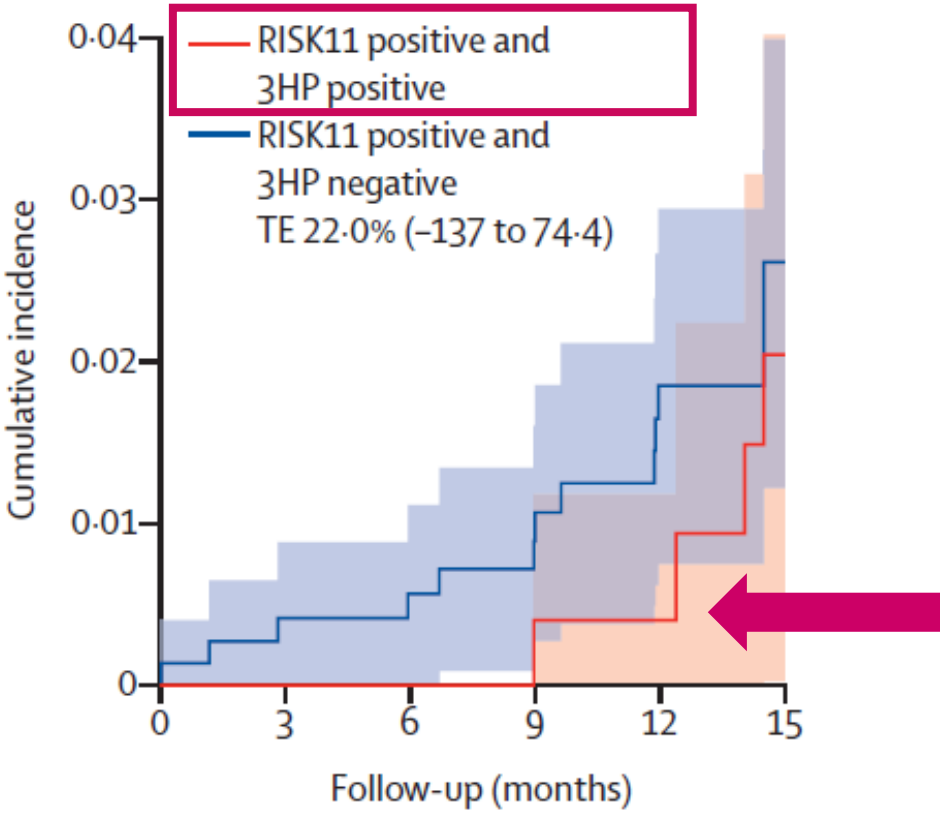
Mendelsohn et al, Communication Medicine, 2022

Effect of INH+RFP preventive therapy on incident TB cases

Criteria of treatment adherence per protocol

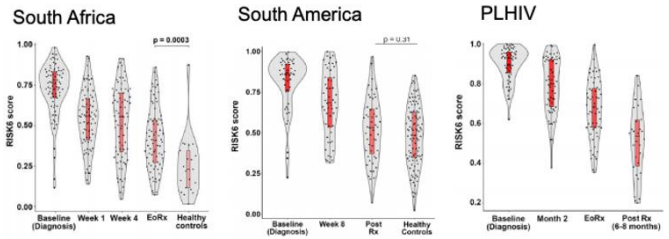
Participants who did not meet **or met**





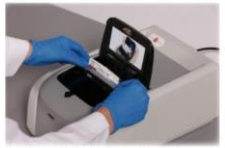
Scriba et al, Lancet ID 2021

Non-sputum-based test for incipient TB and treatment monitoring



Penn-Nicholson A et al, Scientific Reports 2020

FilmArray® pouch
45 marker, new version 30 markers



BIOFIRE® FILMARRAY® performs the extraction, amplification and detection in a closed system, 2h to result

1. Cepheid 3 genes signature (Sweeny Lancet RM 2016)
   - explored for:
     - Screening test for subclinical and clinical TB
     - Treatment monitoring & Risk of progression

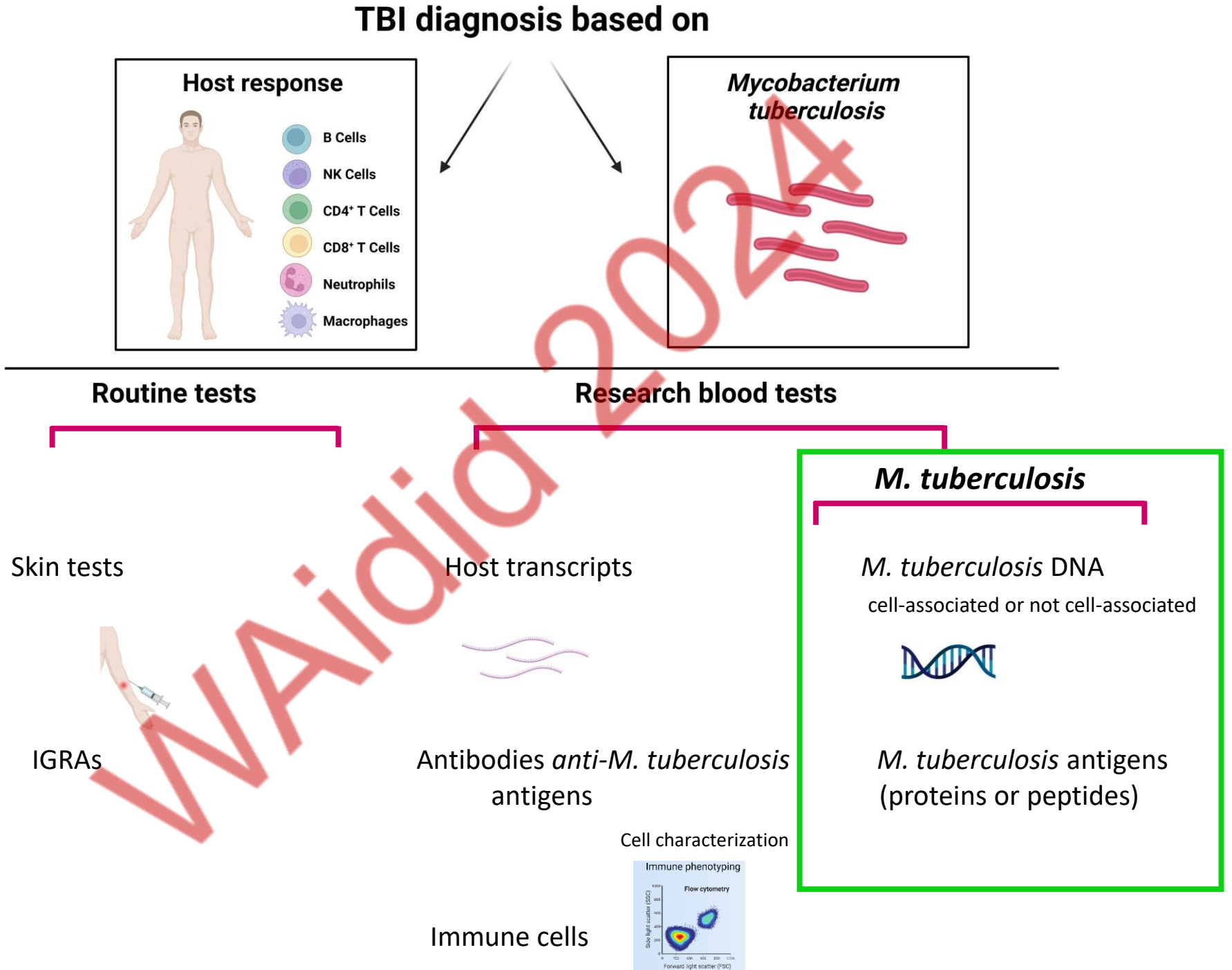
2. Quantun DX 6 genes signature
   - explored for:
     - Screening test for subclinical and clinical TB
     - Treatment monitoring & Risk of progression
     - Ability to predict cure at baseline
     - Correlate with PET-CT

3. BioMerieux Filmarray pouch assay on Biofire platform
   - 30 biomarkers panel (Berry et al Nature 2010)
   - Developed as:
     - Diagnostic for TB (sensitivity ≅93%, specificity ≅ 94%)
     - Evaluated as predictor of cure

Research tests for the diagnosis of tuberculosis infection

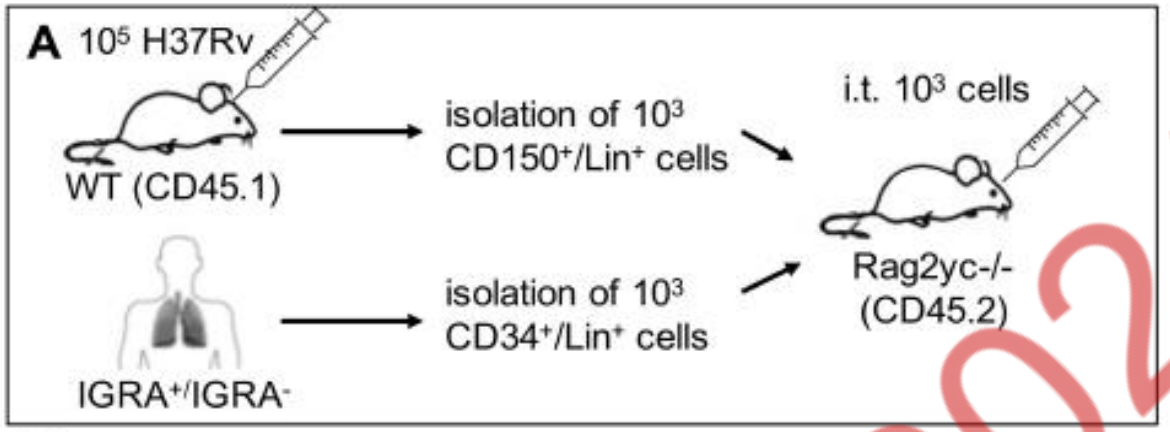
Alonzi T, Repele F, Goletti D. Expert Review of Molecular Diagnostics, 2023

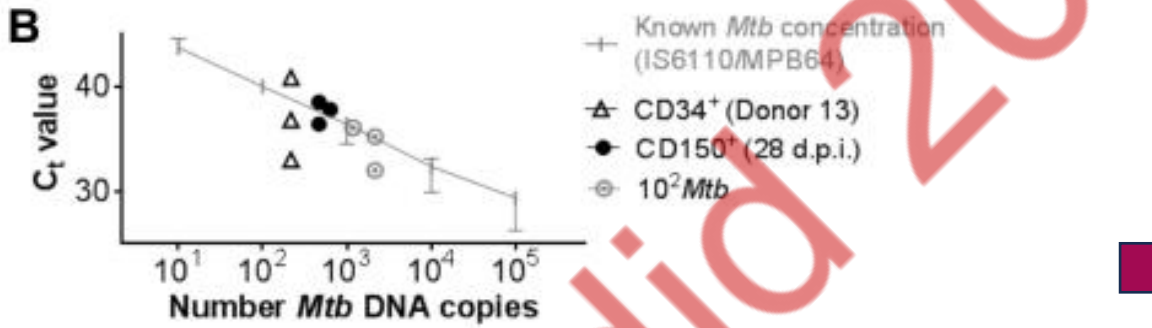
Figure made by F. Repele by Biorender

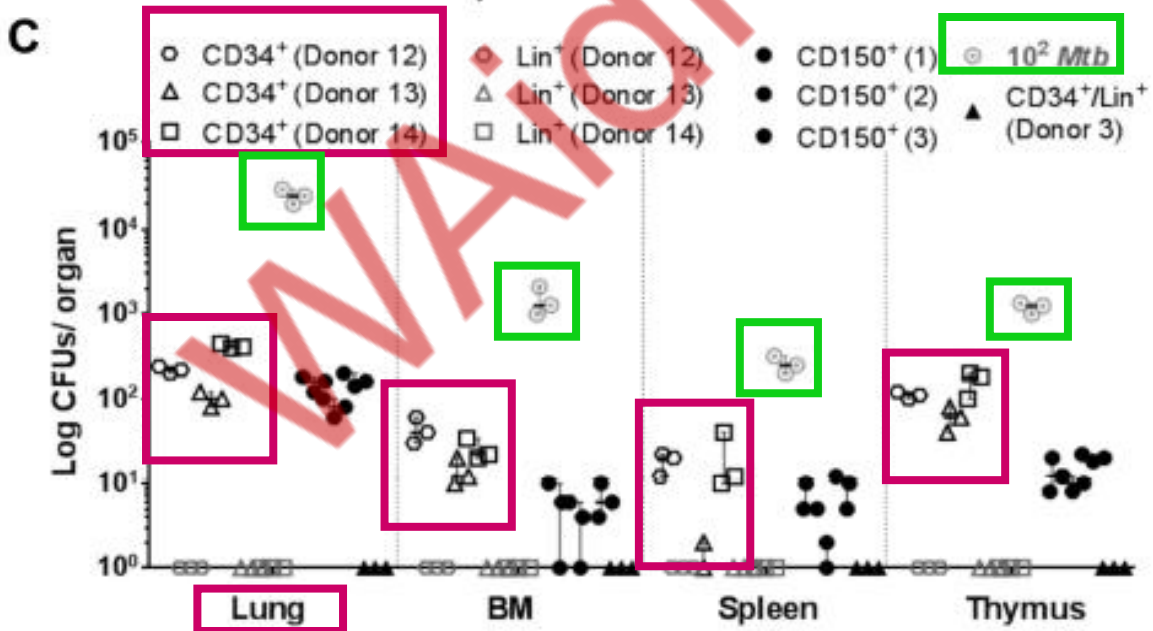


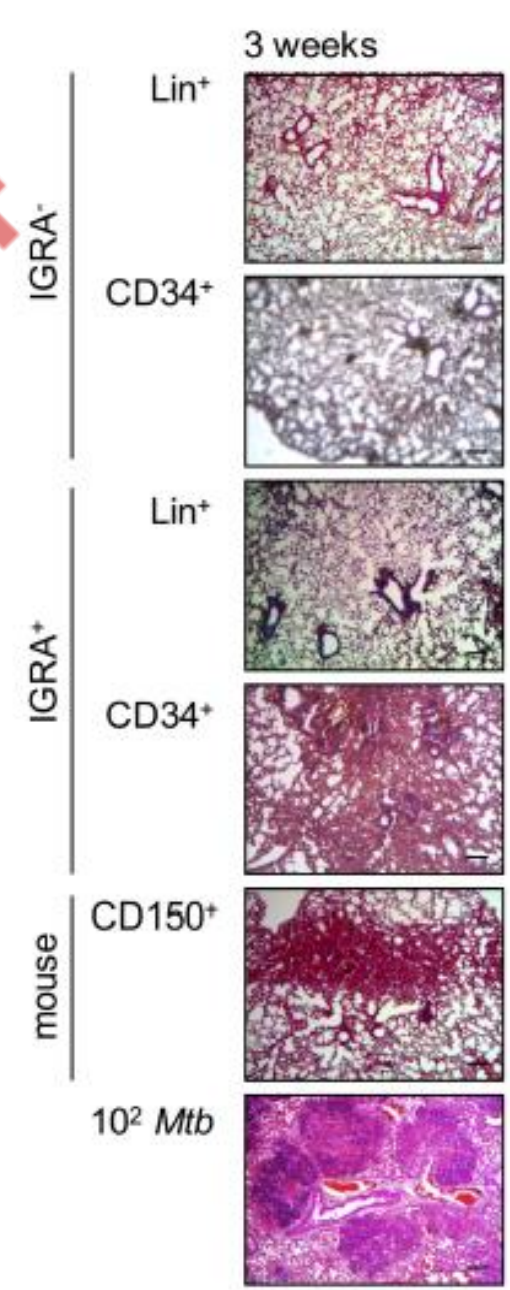
Hematopietic stem cells are a depot for dormant *M. tuberculosis*

Tornack et al, 2017, PLOSOne

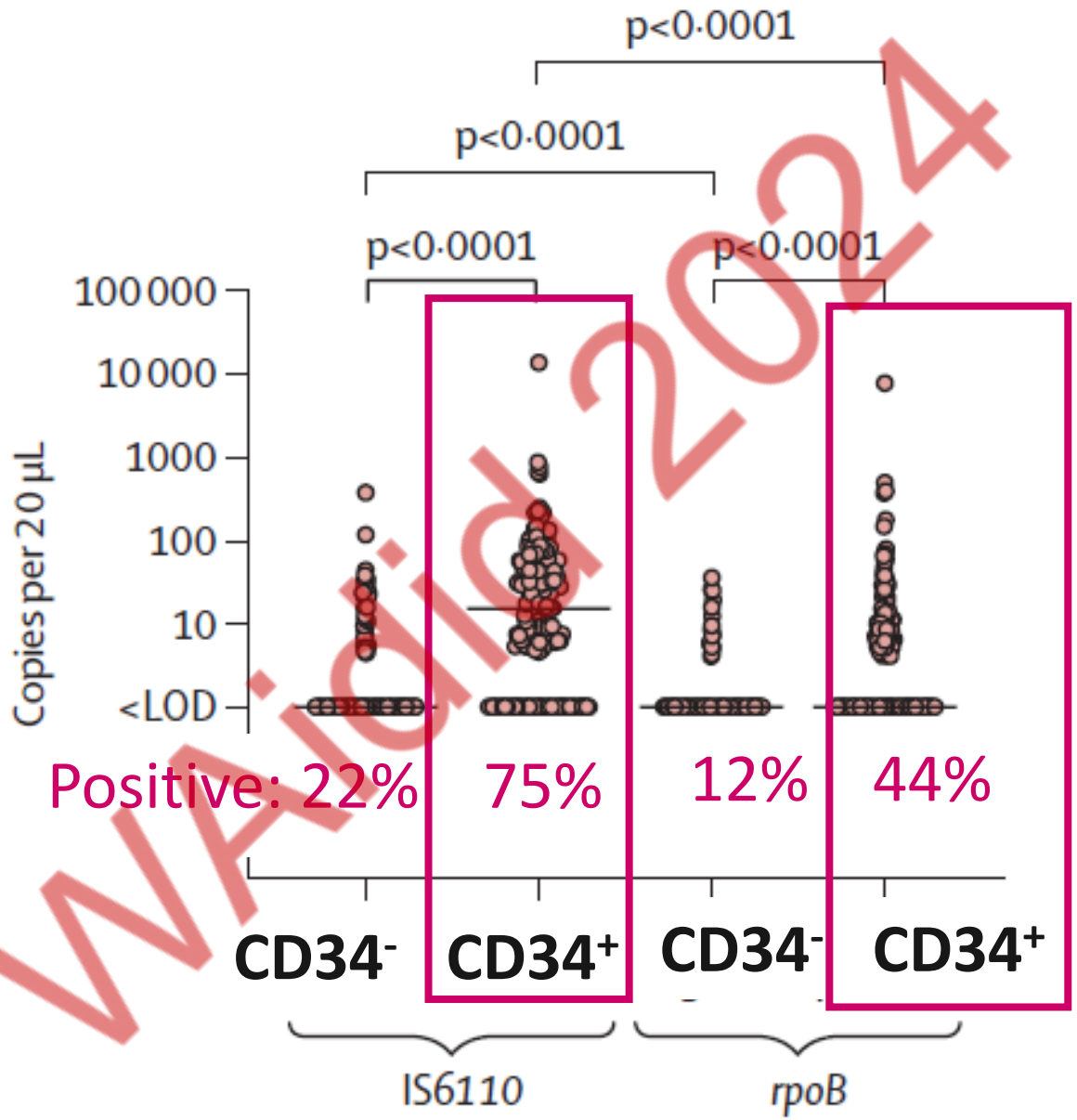








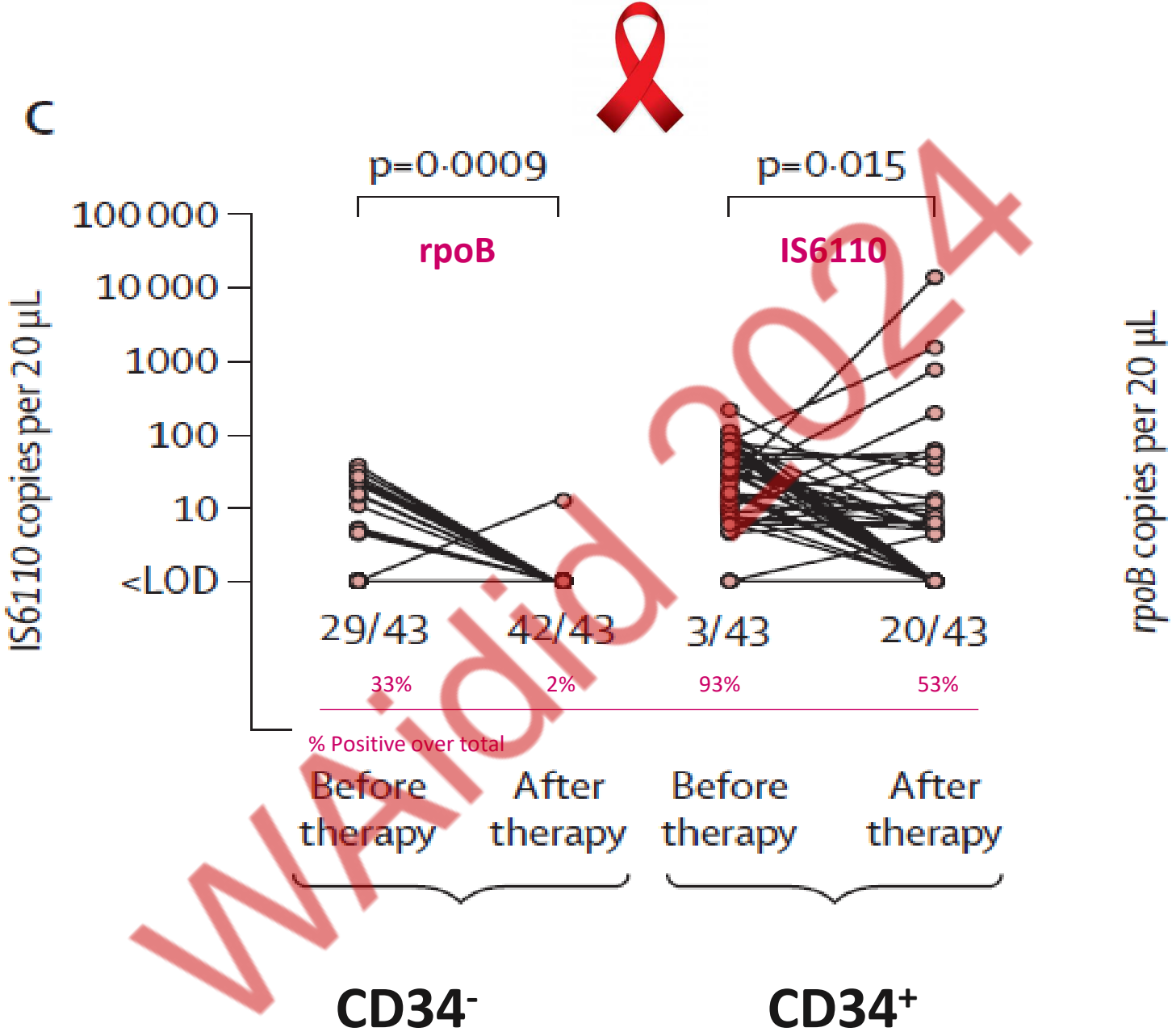
Detection of *M. tuberculosis* complex DNA in CD34-positive peripheral blood mononuclear cells of asymptomatic tuberculosis contacts: an observational study



Belay et al, Lancet Microbiology, 2021

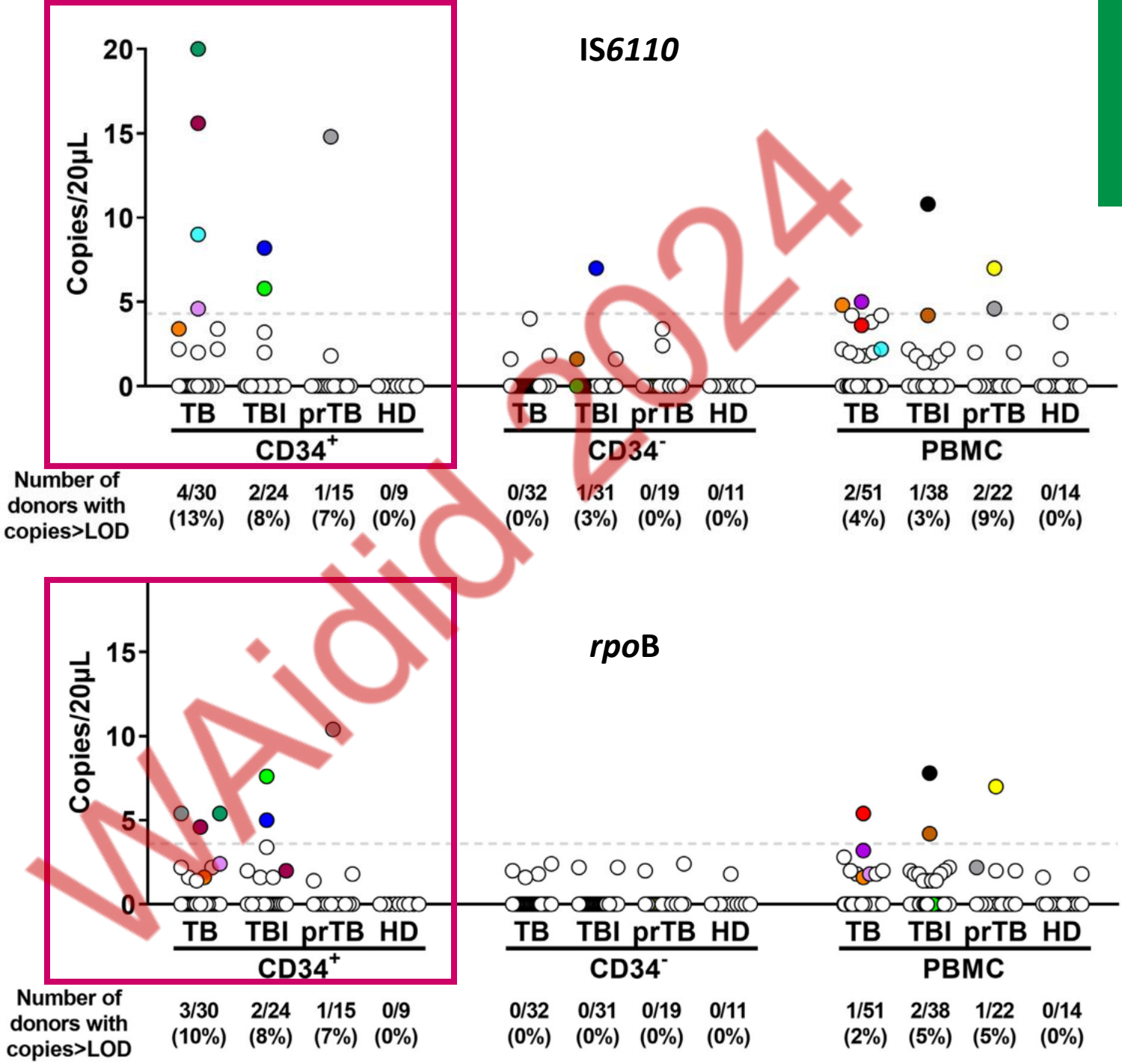
Detection of *M. tuberculosis* complex DNA in CD34-positive peripheral blood mononuclear cells of asymptomatic tuberculosis contacts: an observational study

Belay et al, Lancet Microbiology, 2021



Detection of Mycobacterium tuberculosis DNA in CD34+ peripheral blood mononuclear cells of adults with tuberculosis infection and disease

Repele and Alonzi et al, IJID 2024



Detection of Mycobacterium tuberculosis DNA in CD34+ peripheral blood mononuclear cells of adults with tuberculosis infection and disease

Evaluation of the association between Mtb DNA detection and TB status or cell population.

	aOR	95% confidence interval	p-value
NO TB	Ref.		
TB	2.12	0.38 - 11.91	0.395
TBI	1.89	0.31 - 11.66	0.495
$CD34^+$	Ref.		
$CD34^-$	**0.09**	**0.01 - 0.84**	**0.035**
PBMC	0.58	0.17 - 1.93	0.373

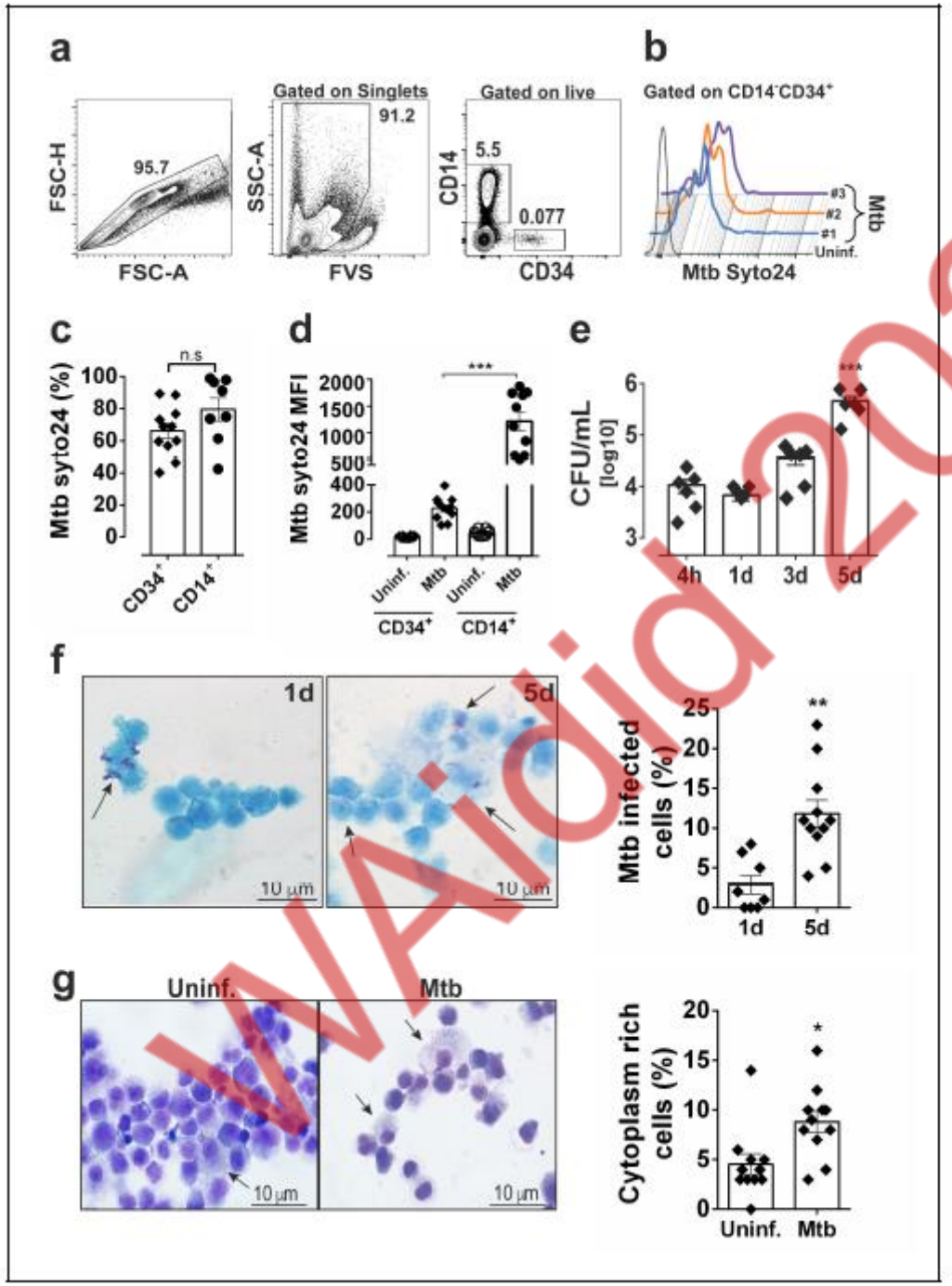
aOR, adjusted odds ratio; CD, cluster of differentiation; TB, tuberculosis; PBMC, peripheral blood mononuclear cells. OR was estimated by multivariable mixed-effects logistic regression.

Repele and Alonzi et al, IJID 2024

Mtb H37Rv replicates in primary human CD34+ cell cultures

Delgobo et al. eLife 2019

DOI: https://doi.org/10.7554/eLife.47013



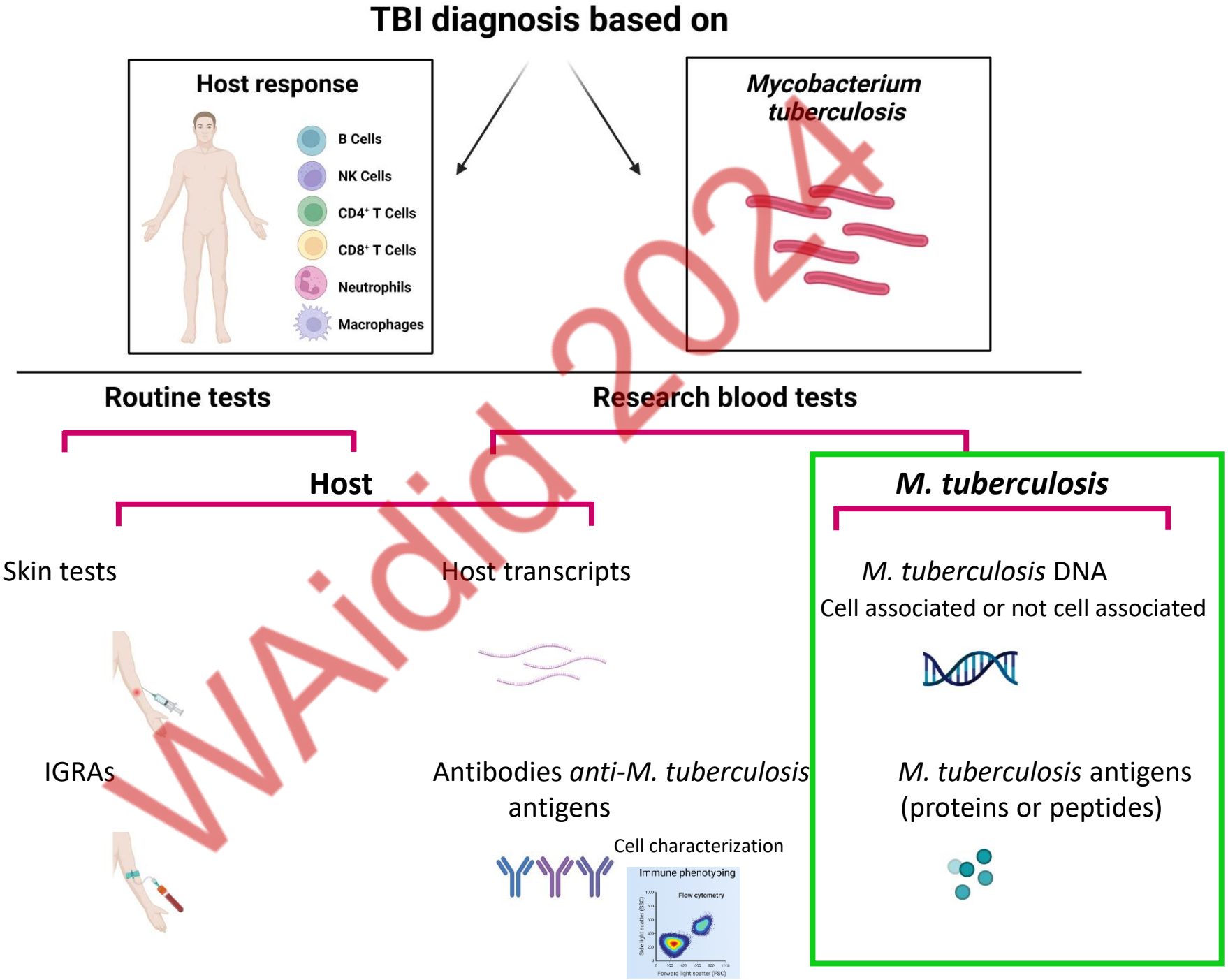
Human Cord Blood (CB) purified CD34+ cells from five different donors were obtained from STEMCELL Technologies and resuspended in StemSpan Expansion Media – SFEM II (STEMCELL Technologies) .

Following 4 days of expansion, cells were washed and diluted in SFEM II media without cytokine cocktail to the desired concentration and then in vitro infected with Mtb H37Rv.

Research tests for the diagnosis of tuberculosis infection

Alonzi T, Repele F, Goletti D. Expert Review of Molecular Diagnostics, 2023

Figure made by F. Repele by Biorede



A novel high sensitivity bacteriophage-based assay identifies low level *M. tuberculosis* bacteraemia in immunocompetent patients with active and incipient TB

		Active Pulmonary TB (n = 15)		Non-TB Acute Respiratory Illness (n = 5)	Pulmonary TB Contacts With LTBI (n = 18)		Healthy Controls: No LTBI (n = 28)
Actiphage Result		Positive (n = 11)	Negative (n = 4)	All Negative	Positive (n = 3)	Negative (n = 15)	All Negative
Male gender, n, (%)		5 (45.5)	2 (50)	2 (40)	1 (33.3)	10 (55.6)	11 (39.3)
Age, in years, mean (± SD)		31.5 (±13.9)	38.8 (±13.5)	50 (±21.7)	25.3 (±6.4)	54.7 (±12.3)	38.9 (±14.6)
Born in United Kingdom, n (%)		3 (27.2)	1 (25)	2 (40)	1 (33.3)	5 (33.3)	10 (35.7)
BCG vaccination	Yes, n (%)[a]	4 (36.4)	2 (50)	2 (40)	2 (66.7)	7 (63.6)	12 (50)
	Unknown, n (%)	0	0	0	0	4 (26.7)	4 (14.3)
BMI, kg/m^2, mean (± SD)		19.9 (±3.6)	20.9 (±3.0)	25.7 (±5.3)	21.9 (±2.0)	26.2 (±6.9)	27.1 (±8.2)
TB disease characteristics	Smear positive	7	0	0	0	N/A	N/A
	Smear negative	4	4	0	2	N/A	N/A
	Xpert-Ultra grade	Medium–high	Very low–low	All negative	Medium[b]	N/A	N/A
	CRP, median (IQR)	63 (36–65)	41 (27–45.5)	84 (45–110)	5 (5–5)[c]	10 (5–13.75)	5 (5–10)
	Days to positive culture, median (IQR)	15 (10.5–22)	21 (21–21)	1 blood culture (*S. aureus*); 1 sputum culture (*M. avium*, 6 days)	26 (23.5–28.5)[b]	N/A	N/A

Abbreviations: BCG, Bacillus Calmette-Guérin; BMI, body mass index; CRP, C-reactive protein; IQR, interquartile range; LTBI, latent TB infection; *M. avium*, *Mycobacterium avium*; N/A, not applicable; *S. aureus*, *Staphylococcus aureus*; SD, standard deviation; TB, tuberculosis.

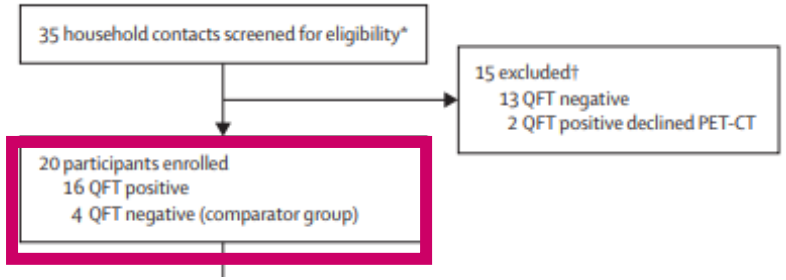
[a]Percentages were calculated from the subgroup for which the BCG status was known.

[b]Data presented are at the time of presentation with TB in 2 contacts.

[c]CRP values refer to data collected at baseline, consistent with the data for the other groups.

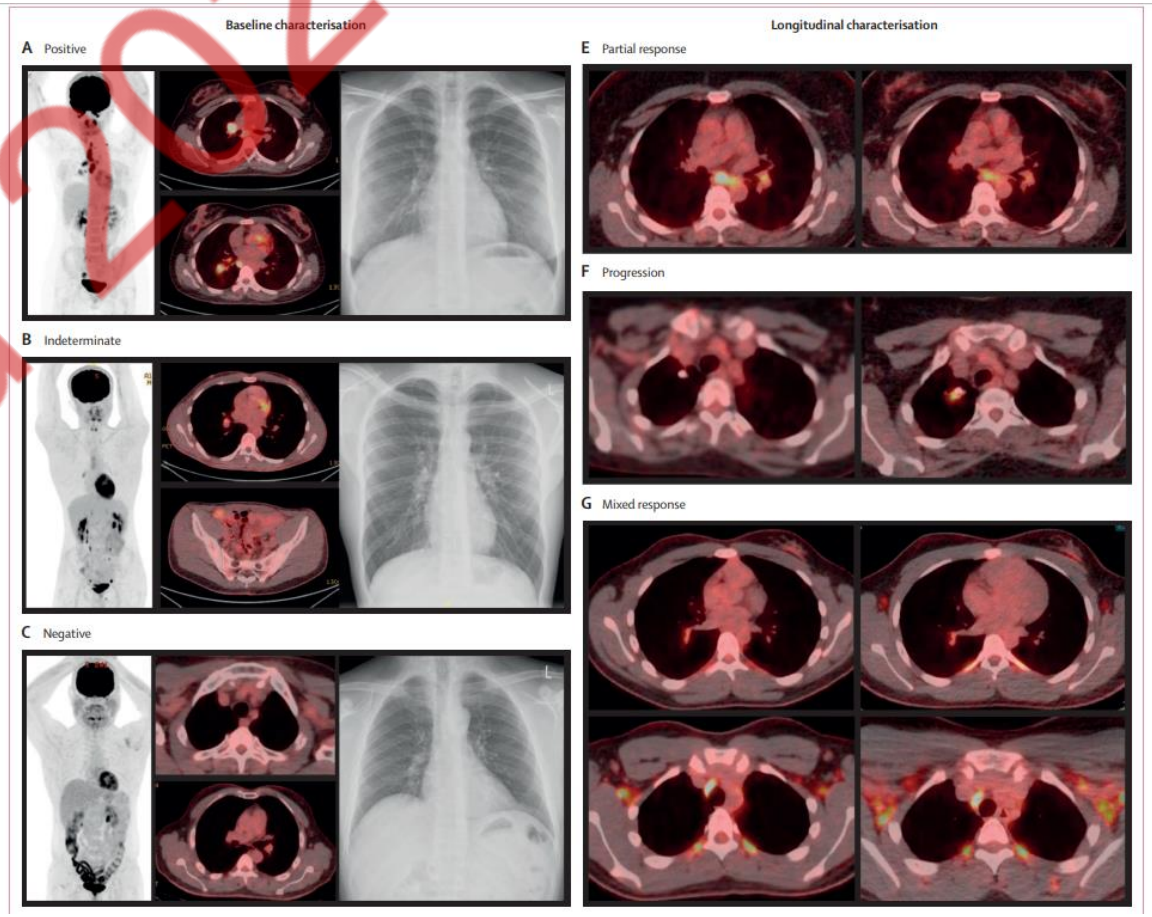
Verma et al, CID, 2020

PET-CT-guided characterization of progressive, preclinical tuberculosis infection and its association with low-level circulating *M. tuberculosis* DNA in household contacts in Leicester, UK: a prospective cohort study



Classification of baseline PET-CT findings	
Positive	[^{18}F]FDG-avid mediastinal or hilar lymph nodes (SUV_{max} >5), with or without uptake in lung parenchyma
Indeterminate	Low absolute [^{18}F] FDG uptake (SUV_{max} <5); extrathoracic uptake at sites associated with *M tuberculosis* infection
Negative	No [^{18}F]FDG uptake exceeding physiological uptake

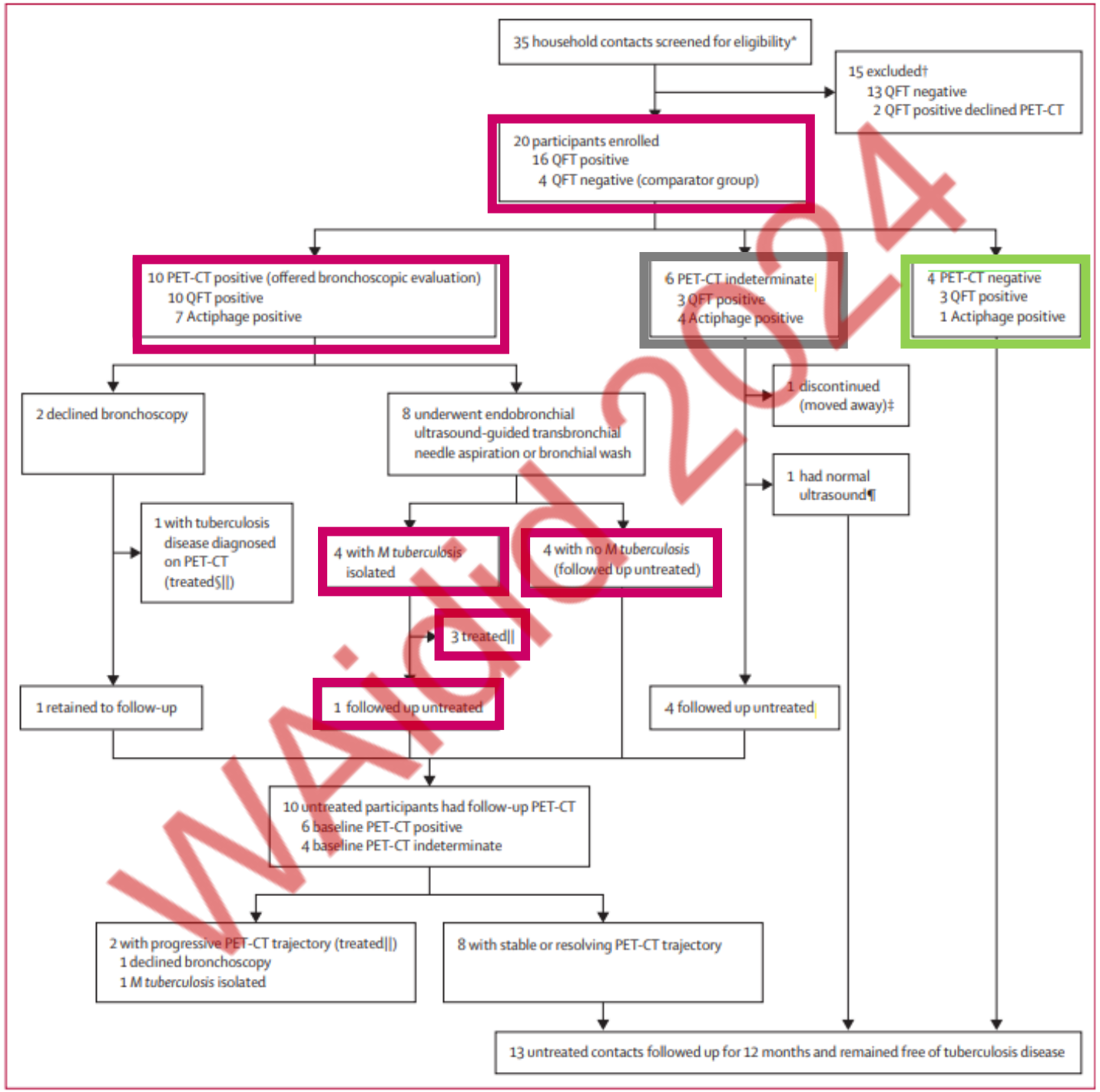
Classification of longitudinal PET-CT changes	
Resolved	Complete resolution of lesions seen on initial PET-CT scan
Partial response	≥20% reduction in SUV_{max} in all lesions
Stable	<20% variation in SUV_{max}
Mixed response	Sites with ≥20% increase and sites with ≥20% reduction in SUV_{max}
Progression	≥20% increase in SUV_{max}; new area of [^{18}F]FDG uptake with SUV_{max} >5



Kim et al, Lancet Microbe, 2024

PET-CT-guided characterization of progressive, preclinical tuberculosis infection and its association with low-level circulating Mycobacterium tuberculosis DNA in household contacts in Leicester, UK: a prospective cohort study

Kim et al, Lancet Microbe, 2024

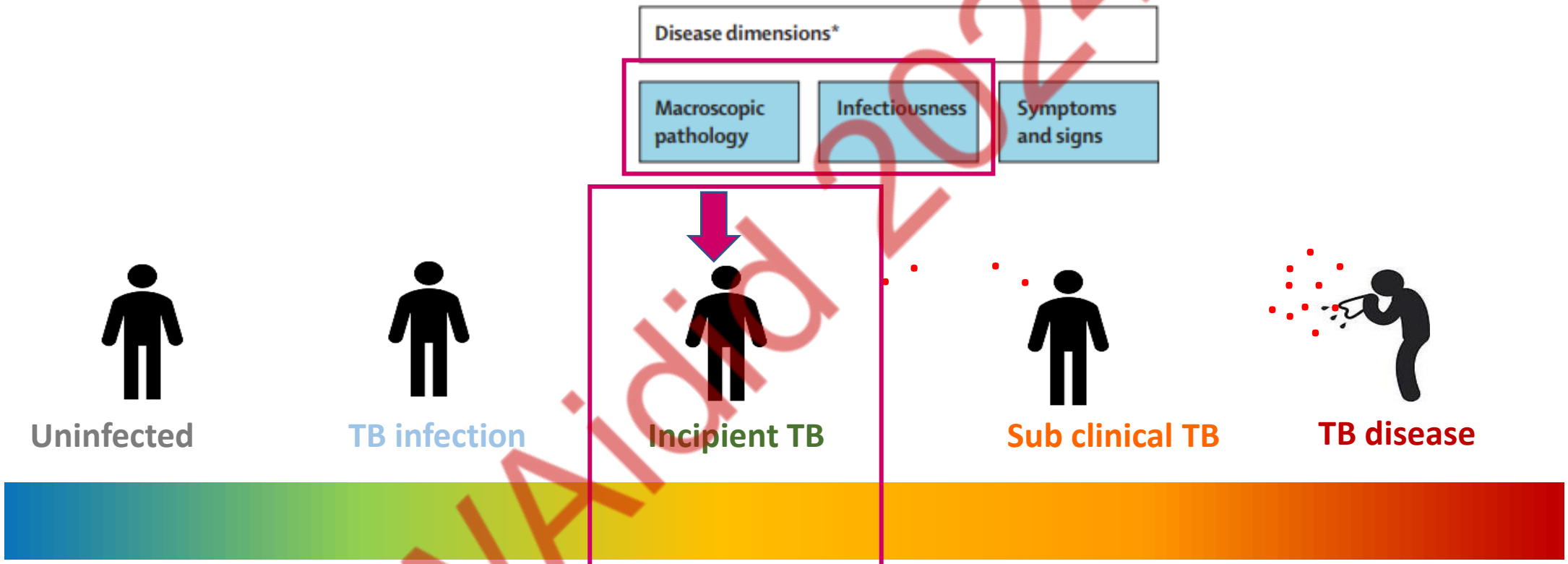


Incipient TB defined based on PET-CT

Incipient TB was defined by PET-CT activity as:

- microbiological detection *of M. tuberculosis* (in culture or WITH XPERT-ULTRA) from sampling at sites of PET-CT activity or
- evidence of progressive metabolic/structural change on serial PET-CT

Tuberculosis as a spectrum



"TB infection" as having evidence of TB infection and no clinical, radiological or microbiological evidence of active TB disease"

"Incipient TB" is an infection that is likely to progress to disease in the absence of further intervention but has not yet induced clinical symptoms or radiographic abnormalities or Mtb isolation

"Subclinical TB disease" is a disease that does not cause clinical TB-related symptoms but causes other abnormalities that can be detected using existing radiologic or microbiologic assays.

"TB disease" as symptomatic disease with radiological or microbiological evidence of TB

Migliori et al, Breath 2021
Goletti et al, IJID 2022

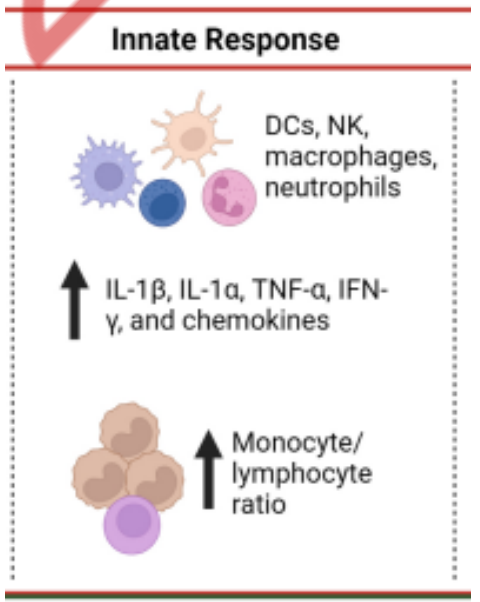
M. tuberculosis infection and local and blood responses

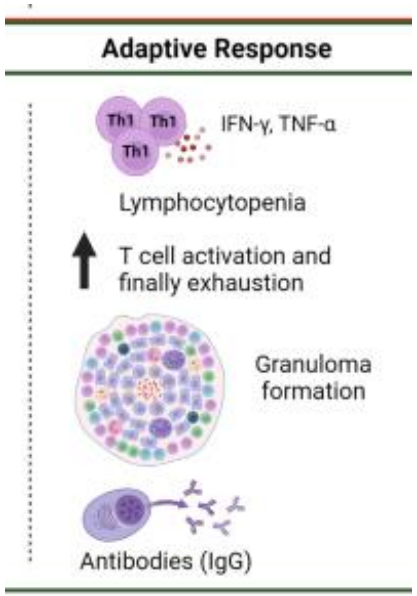
Goletti D, in preparation

***M. tuberculosis* in:**

Local tissues

Blood circulation



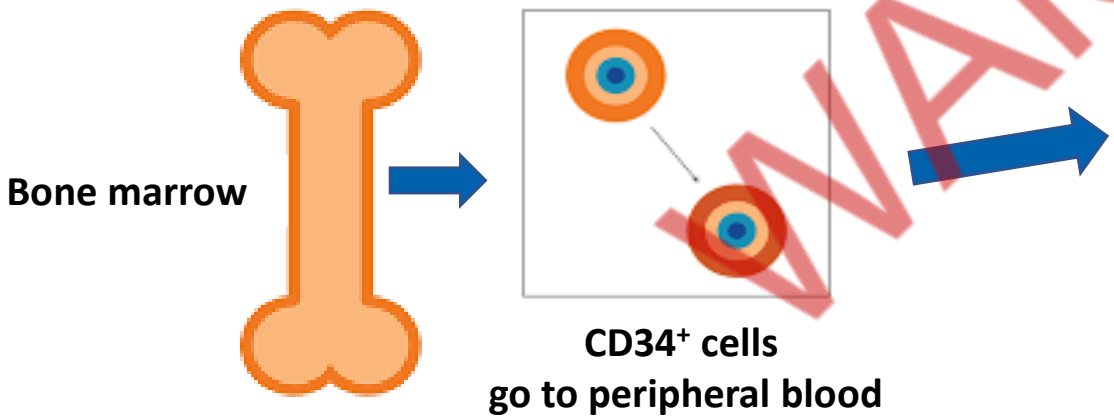


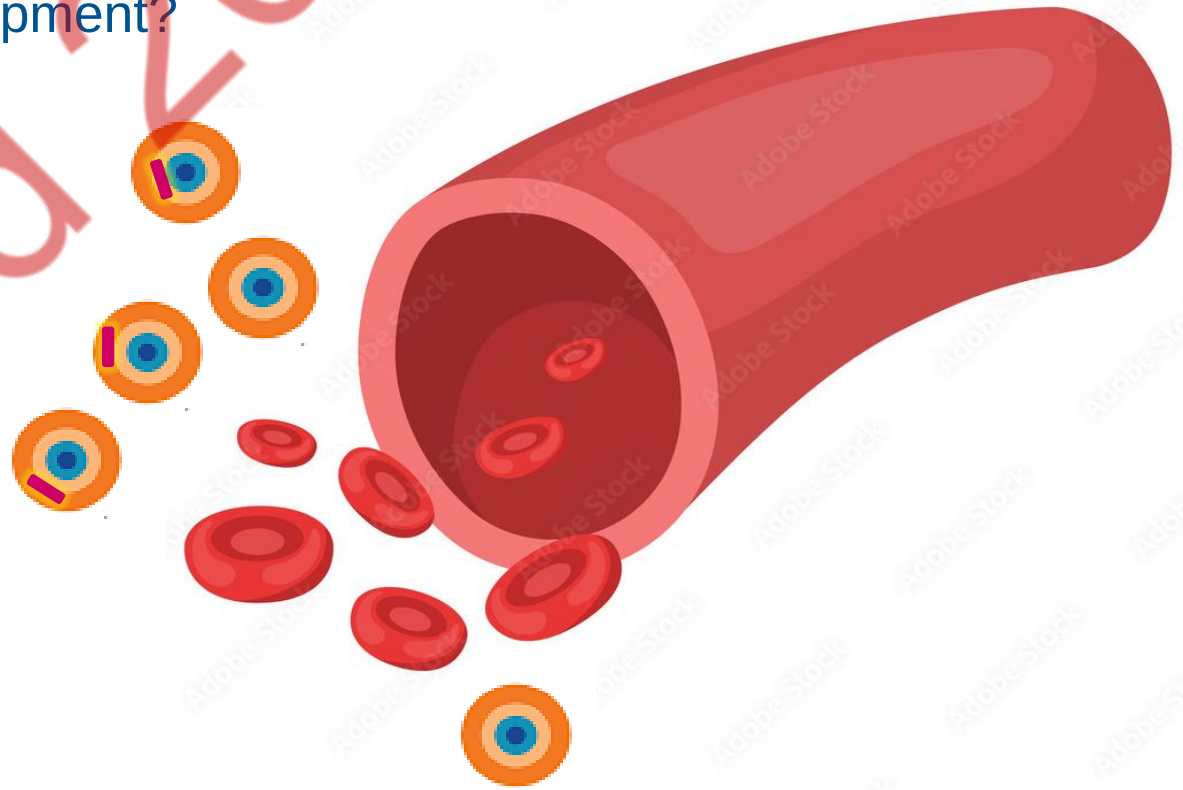
What is the meaning of CD34^{+} cells Mtb-DNA^{+} in the blood of a TBI person?

CD34^{+} cells in the blood of a TBI person:

1. Reservoir of M. *tuberculosis*?
2. Will these cells go to the tissues and infect other resident cells, as alveolar macrophages?
3. Do these cells associate with TB disease development?
4. ?

Monocytes/lymphocytes ratio:
>1 in TB disease and recent contacts





	Blood tests		
	Host-based	***M. tuberculosis*-based**	
	Host signatures	**Actiphage**	**Mtb-DNA in CD34⁺ cells**
Accuracy to predict TB disease	Up to 90% sensitivity and specificity	To define: Only 2 small studies are available	To define: No studies available
Time to repeat the test	To define: every 3 months?	To define	To define
Is the test accurate in those with HIV infection?	No	To define	To define
Time to have the result	Few days	Few days	Few days
If scored positive: preventive treatment or full therapy?	To define	To define	To define:
Can the pathogen-based test be used to evaluate drug resistance?	-	Yes	Yes

Combined tests

Host-based tests with:

- Pathogen-based tests
- IGRA

	Resistance to infection/ Cleared infection	Incipient TB	TB infection
Host biomarkers signature	-	+	-
Mtb-DNA	-	+	+/-
PET CT scan	-	+	-
IGRA	-	+	+

Future directions for the blood tests detecting *M. tuberculosis* DNA

- To validate the test in larger cohorts
- To substantiate the association with TB development in TBI evaluating:
  - cell activation status
  - co-morbidities
  - …

1st screening

2nd screening

Skin test+ or IGRA+

Based on the guidelines,
we offer TB preventive therapy to
all individuals skin test+ or IGRA+

Host-based
diagnostic tests

Pathogen-based
diagnosic tests

TB progressors

We offer TB therapy only to
the individuals scored positive to
the «new tests»

Many thanks to…

Translational Research Unit

Alessandra Aiello
Tonino Alonzi
Gilda Cuzzi
Chiara Farroni
Saeid Najafi Fard
Linda Petrone
Elisa Petruccioli
Valentina Vanini

Anna Maria Altera
Andrea Coppola
Federica Repele
Daniela Peruzzu
Andrea Salmi
Settimia Sbarra

Prof Susanna Esposito
President Organizer